

THE STATE OF SOUTH CAROLINA
In The Supreme Court

APPEAL FROM SPARTANBURG COUNTY
Court of Common Pleas

Roger L. Couch, Circuit Court Judge

Case No. 2007-CP-42-1438

State of South Carolina ex. rel. Alan Wilson in his
capacity as Attorney General of the State of South
Carolina, ... Respondent,

v.

Ortho-McNeill-Janssen Pharmaceuticals, Inc., f/k/a
Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and
Johnson & Johnson, Inc., ... Defendants.

Of whom Ortho-McNeill-Janssen Pharmaceuticals, Inc.
is Appellant.

RECORD ON APPEAL - VOLUME XIV

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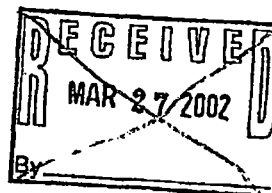
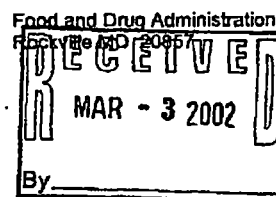


DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-272/S-008
NDA 20-588/S-004

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Edward G. Brann
Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560



Dear Mr. Brann:

Please refer to your supplemental new drug applications dated March 12, 1997, received March 12, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal (risperidone) tablets and oral solution.

We acknowledge receipt of your submission dated January 28, 2002, which constituted a complete response to our January 11, 2002 action letter.

These supplemental new drug applications provide for the longer-term efficacy for risperidone in the treatment of schizophrenia.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. We note that modifications of labeling text to more clearly state that this agent is indicated for the treatment of schizophrenia (requested in our letter of September 25, 2000) have been effected. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-272/S-008, 20-588/S-004." Approval of these submissions by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless FDA waives or defers the requirement (63 FR 66632) [21 CFR 314.55]. The Agency has not made a determination if a health

JJRP 00463739

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D841.1

NDA 20-272/S-008
NDA 20-588/S-004
Page 2

benefit would be gained by studying risperidone in pediatric patients for its approved indication. FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations until February 1, 2005.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

JJRP 00463740
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D841.2

Description of revisions to Risperdal (risperidone) Labeling

Section of Labeling	Description of Revision(s)
DESCRIPTION	Paragraph 1, sentence 1: changed from "an antipsychotic agent" to "a psychotropic agent"
CLINICAL PHARMACOLOGY: Pharmacodynamics	Paragraph 1, sentence 1: changed "antipsychotic drugs" to "drugs used to treat schizophrenia" and "antipsychotic activity" to "therapeutic activity in schizophrenia"
CLINICAL PHARMACOLOGY: Clinical Trials	Before paragraph 1, added subheading "Short-Term Efficacy". Paragraph 1, changed "management of the manifestations of psychotic disorders" to "treatment of schizophrenia" Paragraph 2, sentence 1: changed "effects of drug treatment in psychosis" to "effects of drug treatment in schizophrenia"
CLINICAL PHARMACOLOGY: Clinical Trials	Added subheading "Long-Term Efficacy" and paragraph to describe RIS-USA-79 study design and results
INDICATIONS AND USAGE	Paragraph 1: changed "management of the manifestations of psychotic disorders" to "treatment of schizophrenia" Paragraph 2, changed "antipsychotic efficacy of RISPERDAL®" to "efficacy of RISPERDAL® in schizophrenia" Paragraph 3: replaced first sentence with FDA statement on use of Risperdal in long-term treatment; last sentence: changed "Therefore" to "Nevertheless"
DOSAGE AND ADMINISTRATION: Usual Initial Dose	Paragraph 1: added "short-term" twice as descriptor of clinical trials and sentence on titration schedule from long-term study Paragraph 2, sentence 1: changed "Antipsychotic efficacy" to "Efficacy in schizophrenia" for consistency with the intent of FDA 9/25/00 letter and added "short-term" as descriptor for clinical trials
DOSAGE AND ADMINISTRATION: Maintenance Therapy	Repositioned subsection to follow "Usual Initial Dose" subsection Revised paragraph to provide description and titration schedule from long-term study and to incorporate FDA's changes Added the word "schizophrenic" to describe patients in the first sentence.
DOSAGE AND ADMINISTRATION: Switching from Other Antipsychotics	Added "schizophrenic" as a descriptor for "patients" in three places and changed "other patients" to "others"

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**JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.**

**RISPERDAL[®]
(risperidone)
TABLETS/ORAL SOLUTION**

DESCRIPTION

RISPERDAL[®] (risperidone) is ~~an antipsychotic~~ a psychotropic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:

(insert structure)

Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL[®] tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide, the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL[®] is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are: tartaric acid, benzoic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia antipsychotic drugs, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia antipsychotic activity is mediated through a combination of dopamine type 2 (D₂) and serotonin type 2 (5HT₂) antagonism. Antagonism at receptors other than D₂ and 5HT₂ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (K_i of 0.12 to 7.3 nM) for the serotonin type 2 (5HT₂), dopamine type 2 (D₂), α_1 and α_2 adrenergic, and H₁ histaminergic receptors. RISPERDAL® antagonizes other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin 5HT_{1C}, 5HT_{1D}, and 5HT_{1A} receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D₁ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations > 10⁻⁵ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ¹⁴C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome P₄₅₀1D₆ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

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The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome P₄₅₀11D₆, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome P₄₅₀ 11D₆ is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome P₄₅₀11D₆ could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome P₄₅₀11D₆. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

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The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1 -acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 μ g/mL), warfarin (10 μ g/mL) and carbamazepine (10 μ g/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL[®] doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1 -acid glycoprotein. RISPERDAL[®] doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE AND ADMINISTRATION).

Race and Gender Effects: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Short-Term Efficacy

The efficacy of RISPERDAL[®] in the treatment of schizophrenia management of the ~~manifestations of psychotic disorders~~ was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

- (1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL[®] in doses up to 10 mg/day (BID schedule), RISPERDAL[®] was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.
- (2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL[®] (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL[®] groups were generally superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL[®] dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.
- (3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL[®] (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL[®] dose groups were generally superior to the 1 mg RISPERDAL[®] dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.
- (4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL[®] (4 and 8 mg/day on a QD schedule), both RISPERDAL[®] dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS

psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia management of the manifestations of psychotic disorders.

The antipsychotic efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® in long-term use, that is, more than 6 to 8 weeks, has not been systematically evaluated in controlled trials. The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Therefore Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of Risperdal® and antihypertensive medication.

Seizures: During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL® treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class

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of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL[®] treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL[®] 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL[®] 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL[®] has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL[®] therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL[®] use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL[®] may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL[®] in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL[®] therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with Risperdal[®] use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL[®] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

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Nursing: Patients should be advised not to breast feed an infant if they are taking RISPERDAL®.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking RISPERDAL®.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome P₄₅₀IID₆ and Other P₄₅₀ Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome P₄₅₀IID₆, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n = 70) does

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not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, 11C9, MP, and 11A4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome P_{450} IID₆: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome P_{450} IID₆. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m^2 (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	None
	rat	female	0.4 (2.4)	None
	rat	male	6 (37.5)	1.5 (9.4)

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Mammary gland neoplasms, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1

to 3 times the human dose on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL[®] therapy is unknown.

RISPERDAL[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL[®] on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. Therefore, women receiving RISPERDAL[®] should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL[®] did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg

BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See DOSAGE AND ADMINISTRATION).

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ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events ($\geq 0.3\%$) associated with discontinuation and considered to be possibly or probably drug-related included:

<u>Adverse Event</u>	<u>RISPERDAL®</u>	<u>Placebo</u>
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation,

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micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgasmic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-

Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1: Treatment-Emergent Adverse Experience Incidence in 6 to 8-Week Controlled Clinical Trials¹

Body System/ Preferred Term	RISPERDAL®		Placebo
	≤ 10 mg/day (N = 324)	16 mg/day (N = 77)	(N = 142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms ²	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%

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Body System/ Preferred Term	RISPERDAL®		Placebo
	≤ 10 mg/day (N = 324)	16 mg/day (N = 77)	(N = 142)
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

¹ Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

- ² Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≥ 10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events:

Extrapyramidal symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p < 0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes: RISPERDAL[®] is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: The proportions of RISPERDAL[®] and placebo-treated patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of 6 to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL[®] (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL[®]/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL[®]/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL[®] administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL[®] and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL[®] whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL[®]

During its premarketing assessment, multiple doses of RISPERDAL[®] (risperidone) were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL[®] varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

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In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL[®] who experienced an event of the type cited on at least one occasion while receiving RISPERDAL[®]. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL[®], they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

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Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgasmic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

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Reproductive Disorders, Male: Frequent: erectile dysfunction*. Infrequent: ejaculation failure.

White Cell and Resistance Disorders: Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL[®] therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL[®]. A causal relationship with RISPERDAL[®] has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL[®] (risperidone) is not a controlled substance.

Physical and Psychologic Dependence: RISPERDAL[®] has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL[®] misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Premarketing experience included eight reports of acute RISPERDAL® overdose with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage: In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

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DOSAGE AND ADMINISTRATION

Usual Initial Dose: RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early short-term clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent short-term controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. In a long-term controlled trial in stable patients, RISPERDAL® was administered on a QD schedule at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in the short-term clinical trials supporting effectiveness of RISPERDAL®, however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy: While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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Dosage in Special Populations: The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL[®] than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

~~**Maintenance Therapy:** While there is no body of evidence available to answer the question of how long the patient treated with RISPERDAL[®] should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on RISPERDAL[®], but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.~~

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL[®], the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL[®], or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others other patients. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL[®] therapy in place of the next scheduled

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injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL[®] (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL[®] (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that Risperdal[®] (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

Storage and Handling

RISPERDAL[®] tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL[®] 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F).

Protect from light and freezing.

Keep out of reach of children.

~~7503248~~ 7503220

US Patent 4,804,663

~~May 1999~~, December 2000, January 2002

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Russell Katz
3/3/02 11:33:45 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

EDMS-P6DB-3349331

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-026, S-027
NDA 20-588/S-017, S-018
NDA 21-444/S-002, S-003

Johnson & Johnson Research & Development, L.L.C
Attention: Megan L. Zoschg, Pharm.D.
Associate Director, Regulatory Affairs
1125 Trenton Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Dr. Zoschg:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Application	Drug Name	Submission Date	Receipt Date	Provides For
NDA 20-272/S-026	Risperdal (risperidone) Tablets	December 13, 2002	December 13, 2002	Monotherapy - for short term treatment of acute manic or mixed episodes associated with Bipolar I Disorder
NDA 20-588/S-017	Risperdal (risperidone) Oral Solution			
NDA 21-444/S-002	Risperdal (risperidone) Orally Disintegrating Tablets	August 13, 2003	August 13, 2003	
NDA 20-272/S-027	Risperdal (risperidone) Tablets	December 13, 2002	December 13, 2002	Adjunctive Therapy - for short term treatment of acute manic or mixed episodes associated with Bipolar I Disorder
NDA 20-588/S-018	Risperdal (risperidone) Oral Solution			
NDA 21-444/S-003	Risperdal (risperidone) Orally Disintegrating Tablets	August 13, 2003	August 13, 2003	

We also acknowledge receipt of your additional submissions dated October 31, 2003.

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Your submissions on October 31, 2003 constituted a complete response to our October 14, 2003 action letter.

We have completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Labeling

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled "*Providing Regulatory Submissions in Electronic Format - NDA*". Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-272/S-026, S-027; NDA 20-588/S-017, S-018; NDA 21-444/S-002, S-003." Approval of these submissions by FDA is not required before the labeling is used.

Post-Marketing Study Commitments

We remind you of your post-marketing study commitment in your submission dated October 31, 2003. Details of this commitment are as follows:

1. A study exploring the question of longer-term efficacy of Risperdal in patients with either manic or mixed episodes who have responded during acute treatment.

Protocol Submission:	by February 2004
Study Start:	by August 2004
Final Report Submission:	by December 2007

Submit this clinical protocol to your IND for one of these products. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of this commitment in your annual report to these NDAs. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these post-marketing study commitments must be prominently labeled "Post-Marketing Study Protocol", "Post-Marketing Study Final Report", or "Post-Marketing Study Correspondence."

NDA 20-272/S-026, S-027
NDA 20-588/S-017, S-018
NDA 21-444/S-002, S-003
Page 3

Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MedWatch

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Other

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-2850.

Sincerely,

(See appended electronic signature page)
Russell Katz, M.D.

Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure
-Package Insert

JJRP 00476490
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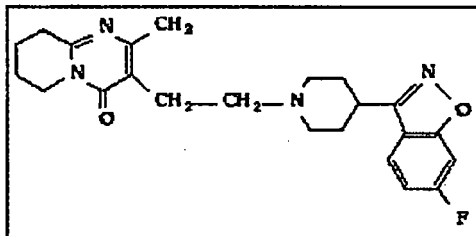
**JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.**

**RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION**

**RISPERDAL® M-TAB™
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS**

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are available in 0.5 mg, 1.0 mg, and 2.0 mg strengths and are light coral in color.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT₂) receptor antagonism. Antagonism at receptors other than D₂ and 5HT₂ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (K_i of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT₂), dopamine Type 2 (D₂), α₁ and α₂ adrenergic, and H₁ histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin 5HT_{1C}, 5HT_{1D}, and 5HT_{1A} receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D₁ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10⁻⁵ M) for cholinergic muscarinic or β₁ and β₂ adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB™ Orally Disintegrating Tablets are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1 -acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 $\mu\text{g/mL}$), warfarin (10 $\mu\text{g/mL}$), and carbamazepine (10 $\mu\text{g/mL}$) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (i.e., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see Drug Interactions under PRECAUTIONS). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number ($n \approx 70$) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine (20 mg QD) has been shown to increase the plasma concentration of risperidone 2.5-2.8 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected.

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg QID) (see Drug Interactions under PRECAUTIONS).

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ^{14}C -risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1 -acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Schizophrenia

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL[®] (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL[®] groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL[®] dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL[®] (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL[®] dose groups were generally superior to the 1 mg RISPERDAL[®] dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL[®] (4 and 8 mg/day on a QD schedule), both RISPERDAL[®] dose groups were generally superior to placebo on several PANSS measures, including a response measure (>20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL[®] (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL[®] experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Bipolar Mania

Monotherapy— The efficacy of Risperdal in the treatment of acute manic or mixed episodes was established in 2 short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

- In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of Risperdal 1-6 mg/day, once daily, starting at

3 mg/day (mean modal dose was 4.1 mg/day), Risperdal was superior to placebo in the reduction of Y-MRS total score.

- In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), Risperdal was superior to placebo in the reduction of Y-MRS total score.

Combination Therapy — The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

- In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive Risperdal, placebo, or an active comparator, in combination with their original therapy. Risperdal, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.
- In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive Risperdal or placebo, in combination with their original therapy. Risperdal, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 µg/mL to 125 µg/mL for valproate, or 4-12 µg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of Y-MRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9-hydroxy risperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxy risperidone.

INDICATIONS AND USAGE

Schizophrenia

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse

during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

Monotherapy — RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy — The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® in combination with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL® for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use RISPERDAL® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both

serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated on RISPERDAL[®], drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL[®] despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL[®] is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL[®]. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL[®] (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL[®]-treated patients in Phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to

2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about

operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL[®] therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL[®] use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL[®] may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL[®] in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL[®] therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL[®] use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL[®] should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL[®] in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL[®] in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL[®] has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylketonurics

Phenylalanine is a component of aspartame. Each 2 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.56 mg phenylalanine; each 1 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine

Fluoxetine (20 mg QD) has been shown to increase the plasma concentration of risperidone 2.5-2.8 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected. When concomitant fluoxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone.

Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m ² (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of

agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL[®] therapy is unknown.

RISPERDAL[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL[®] on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL[®] did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, premarketing trials for schizophrenia and acute bipolar mania. In patients with Bipolar I disorder, treatment-emergent adverse events are presented separately for risperidone as monotherapy and as adjunctive therapy to mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse events, vital sign changes, weight gain,

laboratory changes, and ECG changes are derived from studies in patients with schizophrenia. However, this information is also generally applicable to bipolar mania.

Associated With Discontinuation of Treatment

Schizophrenia: Approximately 9% (244/2607) of RISPERDAL[®] (risperidone)-treated patients in Phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events ($\geq 0.3\%$) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL [®]	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL[®]-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL[®] compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL[®] related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2-3 trials.

Bipolar Mania: In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL[®]-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included: paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL[®]-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL[®] vs 4% for placebo).

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia: In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL[®] groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL[®] at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgasmic dysfunction.

Bipolar Mania: In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL[®] (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL[®] were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence.

Adverse Events Occurring at an Incidence of 1% or More Among

RISPERDAL[®]-Treated Patients - Schizophrenia: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent among RISPERDAL[®]-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-week controlled trials. Patients received RISPERDAL[®] doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do

provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1. Incidence of Treatment-Emergent Adverse Events in 6 to 8-Week Controlled Clinical Trials¹

Body System/ Preferred Term	RISPERDAL [®]		Placebo (N=142)
	≤10 mg/day (N=324)	16 mg/day (N=77)	
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms ²	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%

(continued)

Table 1. Incidence of Treatment-Emergent Adverse Events in 6 to 8-Week Controlled Clinical Trials¹

Body System/ Preferred Term	RISPERDAL [®]		Placebo (N=142)
	≤10 mg/day (N=324)	16 mg/day (N=77)	
Cardiovascular			
Tachycardia	3%	5%	0%

¹ Events reported by at least 1% of patients treated with RISPERDAL[®] ≤10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL[®] 16 mg/day and placebo are provided as well. Events for which the RISPERDAL[®] incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

² Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '≤10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see DOSE DEPENDENCY OF ADVERSE EVENTS).

Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL[®]-Treated Patients - Bipolar Mania: Tables 2 and 3 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL[®] (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania¹

Body System/ Preferred Term	RISPERDAL® N = 134	Placebo N = 125
Central & peripheral nervous system		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal system		
Dyspepsia	11%	6%

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania¹

Body System/ Preferred Term	RISPERDAL® N = 134	Placebo N = 125
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a whole - general		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%
Respiratory system		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and appendage		
Acne	2%	0%
Pruritus	2%	1%
Musculoskeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and nutritional		
Weight increase	2%	0%
Vision disorders		
Vision abnormal	6%	2%
Cardiovascular, general		
Hypertension	3%	1%
Hypotension	2%	0%
Heart rate and rhythm		
Tachycardia	3%	2%

¹ Events reported by at least 2% of patients treated with RISPERDAL® are included, and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

Table 3. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania¹

Body system/ Preferred term	RISPERDAL® +mood stabilizer N = 52	Placebo + mood stabilizer N = 51
Gastrointestinal system		
Saliva increased	10%	0%
Diarrhea	8%	4%

Table 3. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania¹

Body system/ Preferred term	RISPERDAL[®] +mood stabilizer N = 52	Placebo + mood stabilizer N = 51
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Tooth ache	4%	0%
Tooth disorder	4%	0%
Central & peripheral nervous system		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory system		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a whole - general		
Asthenia	4%	2%
Urinary system		
Urinary incontinence	6%	2%
Heart rate and rhythm		
Tachycardia	4%	2%
Metabolic and nutritional		
Weight increase	4%	2%
Skin and appendages		
Rash	4%	2%

¹ Events reported by at least 2% of patients treated with RISPERDAL[®] are included, and are rounded to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL[®] that were less than the incidence reported by patients treated with placebo are not listed in the table, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a

parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p < 0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of 6 to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all

RISPERDAL[®] doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL[®]

During its premarketing assessment, multiple doses of RISPERDAL[®] (risperidone) were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL[®] varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL[®] who experienced an event of the type cited on at least one occasion while receiving RISPERDAL[®]. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL[®], they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness.

Infrequent: impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders

Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia*, orgasmic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders

Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL[®] therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL[®]. A causal relationship with RISPERDAL[®] has not been established. It is important to note that sudden and unexpected

death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdose with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® overdose, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of risperidone orally disintegrating tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Initial Dose

RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

Bipolar Mania

Usual Dose

Risperidone should be administered on a once daily schedule, starting with 2 mg to 3mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day (see Clinical Trials, under CLINICAL PHARMACOLOGY). RISPERDAL® doses higher than 6 mg per day were not studied.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (i.e., beyond 3weeks).

Pediatric Use

Safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or acute mania associated with Bipolar I disorder have not been established.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (See CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine has been shown to increase the plasma concentration of risperidone 2.5-2.8 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected. The dose of risperidone needs to be titrated accordingly when fluoxetine, is co-administered (See CLINICAL PHARMACOLOGY and PRECAUTIONS).

Directions for Use of RISPERDAL® M-TAB™ Orally Disintegrating Tablets

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are supplied in blister packs of 4 tablet units each.

Tablet Accessing

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB™ Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB™ Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB™ Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL® M-TAB™ (risperidone) Orally Disintegrating Tablets are etched on one side with R0.5, R1, and R2, respectively, and are packaged in blister packs of 4 (2 X 2) tablets.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box,
NDC 50458-395-28, bingo card of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box,
NDC 50458-315-28, bingo card of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box,
NDC 50458-325-28.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Keep out of reach of children.

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US Patent 4,804,663
December 2003
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RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB™ Orally Disintegrating Tablets, and oral
solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

**Russell Katz
12/4/03 09:55:12 AM**

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D843.38**

21 DEC 2003

JJRP 00476526
Confidential/Produced in Litigation Pursuant to Protective Order
D843.39

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

1125 Trenton-Harbourton Road
P.O. Box 200, Titusville, NJ 08560

29 MAR 2004

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Office of Drug Evaluation I
U.S. Food and Drug Administration
Attn: Document Control Room 10B-40
1451 Rockville Pike
Rockville, MD 20857

Subject: NDA 20-272
Cross reference: NDA 20-588, 21-444, and 21-346
RISPERDAL® (risperidone) Tablets
General Correspondence – Hyperglycemia/Diabetes Data For
RISPERDAL®

Dear Dr. Katz,

On behalf of Janssen Pharmaceutica, L.P., please refer to the joint consensus development conference of the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity held November 19-21, 2003 and the resulting Consensus publication (Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes, Diabetes Care, Volume 27, 2, February 2004, pages 596-601).

At that meeting, Dr. Judy Racoosin, presenting the FDA position, indicated that the FDA is willing to review additional data and reconsider its position if supported by the data. We believe that we have substantial new information concerning the risk of diabetes and related serious adverse events with RISPERDAL® treatment, and would like to share that information. We believe this new data is necessary for a thorough evaluation by the FDA of all the available risperidone data and for an accurate assessment of risk for diabetes and related adverse events among approved antipsychotics.

In response to the November expression of FDA's willingness to consider data on this issue, Johnson and Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) has reviewed all of the available risperidone data and is providing an information package that includes the following:

- A summary of epidemiology data from our studies, including new data, and an overview of all 10 published studies on the topic, in addition to a summary of all non-published results presented at scientific congresses (e.g., both V.A. studies reported in the press in August 2003);

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- A review of studies of related physiology and differential mechanism of action, including new data;
- An update to previously submitted clinical data from the J&JPRD clinical trial database, which now includes over 12,000 Risperdal-treated subjects; and
- An update to the RISPERDAL® pharmacovigilance database.

Taken together, these data demonstrate the following:

- Epidemiology evidence does not support an increased risk of diabetes with risperidone treatment. In particular, serious or life-threatening events (e.g. diabetic ketoacidosis) are not more common than with haloperidol. The weight of epidemiologic evidence suggests that diabetes among risperidone-treated patients is not more common than in untreated patients with psychotic disorders or in patients treated with conventional antipsychotics and is less common than in patients treated with olanzapine or clozapine;
- Understanding the critical caveat that trials conducted for primarily psychiatric research purposes lack sensitivity to detect glucoregulatory disturbances and may therefore be relatively uninformative. Nevertheless, in the clinical database for risperidone, disturbances of glucose metabolism are not very common and, in general, the risk with risperidone is similar to that with placebo;
- Pharmacovigilance data from the Johnson & Johnson pharmacovigilance database demonstrate no emerging risk for diabetes or related events; and
- Based on the available preclinical and clinical data, risperidone does not affect insulin secretion or Beta-cell function. This reflects a differential effect of risperidone among tested atypical antipsychotics.

We request that FDA consider this comprehensive review of the available data pertaining to risperidone. This dataset is more robust in supporting relative safety with regard to glucose-related adverse events than data available for any of the more recently introduced antipsychotics, which lack comparable patient exposure. Based on this or other data, should the FDA reconsider the broad application of an identical "class label" on this issue to all drugs in this "class," we respectfully request an opportunity to meet with the Agency to help assure that accurate label language reflecting the most current evidence is applied to risperidone.

As documented and approved in a series of electronic mail communications with Kenneth Edmunds, Jr. of the FDA, a variation of the bookmarking requirements under *FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, January 1999* for this submission was requested. Per Mr. Edmund's approval, this submission is bookmarked as follows:

- The document table of contents is hyperlinked to the sections and attachments in the volumes.

- The text within the primary report is hyperlinked to appropriate key references, tables, etc.

This submission is presented electronically and is designed to meet electronic archival requirements as outlined within the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, January 1999* with the exceptions noted above. Submission files are presented in Adobe Acrobat Portable Document Format (PDF) on one CD-ROM and totals approximately 25 MB. McAfee VirusScan v4.5.1 SP1 as used to ensure a virus free submission.

Please call me at 609-730-2712 if you have further questions.

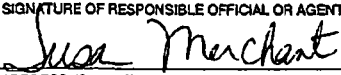
Yours sincerely,



Susan Merchant
Associate Director, Regulatory Affairs
Global Marketed Products

JJRPrev 00481494
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D919.3

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i>		Form Approved: OMB No. 0910-0338 Expiration Date: August 31, 2005 See OMB Statement on page 2.
		FOR FDA USE ONLY
		APPLICATION NUMBER
APPLICANT INFORMATION		
NAME OF APPLICANT Janssen Pharmaceutica Products, L.P.	DATE OF SUBMISSION 29 MAR 2004	
TELEPHONE NO. (Include Area Code) 609-730-2712	FACSIMILE (FAX) Number (Include Area Code) 609-730-3091	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Johnson & Johnson Pharmaceutical Research & Development, LLC 1125 Trenton-Harbourton Road Titusville, New Jersey 08560-0200	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	
On behalf of Janssen Pharmaceutica Products, L.P. 1125 Trenton-Harbourton Road Titusville, New Jersey 08560-0200		
PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-272		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) risperidone	PROPRIETARY NAME (trade name) IF ANY RISPERDAL®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one		CODE NAME (If any) R084766
DOSAGE FORM: Tablets	STRENGTHS: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Treatment of Schizophrenia and Bipolar Mania		
APPLICATION INFORMATION		
APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.60) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)		
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION		
Name of Drug _____ Holder of Approved Application _____		
TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER		
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)		
REASON FOR SUBMISSION General Correspondence - Hyperglycemia/Diabetes Data For RISPERDAL®		
PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC		
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFR), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) NDA 20-588, NDA 21-346, NDA 21-444 IND 31.931, IND 52.982		

This application contains the following items: (Check all that apply)					
☐	1. Index				
☐	2. Labeling (check one)	☐ Draft Labeling ☐ Final Printed Labeling			
☐	3. Summary (21 CFR 314.50 (c))				
☐	4. Chemistry section				
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)				
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)				
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)				
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)				
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☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)				
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)				
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)				
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))				
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))				
☐	15. Establishment description (21 CFR Part 600, if applicable)				
☐	16. Debarment certification (FD&C Act 308 (k)(1))				
☐	17. Field copy certification (21 CFR 314.50 (f)(3))				
☐	18. User Fee Cover Sheet (Form FDA 3397)				
☐	19. Financial Information (21 CFR Part 54)				
☒	20. OTHER (Specify) General Correspondence - Hyperglycemia/Diabetes Data For RISPERDAL®				
CERTIFICATION I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following: 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR Parts 201, 608, 610, 660, and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202. 5. Regulations on making changes in application in FD&C Act Section 508A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81. 7. Local, state and Federal environmental impact laws. If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision. The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.					
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DATE 29 MAR 2004					
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RISPERDAL® (risperidone) Tablets
General Correspondence – Hyperglycemia/Diabetes Data
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**Johnson & Johnson Pharmaceutical Research & Development, L.L.C. and
Janssen Pharmaceutica, Inc.**

Summary

Atypical Antipsychotic Medication and Disturbances of Glucose Metabolism

R064766 (risperidone)

Issue/Report Date: 26 March 2004
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	American Diabetes Association
AP	antipsychotic
APA	American Psychiatric Association
ATYP	atypical (antipsychotic)
BMI	body mass index
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CONV	conventional (antipsychotic)
CT	computed tomography
DEXA	dual-energy X-ray absorptiometry
DI	disposition index
DKA	diabetic ketoacidosis
Dx	diagnosis
ECG	electrocardiogram
EGC	euglycemic hyperinsulinemic clamp
EPS	extrapyramidal side effects
FDA	Food and Drug Administration
FFA	free fatty acids
FSIVGTT	Frequent Sample Intravenous Glucose Tolerance Test
HOMA	Homeostatic Model Assessment
HOMA-IR	HOMA - Insulin Resistance
HR	hazard ratio (odds ratio)
IR	insulin resistance
IRR	incidence rate ratio
ITT	intent to treat
J&JPRD	Johnson & Johnson Pharmaceutical Research and Development, LLC
JPI	Junssen Pharmaceutica, Inc.
MedDRA	Medical Dictionary for Regulatory Activities
MCO	managed care organization
MRI	magnetic resonance imaging
NCHS	National Center for Health Statistics
NR	not reported
NS	not significant
OGTT	Oral Glucose Tolerance Test
OLZ	olanzapine
OR	odds ratio (hazard ratio)
PPAR γ	peroxisome proliferator-activated receptor gamma
PPO	preferred provider organization
RIS	risperidone
RR	relative risk
Rx	prescription
S ₁	insulin sensitivity index
SD	standard deviation
STEP	stepwise stimulation test
VA	Veteran's Administration
VISN	Veteran's Integrated Service Network
WHO	World Health Organization

Definitions

EBGM	empirical Bayes geometric mean: ratio of the observed count to the expected count for a given drug event combination

1. INTRODUCTION

RISPERDAL[®] (risperidone) is a benzisoxazole derivative with potent serotonin 5-HT_{2A} and dopamine D₂ receptor-blocking properties; it is approved for the treatment of a broad range of patients for indications including first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia, and other psychotic conditions in which positive symptoms and/or negative symptoms are prominent, and is indicated as maintenance therapy in schizophrenia and other psychiatric disorders, including Bipolar I Disorder.

Risperidone is a member of the class of drugs referred to as 'atypical' antipsychotics since they have the primary advantage over 'typical' (conventional) antipsychotics of decreased side effect profiles, particularly with regard to extrapyramidal side effects (EPS). It should be emphasized, however, that although medications of this class share this and several other clinical effects, they have diverse chemical structures, e.g., benzisoxazole (risperidone), dibenzodiazepines (clozapine and olanzapine).

Recent concern has been directed at the potential association between treatment with 'atypical' antipsychotics and abnormalities in glucose homeostasis. In particular, as a member of this class of drugs, the risperidone label currently includes a class warning for 'atypical antipsychotics' that hyperglycemia has been reported in patients treated with these drugs. In light of Food and Drug Administration's (FDA) expressed willingness to consider data on this issue (at the consensus development conference on antipsychotic drugs and obesity on November 19-21, 2003), Johnson & Johnson Pharmaceutical Research and Development L.L.C. (J&JPRD) and Janssen Pharmaceutica, Inc. (JPI) are providing a review of all the available risperidone data relevant to this issue. This report presents a summary of evidence from the following areas:

- Epidemiology studies - data and overview of 21 publicly available reports, 10 of which are from the peer-reviewed literature;
- Mechanistic studies of physiology - recent data about glucoregulatory physiology and different effects of several antipsychotics on regulatory mechanisms;
- Clinical studies - safety data from over 12,000 risperidone-treated patients in clinical trials conducted by J&JPRD; and

- Reports from worldwide pharmacovigilance – safety data from all spontaneous reports derived from an estimated worldwide exposure of over 17 million patient years.

Taken together, these data demonstrate the following:

- Epidemiology evidence does not support increased risk of diabetes with risperidone treatment. In particular, serious or life-threatening events (e.g. diabetic ketoacidosis [DKA]) are not more common in risperidone-treated patients than in untreated patients with psychotic disorders or in patients treated with conventional antipsychotics. The weight of epidemiologic evidence suggests that diabetes among risperidone-treated patients is not more common than in untreated patients with psychotic disorders or in patients treated with conventional antipsychotic, and is less common than in patients treated with olanzapine or clozapine;
- Understanding the critical caveat that trials conducted for primarily psychiatric research purposes lack sensitivity to detect glucoregulatory disturbances and may therefore be relatively uninformative, nevertheless, in the clinical database for risperidone, disturbances of glucose metabolism are not very common; in general, risk with risperidone treatment is similar to that with placebo;
- Pharmacovigilance data from the Johnson & Johnson pharmacovigilance database demonstrate no emerging risk for diabetes or related events;
- Based on the available preclinical data, risperidone does not affect insulin secretion or beta-cell function, and this reflects a differential effect of risperidone among tested atypical antipsychotics.

Small to moderate weight gain is associated with risperidone treatment. The cumulative body of data discussed in this report was gathered to document the relative safety of risperidone with regard to glucose-related adverse events; the data are large and robust. At this time, a broad base for similar evaluation cannot be provided for any of the more recently introduced antipsychotics, since patient exposure is not comparable.

1.1. Epidemiology Summary

1.1.1. Serious/Life-Threatening Glucose-Related Adverse Events

The most important short-term diabetes-related risks are those with high mortality, including diabetic ketoacidosis, diabetic coma, and death. Because these risks may be qualitatively different from risks of Type 2 diabetes and may be lost when considered in combination with the other far more prevalent diabetes-related diagnoses, risk for life-threatening events merits

separate consideration. Recent research described below has found that risperidone is not associated with more serious/life-threatening glucose-related adverse events than the typical antipsychotic haloperidol. The additional finding that both dibenzodiazepine-related atypical antipsychotics studied (clozapine and olanzapine) are associated with substantially more of these adverse events than risperidone or haloperidol suggests that any "class" effect does not relate to any similarities in the mechanisms of action affecting psychosis shared by all 4 drugs studied, but instead may relate to other properties shared by medications such as clozapine and olanzapine. The data do not demonstrate there is no effect on diabetic life-threatening events by risperidone and haloperidol, but that the effect is significantly greater with clozapine and olanzapine.

1.1.2. Diabetes and Other Glucose-Related Adverse Events

When all epidemiology studies are weighed in accordance with their methodologic strengths, it appears quite consistent that treatment with risperidone does not pose a greater risk of development of new-onset diabetes than that associated with no treatment for major psychiatric illness or treatment with conventional antipsychotics. A comparable consistent body of evidence also suggests that treatment with olanzapine is associated with a higher risk of developing diabetes than no treatment for major psychiatric illness, arguing against a "class effect" based on a common mechanism of action on psychosis. Whether or not clozapine is associated with a greater risk of diabetes than no treatment in patients with major psychiatric disorder remains unclear on the basis of this type of data. Data regarding risk of diabetes associated with quetiapine relative to untreated patients are based on small numbers. Finally, the preponderance of comparative data on the relative risk of diabetes associated with risperidone compared with olanzapine, the comparison for which the most evidence exists, also argues against an atypical antipsychotic "class effect". The studies comparing risperidone and olanzapine do not suggest that risperidone has no effect on diabetes, simply that the risk of diabetes is significantly greater with olanzapine, although the magnitude of this risk varies from study to study.

1.2. Summary of Studies of Glucoregulatory Physiology / Mechanism of Action

Several mechanistic studies have been conducted to evaluate the potential diabetogenic effects of the 6 atypical antipsychotics. They consistently show that (1) some of these drugs appear to be diabetogenic (clozapine and

olanzapine) (2) risperidone is associated with significantly lower impact on glucose metabolism than the chemically distinct dibenzodiazepines studied (e.g., olanzapine, clozapine), and (3) preliminary evidence suggests that mechanisms of action for olanzapine-associated glucose dysregulation are not shared by risperidone.

Studies evaluating changes in Homeostatic Model Assessment (HOMA) values (with and without Oral Glucose Tolerance Tests [OGTT]) in psychiatric patients fail to demonstrate any risk of insulin resistance associated with risperidone treatment. Pronounced insulin resistance in non-obese patients taking clozapine and olanzapine was observed in a cross-sectional survey, using the Frequent Sample Intravenous Glucose Tolerance Test (FSIVGTT) with Minimal Model Analysis. In this survey, risperidone was not associated with insulin resistance.

Although a small insulin clamp study failed to differentiate the effects of risperidone from olanzapine in normal volunteers, this result likely represents a “false negative” due to flaws in the study design and data interpretation as described in detail in Section 3.5.4.

The effects of risperidone and olanzapine in dogs, utilizing both a euglycemic clamp to assess insulin sensitivity and a full stepwise hyperglycemic clamp for insulin secretion were evaluated. Olanzapine was associated with significant increases in adiposity (magnetic resonance imaging [MRI]), hepatic insulin resistance, and beta-cell dysfunction. Risperidone-treated dogs were comparable to placebo in these 3 parameters. Preliminary molecular data from this study raise the possibility that the mechanism of action of olanzapine that leads to glucose metabolism dysregulation is not shared by risperidone.

Although the contributions of weight gain, adiposity, insulin resistance, and beta-cell dysfunction to antipsychotic-associated diabetes have not yet been precisely defined, the evidence from physiology studies strongly suggests that a “class effect” among these chemically distinct compounds is not likely, but rather that certain antipsychotics (e.g., olanzapine) have higher diabetogenic potential compared to others (e.g., risperidone, haloperidol), and the difference is due to agent-specific interaction with the glucoregulatory machinery.

1.3. Clinical Trials and Pharmacovigilance Summary

The information derived from a large number of clinical trials reporting on more than 12,000 subjects in short-term trials (≤ 3 months) and over 7500 subjects in long-term trials (≥ 6 months) supports the conclusion that disturbances of glucose metabolism during risperidone treatment are not very common. Overall, the incidence of glucose-related adverse events in short-term trials was lower in the risperidone compared to both the placebo and olanzapine treatment groups, and was comparable to that in the olanzapine treatment group in long-term trials. Serious glucose-related adverse events were rare and were not more frequent with risperidone than with placebo. One glucose-related fatal event in a risperidone-treated subject was reported; the cause of death was urosepsis. In the pediatric and adult populations, the incidence of glucose-related adverse events in the risperidone treatment group was similar to, if not lower than, that in placebo, and lower than that in the olanzapine group. Elderly patients showed a higher incidence of abnormalities in glucose metabolism than adults and had a slightly higher incidence with risperidone compared to placebo in short-term trials. In the clinical database, most observations were hyperglycemia that occurred in patients with a history of diabetes; new-onset diabetes was infrequent.

Based on a review of the sponsor's pharmacovigilance database of postmarketing spontaneous reports, overall, adverse events involving glucose metabolism are relatively rare in patients receiving risperidone. The pharmacovigilance database provides no evidence to suggest an increased risk of diabetes or related events in association with risperidone treatment.

1.4. Weight of Evidence

In view of the data summarized above, there is limited evidence for increased risk associated with risperidone compared to conventional antipsychotics or no treatment, and there is a particular lack of evidence suggesting an increased risk of serious and life-threatening events, such as diabetic ketoacidosis. Furthermore, a substantial body of epidemiologic evidence supports a differential effect among atypical antipsychotics. Data concerning physiologic mechanisms of action also suggest that risk for both diabetes and ketoacidosis is not a class effect.

1.5. Conclusion

It is well accepted that patients with an established diagnosis of schizophrenia should receive chronic treatment with antipsychotics. Given the chronicity of the treatment, it is especially relevant that physicians make an informed decision about the different risks and benefits that individual antipsychotics might bring about. There is strong evidence that shows that olanzapine and clozapine are associated with higher risk of glucose-related adverse effects than is risperidone, for which risk is similar to that for haloperidol. This information should be available in the risperidone labeling.

2. EPIDEMIOLOGIC EVIDENCE REGARDING DIABETES

2.1. Introduction

There is a substantial body of epidemiological evidence comparing glucose-related adverse events in patients on risperidone therapy with those in patients treated with other antipsychotics, conventional and atypical, and with those who are not receiving treatment with antipsychotics.

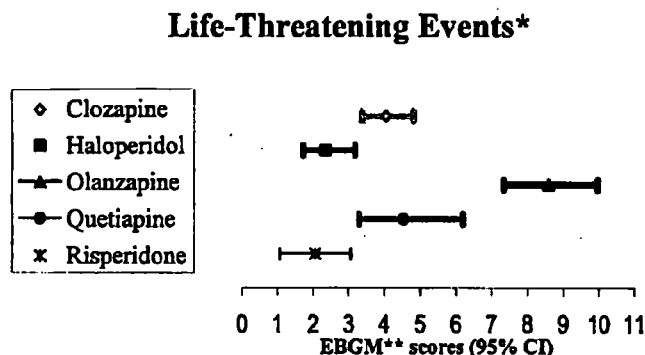
- 2 new studies examined the incidence of serious life-threatening glucose-related adverse events (e.g., diabetic ketoacidosis)
- 21 studies, 10 of which are published in peer-reviewed journals, studied the development of diabetes in risperidone and other antipsychotic treated patients.

2.2. New Epidemiologic Evidence Concerning Risk of Serious/Life-Threatening Glucose-Related Adverse Events

An analysis of MedWatch data through first quarter 2002 utilizing an empirical Bayes geometric mean (EBGM; ratio of the observed count to the expected count for a given drug event combination) examined the relationship of 6 antipsychotics (risperidone, olanzapine, quetiapine, clozapine, ziprasidone, haloperidol) to specific diabetes-related terms in the Medical Dictionary for Regulatory Activities (MedDRA). Insufficient data were available for quetiapine and ziprasidone due to the significantly lower usage of these drugs. Of the remaining 4 agents, when examining 'diabetes mellitus, insulin dependent' or 'diabetes mellitus, non-insulin dependent' as terms, risperidone was not associated with higher mean scores than haloperidol. Further, a substantially different (larger) effect was seen with dibenzodiazepine-related drugs, clozapine and olanzapine. When specifically examining the issue of serious/life-threatening events (Figure 1), identified

by terms such as 'diabetic ketoacidosis', risperidone was not associated with a different risk than haloperidol. A substantial increased risk was observed for the dibenzodiazepine-related drugs olanzapine and clozapine compared to risperidone and haloperidol. A description of the methods and results of this analysis is attached.¹

Figure 1: Glucose-Related Life-Threatening Events: Empirical Bayes Geometric Mean



* MedDRA terms included: diabetic coma NOS, diabetic hyperglycemic coma, diabetic hyperosmolar coma, diabetic ketoacidosis

** EBGM: Empirical Bayes Geometric Mean; relative reporting ratio for any drug-event combination (observed count divided by expected count).

In order to specifically analyze the risk of serious/life-threatening events in risperidone- versus olanzapine-treated patients, JPI recently performed an analysis of a Medicaid claims database containing reports from >100,000 individuals. This analysis adjusted for covariates including age, sex, race, pre-existing diabetes, diagnosis of schizophrenia, and use of other diabetogenic agents. Olanzapine was associated with a 60% increased risk (odds ratio [OR] = 1.6) of diabetic ketoacidosis as compared to risperidone. The plausibility of the association was strengthened by the additional finding that duration of exposure was correlated with difference in risk (higher risk of DKA with increasing duration of exposure to olanzapine). For example, subgroup analysis of 38,552 patients exposed to risperidone or olanzapine for at least 180 days showed that olanzapine was associated with a 250% increased risk (OR=3.5) of DKA as compared to risperidone.² Details of this study are attached.

In conclusion, based on this epidemiological evidence, the atypical antipsychotic risperidone is not associated with more serious/life-threatening

glucose-related adverse events than the typical antipsychotic haloperidol. The additional finding that both dibenzodiazepine atypical antipsychotics studied, clozapine and olanzapine, induce substantially more of these adverse events than risperidone or haloperidol suggests that any "class" effect does not relate to the mechanisms of action on psychosis shared by all 4 drugs or shared by the 3 atypical antipsychotics studied, but instead may relate to other properties shared by medications such as clozapine and olanzapine.

2.3. Evaluation of Epidemiologic Evidence for Risk of Diabetes and Related Adverse Events

2.3.1. Evaluation Framework and Scope

Although most epidemiologic data suggest that treatment with certain atypical antipsychotics can increase the risk of diabetes, interpretation of the epidemiologic data has not been clear-cut. Reported excess risk and relative risk are inconsistent.³⁻²³ To add to the complexity of the issue, factors such as age, ethnicity, sex, weight, antipsychotic dose, and concomitant medications can affect the risk of diabetes and are not controlled for in some studies. This is further complicated by the fact that abnormal glucose regulation and diabetes appear to occur more commonly in patients with schizophrenia or other major psychiatric illnesses than in the general population.²⁴⁻²⁶

A possible association between antipsychotic use and new-onset diabetes can be explored by answering 2 questions: (1) What is the *excess risk* of diabetes associated with antipsychotics, beyond that posed by the presence of a major psychiatric illness? (2) What is the *relative risk* of diabetes associated with individual antipsychotic agents when compared to each other in comparison to one another?

To address these questions, a review of all published epidemiologic studies as well as all available abstracts and posters from scientific meetings that address the association between diabetes and atypical antipsychotics as well as available abstracts and posters that addressed the association between diabetes and atypical antipsychotics and were presented at scientific meetings was performed. All systematic retrospective studies assessing risk of diabetes associated with exposure to an atypical antipsychotic with diabetes as an outcome measure were included. For purposes of comparability, only studies that expressed risk in terms of hazard ratios, risk ratios, or odds ratios for individual antipsychotic agents were included.

Because poor study design or model specification can interfere with drawing substantive conclusions, seeming contradictions in the findings of various epidemiologic studies were assessed to determine if these arose from true differences in evidence or whether inconclusive or divergent results could have been reached due to limitations in study design. A framework of rules based on generally accepted epidemiologic methods was created for assessing these studies. Sample, design, and execution of each study were evaluated to assess the merits of the findings. Factors reviewed included selection of treatment and comparison groups, study design, definition of outcome measure, selection and inclusion of covariates, and statistical tests used.

Specifically, the review framework considered the issues described below, and listed in Table 1, when assessing the methodology of studies examining the association between atypical antipsychotic use and diabetes.

Reference group. Given the evidence for greater risk of Type 2 diabetes in patients with schizophrenia or mood disorders compared with the general population,²⁴⁻²⁶ data from studies that used populations of untreated patients with major psychiatric illness as a reference group in assessing excess risk are more appropriate to separate potential drug-related risk from population-specific risk. In studies reporting relative risk of diabetes for a specific atypical antipsychotic compared with other antipsychotics, the appropriate reference groups were patients receiving therapy with another atypical agent, another conventional agent, or combined groups of all atypical or all conventional antipsychotics.

Longitudinal versus cross-sectional study design. Longitudinal studies allow for estimation of incidence-based rate ratios, which provide a truer approximation of risk than do prevalence rate ratios. Prevalence studies ignore temporality of association between risk factor and outcome and therefore cannot establish causality; however, they are useful as preliminary measures of risk.

Cohort versus case-control design. The case-control design identifies cases with the outcome of interest and typically addresses covariates such as age, sex, and other potential risk factors for diabetes by matching patients to this group with respect to these factors. This is a sound design for assessing relative risk between 2 risk factors, especially when incidence rates of the

outcome are small. The retrospective cohort design identifies patients with the putative given risk factor as of an index date and follows them for a fixed time period, permitting calculation of incidence rates, excess risk, and relative risks for multiple risk factors.

Temporal relationships. Studies that accounted for the temporal association between outcome and purported putative risk factor, including duration of exposure to antipsychotics and uniformity of observation period among groups are of sounder design than those that do not (i.e., whether diabetes is known to follow rather than precede drug exposure).

Definition of outcome measure. Because use of a diagnosis code to identify cases of diabetes may underestimate numbers of patients with undiagnosed diabetes or those in whom a diagnosis is made but not assigned a formal code, and because prescription claims may underestimate those diagnosed but not receiving or filling prescriptions for anti-diabetic medication, use of both sources of information for the incidence of diabetes is more sensitive than use of either one alone. Insensitive outcome assessment would be expected to increase the risk for a false negative differentiation between comparison groups.

Identification of risk factors. Numerous factors, including duration of drug exposure, switching between drugs, doses administered, and number of antipsychotics co-prescribed, could substantially affect risk of diabetes. Studies that account for reasonably suspect drug-exposure risk factors are considered to be of sounder design.

Selection and inclusion of covariates. Potential confounders of the association between drug use and new-onset diabetes such as patient age, severity of psychiatric disease, sex, race, and other concomitant medications should be included in the analysis. In addition, because known diabetogenic drugs, such as adrenergic blockers, thiazide diuretics, corticosteroids, phenytoin, norgestrel-containing oral contraceptives, and valproate, are commonly prescribed in patients with schizophrenia, studies should include this factor in covariate analysis.

Scope of available data. Twenty one epidemiologic studies have examined the relationship between specific atypical antipsychotic use and diabetes, 10 of which have been published in peer-reviewed journals, and 1 in a non peer-reviewed journal (Table 1). The remaining 10 were presented as posters

at scientific meetings (most recently, the largest Veteran's Administration study yet performed, authored by Leslie and Rosenheck²²), and therefore may represent preliminary results that differ from what may appear in publication. All studies are secondary analyses of private insurance, managed care, or governmental claims databases and many included large numbers of patients exposed to antipsychotics. Three studies examined only excess risk of diabetes versus untreated patients,^{10,14,18} 5 reported data for both excess risk and relative risk,^{7-9,13,15} and 13 compared only relative risk of diabetes between individual or grouped antipsychotics.^{3-6,11,12,16,17,19-23}

One of the 3 studies that reported only excess risk (Cavazzoni et al)¹⁴ and 2 of the 5 that reported both excess and relative risk (Buse et al, Feldman et al)^{13,15} compared antipsychotic users with a general patient population. Because the excess risk of diabetes inherently conferred by the presence of schizophrenia or mood disorders is a confounder not accounted for in these studies, the excess risk data from these studies is inconclusive. Therefore, only the relative risk data from the Buse et al and Feldman et al studies are reviewed; the non-peer-reviewed Cavazzoni et al study is reviewed only for the purpose of discussion of methodology.

Sections 2.3.2 through 2.4.3 evaluate the specific findings from all available epidemiological studies. More detailed results for each study are presented in Tables 2 to 4 in the Supporting Tables and Figures Section (Section 2.6 in this chapter). In addition, following each of these tables, a graphical representation of the results by medication is provided, with the size of the risk point estimate varying according to the sample size.

2.3.2. Excess Risk Findings

Excess risk is the most important factor in considering whether epidemiologic evidence supports a drug effect with risperidone and other atypical antipsychotics. Five studies^{7-10,18} addressed the issue of excess risk of new-onset diabetes associated with treatment with atypical antipsychotics by making comparisons with patients with untreated psychiatric illness (Table 2). Four of these 5 presented data for risperidone and olanzapine and demonstrated no significant excess risk associated with risperidone compared with untreated patients with psychiatric illness (OR: range = 0.660 to 2.2; $P = \text{NS}$ for each), though a statistically significant excess risk of diabetes was always associated with olanzapine (OR: range = 1.426 to 5.8; $P < 0.05$ for each). Gianfrancesco et al⁸ reported significant excess risk

(OR = 7.44; $P < 0.05$), whereas Wang et al¹⁸ reported no excess risk (OR = 0.98; $P = \text{NS}$) associated with clozapine. The only study that examined excess risk for quetiapine demonstrated no excess risk associated with quetiapine versus untreated psychiatric patients (OR = 0.976; $P = \text{NS}$).¹⁰ The estimation of excess risk of diabetes with atypical antipsychotics compared to untreated patients with psychiatric illness is therefore consistent in the literature.

Results argue uniformly against a conclusion of increased risk with risperidone although they are equally uniform in suggesting that treating a patient with olanzapine increases the risk of developing diabetes approximately 40% to 480% (OR = 1.4 to 5.8) over and above the risk associated with the disease itself.

From a research quality perspective, confounders and covariates including age, sex, diagnosis, exposure to at least some other diabetogenic drugs, and switching between antipsychotics were controlled for in all 5 studies. The demonstration of dose-dependent and exposure-dependent excess risk for olanzapine in 2 studies^{8,9} adds further weight to the findings. It must be noted that different patient subpopulations by diagnosis (mood disorders, mixed psychiatric diagnoses) or different sampling intervals were extracted from the same database in the 3 studies by Gianfrancesco et al⁸⁻¹⁰ with consistent results, which supports the conclusion that the results reached are robust, but may limit generalizability. Results of the Gianfrancesco studies are supported by the similar results of the UK-based study by Koro et al⁷. Although the number of diabetes cases in the Koro et al study is small, the case-control design, 6:1 matching of controls to cases, and rigorous accounting for covariates in the regression model strengthens the study. In contrast, the Cavazzoni et al study¹⁴ of the same database, which reported greater risk of diabetes for all antipsychotic users, risperidone, and thioridazine, used a cohort design, and the excess risk numbers cannot be meaningfully interpreted due to use of a general population rather than untreated psychiatric patients as a reference group. In other words, this study's finding of increased risk with all treatments is equally consistent with simple increased risk associated with psychiatric illness. The study was further limited by extremely small and unbalanced cell sizes, unequal exposure periods, and inadequate control for potential confounders. Findings regarding excess risk associated with clozapine are limited and

contradictory. The number of clozapine users in the Gianfrancesco et al study⁸ was acknowledged to be quite small, and Wang et al¹⁸ matched each case of diabetes to less than one control, a serious limitation in a case-control study.

2.4. Relative Risk Findings

2.4.1. Comparison of Atypical Versus Conventional Antipsychotics

Results of the studies assessing relative risk of diabetes associated with atypical antipsychotics compared with conventional antipsychotics varied and depended on whether comparisons were made with conventional antipsychotics as a group or with haloperidol alone (Table 3). Most comparisons did not reach statistical significance.

Eleven studies (Table 3, Figures 3A and 3B) compared grouped conventional antipsychotics with risperidone, olanzapine, clozapine, or grouped atypical antipsychotics.^{5,7,8,11-13,15-17,20,21,22} In summary, Lee et al¹⁷, Lage et al¹⁶, and Kennedy et al²¹ found no significantly greater relative risk associated with risperidone or olanzapine or with atypical antipsychotics as a group relative to conventional antipsychotics. The studies of L'Italien et al¹² and Koro et al⁷ reported an elevated but marginally nonsignificant risk (OR = 3.92; 95% CI = 1.0 to 15.6) and significantly greater risk (OR = 4.2), respectively, for olanzapine relative to all conventional antipsychotics and a nonsignificant risk for risperidone (OR = 2.22 and 1.6, respectively). Cunningham et al²⁰ found an elevated risk for all treatments; statistically significant for risperidone (OR = 1.47) and olanzapine (OR = 1.50) and similar but nonsignificant for quetiapine (OR = 1.54). Lambert et al¹¹ also found significantly greater risk for olanzapine (OR = 1.30) and clozapine (OR = 1.35) compared with conventional antipsychotics and a nonsignificant risk for risperidone (OR = 1.06). Leslie and Rosenheck²² found a significantly greater risk for clozapine (hazard ratio [HR] = 1.57, $p < 0.001$) and olanzapine (HR = 1.15, $p < 0.001$) and a greater but statistically nonsignificant risk for quetiapine (HR = 1.20; p value not significant), and no increased risk with risperidone compared to the group of conventional antipsychotics. Sernyak et al⁵ reported similar significant results in a prevalence study (OR = 1.11, 1.25, and 1.31, for olanzapine, clozapine, and quetiapine, respectively), as well as a significantly greater risk for all atypical antipsychotics combined (OR = 1.09), but a nonsignificant increased risk for risperidone (OR = 1.05). Lastly, Gianfrancesco et al⁸ separately

compared low- and high-potency conventional antipsychotics with risperidone and, consistent with previously reported suggestive evidence for chlorpromazine-related risk, found a significantly increased risk associated with low-potency conventional antipsychotic use relative to risperidone (OR = 3.93; $P < 0.05$).

The following 4 studies compared specific atypical antipsychotics with haloperidol. In the study by Buse et al,¹³ there was a marginally significant increased risk for risperidone (HR = 1.23; 95% confidence interval [CI] = 1.01 - 1.50) relative to haloperidol and a nonsignificant differential risk for olanzapine (HR = 1.09) and clozapine (OR = 1.31) relative to haloperidol. In the same study, quetiapine had a significantly lower relative risk (OR = 0.67) compared with that for haloperidol. The Feldman et al study¹⁵ demonstrated significant increased risk in older patients for risperidone compared with haloperidol (OR = 1.295) but a nonsignificant differential risk for olanzapine (OR = 1.172), clozapine (OR = 1.403), and quetiapine (OR = 0.732) compared with haloperidol for low-dose therapy in an elderly population. In contrast, Fuller et al⁶ reported no statistically significant difference in risk between haloperidol and risperidone (HR = 0.89). Feldman et al¹⁵ and Kennedy et al²¹ also reported no significant difference in relative risk for atypical antipsychotics as a group compared with haloperidol.

Based on this evidence, the issue of relative risk is more complex than that of excess risk, and merits further discussion. Four of the 5 studies^{15-17,21} that compared grouped atypical with conventional antipsychotics did not demonstrate a significantly greater risk of diabetes for atypical over conventional antipsychotics. The only study that did demonstrate a significantly greater risk was the prevalence study⁵, from which no conclusive inference can be drawn. The nonsignificant results suggest that some atypical antipsychotics may have a lower or comparable risk compared to conventional antipsychotics, whereas others have a higher risk; therefore, grouping them together tends to bias analysis to the null.

Some important lines of evidence appear to converge among the studies. Comparisons of risperidone with conventional antipsychotics as a group consistently indicated that risperidone did not pose a greater relative risk of diabetes in 8 of 9 studies (Table 3).^{5,7,11,12,16,17,20,21,22} There also appeared to be no greater risk for risperidone compared with haloperidol⁶ or grouped

high-potency conventional antipsychotics⁸ in 2 of 4 studies that made these comparisons. The 2 studies (Buse et al, Feldman et al)^{13,15} that reported a greater relative risk for risperidone compared with haloperidol studied low doses of antipsychotics, but dosage was not accounted for in the hazards models, making interpretation difficult. In the Buse et al study, the finding of greater risk was marginally significant (Table 3). In the Feldman et al study, the finding appeared to be largely driven by a subset of patients older than age 75, and no co-morbidities or concomitant medications were examined and controlled for in this susceptible population.

Comparisons of olanzapine with conventional antipsychotics yielded varying results. The most rigorously designed study that makes this comparison is that by Koro et al⁷, which concluded a significantly higher risk of diabetes with olanzapine (OR = 4.2). Sernyak et al⁵, Lambert et al¹¹, Cunningham et al²⁰ and Leslie and Rosenheck²² (a recent study based on greater than 56,000 VA patients) concluded that there was a smaller but significantly increased risk (1.11, 1.30, 1.50 and 1.15 respectively), while L'Italien et al¹² found a larger (OR= 3.92) but marginally significant risk for olanzapine compared with conventional antipsychotics. However, the Sernyak et al⁵ study was a prevalence study that did not account for pre-existing diabetes or temporality (order of cause and effect) precluding any inference of causality. The case-control study by Lambert had large numbers of diabetics and controlled for covariates such as known diabetogenic agents and ethnicity. Both Buse and Feldman et al^{13,15} concluded that there was no differential risk for olanzapine at low dosage levels versus haloperidol. These data appear internally consistent, as they were based on slightly different populations as defined by age extracted from the same claims database. In addition, the studies by Lcc¹⁷ and Lage¹⁶ found no added risk with either olanzapine or risperidone compared to grouped conventional antipsychotics.

2.4.2. Comparisons of Risperidone Versus Olanzapine

In order to understand these contradictory findings when conventional antipsychotics are compared to olanzapine, it is useful to examine studies directly comparing risperidone and olanzapine. Ten studies assessed the relative risk of diabetes associated with olanzapine compared with that for risperidone (Table 4). Of these, 7 studies^{3,4,6,8,9,19,23} found a significantly increased risk of diabetes associated with olanzapine compared with risperidone (OR = 1.30, 3.53, and 4.189; relative risk [RR] = 1.90, 1.37,

and 2.23; incidence rate ratio [IRR] = 1.21), whereas 3 studies^{13,16,17} found no statistically significant difference in risk of diabetes associated with olanzapine compared with risperidone (Table 4).

Although 3 of the 10 studies did not demonstrate a statistically significant difference in risk between the 2 drugs, differences in methods may account for these disparate results. Among the studies that demonstrated a significant difference in relative risk for olanzapine and risperidone, the studies by Gianfrancesco et al,^{8,9} Fuller et al,⁶ and to a lesser extent the Grogg et al¹⁹ study accounted for most identifiable covariates in their model, including dose, duration of exposure, and switching between antipsychotics (Table 1). The 2 studies by Gianfrancesco^{8,9} used an exponential extrapolation of risk for 1 month of exposure to 12 months, a standard method in logistic regression²⁷, which may imprecisely estimate the magnitude of risk if the risk of developing diabetes is not cumulative over time. However, similar results of smaller magnitude were also found by Grogg et al¹⁹ and Fuller et al.⁶ The congruence of the results of the Caro et al⁴ and Moisan et al³ studies of a Canadian population involving relatively long periods of exposure (approximately 1 year) and observation (2 and 4 years, respectively) lend weight to the strength of these findings.

In contrast, the studies by Buse et al,¹³ Lee et al,¹⁷ and Lage et al¹⁶ found no difference in risk of diabetes between risperidone and olanzapine. All 3 failed to control for concomitant use of other drugs, including known diabetogenic agents, whereas 5 of the 7 studies that demonstrated differential risk controlled for some or many of these agents. The studies by Lee et al and Lage et al did, however, control for comorbid conditions, such as heart disease and hypertension, which may be a proxy for known diabetogenic drugs used for these conditions.

Additional methodologic differences in these studies are related to duration of antipsychotic exposure. The duration of exposure to antipsychotics was 3 to 4 months in the Buse et al¹³ and Lee et al¹⁷ studies and not accounted for in the Lage et al¹⁶ study. In contrast, exposure times in the majority of studies that demonstrated differential risk between olanzapine and risperidone were approximately 6 to 12 months or longer in duration.^{3,4,8,9,12} A shorter exposure time may fail to detect cases of diabetes that manifest with increasing duration of exposure, including diabetes secondary to

progressive weight gain, the liability for which is greater with olanzapine than with other atypical antipsychotics.

Considerations related to patient age, antipsychotic dosage, and switching between antipsychotics might have obscured differences in relative risk. Although Lage et al¹⁶ found increasing age to be a significant predictor of diabetes, both Lee et al¹⁷ and Lage et al¹⁶ restricted their analysis to patients younger than age 65. In addition, the Buse et al¹³ study (as well as the Caro et al⁴ study that demonstrated differential relative risk) converted age into a categorical variable that consigned all persons over age 65 into 1 category. Treating age as a continuous variable, as in the 3 Gianfrancesco et al⁸⁻¹⁰ studies, using finer categories, or case-control matching, as in the Koro study⁷, are better methods for accounting for age in a regression analysis. This may be particularly important when there are significant differences in age in the 2 groups compared, as in the Buse et al¹³ study, in which the risperidone group had a disproportionately greater proportion of older patients.

Four of the studies reporting a higher relative risk for olanzapine⁶⁻¹⁰ used various methods to account for switching between antipsychotics, whereas none of the studies finding no elevated risk for olanzapine did so, an important distinction in a population in which switching between antipsychotics is common. Use of a so-called "intent-to-treat" analysis in a retrospective, nonrandomized cohort, as was done in the Lee et al study,¹⁷ biases towards the null; and excluding all patients who switch between antipsychotics, as in the Buse et al¹³ studies, may create a highly artificial sample of patients, making it difficult to generalize results to a wider population.

Lastly, in all 3 studies that demonstrated no difference in relative risk of olanzapine and risperidone, the mean dosages of antipsychotics were low (Buse et al¹³ and Lage et al¹⁶) or unknown (Lee et al¹⁷), and dosage was not taken into account in the statistical models. The failure to account for dose is important because 3 other studies (Gianfrancesco et al^{8,9} and Grogg et al¹⁹) suggested that differential risk for diabetes was dose-dependent (lower dose associated with lower risk). It is also important because dose is a proxy measure for severity of illness that may confound risk of new-onset diabetes. In the study by Caro et al⁴, the difference in relative risk between olanzapine and risperidone was marginally significant for the overall population, but

significant for women alone. Greater excess risk in women than men was also demonstrated in the Koro et al study⁷, for which sex was examined as a covariate, and has been reported in the literature.²⁸; women are also known to be at greater risk of diabetes than men in the general population.^{25,29} However, the greater risk for olanzapine than risperidone in the Fuller et al⁶ study, which included only male patients, suggests that this difference in relative risk is not confined to women alone.

2.4.3. Relative Risk Associated With Clozapine and Quetiapine

The 3 studies (Sernyak et al, Lambert et al, Leslie and Rosenheck)^{5,11,22} of relative risk associated with clozapine with respect to grouped conventional antipsychotics suggested that clozapine has a greater relative risk of diabetes (1.25 to 1.57) compared with grouped conventional antipsychotics. The only study that compared clozapine with haloperidol (Feldman et al)¹⁵ did not demonstrate a significant difference; however, only lower doses used in the elderly were included.

Three studies of quetiapine (Buse et al, Feldman et al, Leslie and Rosenheck)^{13,15,22} reported a lower or no increased relative risk compared with haloperidol or grouped conventionals. However, the Leslie and Rosenheck study found a meaningfully elevated point estimate for risk with quetiapine in a Veteran's Administration population, with limited sample size likely contributing to lack of statistical significance. While the Buse and Feldman studies both used lower doses, the examination of dose quartiles in Buse et al adds greater consistency to the results. The well-designed case-control study by Lambert et al¹¹ reported that compared with conventional antipsychotics as a group, quetiapine did not appear to pose a greater risk. However, it is important to note that the number of patients on quetiapine in all these studies was very small compared to the numbers examined for olanzapine and risperidone. Further studies may be necessary to clarify the risk of diabetes associated with clozapine and quetiapine.

2.5. Conclusion

The body of epidemiologic evidence is limited by lack of information regarding race and weight gain and complicated by inconsistent handling of important confounders, including age, antipsychotic dosage, concomitant medications, and comorbid illnesses. In addition, the proportions of patients with specific psychiatric diagnoses varied among studies with

mixed - diagnosis populations, and among some studies that considered only patients with schizophrenia or mood disorders.

Nevertheless, particularly when studies are weighed in accordance with their methodologic strengths, data consistently demonstrate that treatment with risperidone does not pose a risk of development of new-onset diabetes greater than that associated with no treatment for major psychiatric illness or treatment with conventional antipsychotics. A comparable body of consistent evidence also suggests that treatment with olanzapine is associated with a higher risk of developing diabetes than no treatment for major psychiatric illness; this argues against specification of an atypical antipsychotic "class effect" based on common mechanism(s) of action on psychosis. Whether clozapine is associated with a greater risk of diabetes than no treatment for major psychiatric disorder remains unclear on the basis of this type of data. Problems with "confounding by indication" may preclude the possibility that this type of study can adequately inform this issue for clozapine. Data regarding risk of diabetes associated with quetiapine relative to no treatment of patients are based on small numbers. Finally, the preponderance of comparative data on the relative risk of diabetes associated with risperidone compared with olanzapine, the comparison for which the most evidence exists, argues against a "class effect". The studies comparing risperidone and olanzapine do not suggest that risperidone has no effect on diabetes, simply that the risk of diabetes is significantly greater with olanzapine.

2.6. Supporting Tables and Figures

Table 1: Characteristics of Studies Assessing the Excess Risk or Relative Risk of Diabetes Mellitus Among Patients Taking Antipsychotics

Table 2: Excess Risk of Diabetes Associated With Atypical Antipsychotic Treatment Compared With Major Psychiatric Illness Without Antipsychotic Treatment

Figure: Relative Risk of Diabetes: Atypical Versus Untreated (Table 2)

Table 3: Relative Risk of Diabetes Associated With Atypical Antipsychotics Versus Conventional Antipsychotics

Figure: Relative Risk of Diabetes: Atypical Versus Conventional Antipsychotics Figure A (Table 3)

Figure: Relative Risk of Diabetes: Atypical Versus Conventional Antipsychotics Figure B (Table 3)

Table 4: Relative Risk of Diabetes Associated With Olanzapine Compared With Risperidone

Figure: Relative Risk of Diabetes: Olanzapine Versus Risperidone (Table 4)

Risperidone and Glucose Metabolism: Executive Summary

Table 1: Characteristics of Studies Assessing the Excess Risk or Relative Risk of Diabetes Mellitus Among Patients Taking Antipsychotics

Study author; Industry support	Publication type	Study design	Sample population Source	Psychiatric diagnosis (results)	Duration of AP exposure	Diabetes criteria	AP Switches Addressed	Dosage Included	Major covariates addressed
Studies that reported only excess risk^a									
Cavazzoni et al, 2001 ¹⁴	Scientific meeting poster presentation	Cohort	UK General Practice Research (Rx claim) database, Jan 1996 to Dec 1997	Various	Variable; mean 156 days, all APs combined	Dx or Rx	No	No	Age, sex, obesity
Lilly Research Laboratories Wang et al, 2002 ¹⁸	Peer- reviewed journal article	Case- control	New Jersey Medicare, Medicaid and pharmaceutical assistance programs, Jan. 1990 - June 1995	Various	Variable	Rx	Yes	Yes	Age, sex, race, comorbid illness, medications, healthcare use, corticosteroids, psychiatric Dx, other diabetogenic drugs
None									
Gianfrancesco et al, 2003b ¹⁰	Peer- reviewed journal article	Cohort	2 mixed indemnity and managed care plans, April 1997 - Oct 2000	Various; schizophrenia, bipolar and manic, major depressive, other psychosis	Mean 9.9 months; 1-month exposure projected for 12 months	Rx	Yes, 30-day washout specified	Yes	Age, sex, observation period length, diagnosis, type of insurance, prior weight gain, psychotropic drugs, APs, beta- blocker
AstraZeneca Pharmaceuticals, L.P.									

AP = antipsychotic; Dx = diagnosis; ITT = intent to treat; MCO = managed care organization; PPO = preferred provider organization; Rx = prescription;

VA = Veterans Administration; VISN = Veteran's Integrated Service Network; NR = not reported

^aExcess risk defined as increased risk of diabetes compared with patients with major psychiatric illness not taking an antipsychotic.

^bRelative risk of diabetes associated with an individual or grouped atypical antipsychotics compared with another individual or grouped antipsychotics.

(Continued)

Risperidone and Glucose Metabolism: Executive Summary

Table 1: Characteristics of Studies Assessing the Excess Risk or Relative Risk of Diabetes Mellitus Among Patients Taking Antipsychotics

Study author; industry support	Publication type	Study design	Sample population Source	Psychiatric diagnosis (results)	Duration of AP exposure	Diabetes criteria	AP Switches Addressed	Dosage Included	Major covariates addressed
Studies that reported both excess risk^a and relative risk^b									
Buse et al, 2003 ¹³	Peer-reviewed journal article	Cohort	Advance PCS prescription claim database; with, MCOs, Medicaid, Medicare; enrollment Dec 1998 – Feb 29, 2000	Various; unspecified	Mean 90 days, atypical AP; 67 days, conventional AP	Rx	No; monotherapy only; all patients who switched excluded	Ratios calculated by dosage quartiles	Age, sex, amount of antipsychotic
Eli Lilly and Company									
Feldman et al ¹⁵	Peer-reviewed journal article	Cohort	Advance PCS Rx claims database, subset of patients age ≥60 years, Dec 1999 – Feb 2000	Any	Mean 70.2 days conventional, 90.6 days atypical AP	Rx	Yes; all patients who switched excluded	No	Age, sex, treatment duration
Eli Lilly and Company									
Gianfrancesco et al, 2002 ⁵	Peer-reviewed journal article	Cohort	2 mixed indemnity and managed care plans; Jan 1996 – Dec 1997	Any psychosis	Mean, 6.8 months; 1-month risk projected for 12 months	Dx or Rx	Yes, 30-day washout required	Yes	Age, sex, observation period, diagnosis, insurance, diabetogenic drugs
Janssen Pharmaceutica Products, L.P.									
Gianfrancesco et al, 2003a ⁹	Peer-reviewed journal article	Cohort	2 mixed indemnity and managed care plans; Jan 1996 - Dec 1997	Mood disorders	Mean, 6.5 months; 1-month risk projected for 12 months	Dx or Rx	Yes, 30-day washout specified	Yes	Age, sex, observation period, type of mood disorder, type of insurance, psychotropic drugs
Janssen Pharmaceutica Inc.									

AP = antipsychotic; Dx = diagnosis; ITT = intent to treat; MCO = managed care organization; PPO = preferred provider organization; Rx = prescription;

VA – Veterans Administration; VISN – Veteran's Integrated Service Network; NR – not reported

^aExcess risk defined as increased risk of diabetes compared with patients with major psychiatric illness not taking an antipsychotic.

^bRelative risk of diabetes associated with an individual or grouped atypical antipsychotics compared with another individual or grouped antipsychotics.

(Continued)

Risperidone and Glucose Metabolism: Executive Summary

Table 1: Characteristics of Studies Assessing the Excess Risk or Relative Risk of Diabetes Mellitus Among Patients Taking Antipsychotics

Study author; Industry support	Publication type	Study design	Sample population Source	Psychiatric diagnosis (results)	Duration of AP exposure	Diabetes criteria	AP Switches Addressed	Dosage Included	Major covariates addressed
Koro et al, 2002 ^a Bristol-Myers Squibb (provided database)	Peer- reviewed journal article	Case control	UK General Practice Research Data-base, June 1987 – Sept 2000	Schizophrenia	Variable	Dx or Rx	Yes	No	Age, sex, duration of follow-up, index year, diabetogenic drugs
Studies that reported only relative risk^b									
Caro et al, 2002 ^a Janssen Ortho, Inc.	Peer- reviewed journal article	Cohort	Seniors, welfare, uninsured; government claims database, Quebec; Jan 1997- Dec 1999	Schizophrenia and unspecified	Variable; included exposure duration in risk estimation	Dx or Rx	No	No	Age, sex, concomitant antipsychotics, diagnosis of schizophrenia, treatment duration
Cunningham et al, 2003 ²⁰ Bristol-Myers Squibb	Scientific meeting podium presentation	Cohort & case- control	VA population	Schizophrenia	NR	Dx or Rx	Yes, data were censored upon switch	No	Age, gender, ethnicity, concomitant medication
Fuller et al, 2003 ⁶ Janssen Pharmaceutica Products, L.P.	Peer- reviewed journal article	Cohort	VISN-10 VA database, Jan 1997 - Dec 2000; males only	Various; psychotic, mood, other disorders	NR; treatment duration included in statistical model	Dx or Rx	Yes, treatment group as a time- dependent variable	No	Age, race, psychiatric Dx, concomitant medication, psychiatric Dx, substance abuse

AP = antipsychotic; Dx = diagnosis; ITT = intent to treat; MCO = managed care organization; PPO = preferred provider organization; Rx = prescription;

VA = Veterans Administration; VISN = Veteran's Integrated Service Network; NR = not reported

^aExcess risk defined as increased risk of diabetes compared with patients with major psychiatric illness not taking an antipsychotic.

^bRelative risk of diabetes associated with an individual or grouped atypical antipsychotics compared with another individual or grouped antipsychotics.

(Continued)

Risperidone and Glucose Metabolism: Executive Summary

Table 1: Characteristics of Studies Assessing the Excess Risk or Relative Risk of Diabetes Mellitus Among Patients Taking Antipsychotics

Study author; industry support	Publication type	Study design	Sample population Source	Psychiatric diagnosis (results)	Duration of AP exposure	Diabetes criteria	AP Switches Addressed	Dosage Included	Major covariates addressed
Grogg et al, 2003 ¹⁹ Janssen Pharmaceutica Products, L.P.	Scientific meeting poster presentation	Cohort	California Medicaid patients <65 yrs of age	Various; bipolar and/or schizophrenia	NR; however, exposure days included in logistic regression	Dx and/ or Rx	No	Yes	Age, race, dosage, sex, hypertension, medical/ psychiatric comorbidities, antidepressants mood stabilizers, anxiolytics
Kennedy et al, 2002 ²¹ Eli Lilly and Company	Scientific meeting poster presentation	Cohort	IMS Lifelink claims database	Various; patients with APS use ≥65 yrs of age	APS use for at least 1 month	Dx or Rx	Yes; no use of APS for 6 months prior to initiation & use of only 1 APS 12 months post- initiation	No	Age, gender, regional differences, mental and physical health comorbidities, length of APS use
Lage et al, 2001 ¹⁶ Eli Lilly and Company	Scientific meeting poster presentation	Cohort	Rx, outpatient, hospitalization claims database; indemnity and PPO	Schizophrenia, bipolar disorder, depression, other	NR, not accounted for in regression	Dx or Rx	No	No	Age, gender, mental health co- morbidities, regional differences

AP = antipsychotic; Dx = diagnosis; ITT = intent to treat; MCO = managed care organization; PPO = preferred provider organization; Rx = prescription;

VA = Veterans Administration; VISN = Veteran's Integrated Service Network; NR = not reported

^aExcess risk defined as increased risk of diabetes compared with patients with major psychiatric illness not taking an antipsychotic.

^bRelative risk of diabetes associated with an individual or grouped atypical antipsychotics compared with another individual or grouped antipsychotics.

(Continued)

Risperidone and Glucose Metabolism: Executive Summary

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Study author; Industry support	Publication type	Study design	Sample population Source	Psychiatric diagnosis (results)	Duration of AP exposure	Diabetes criteria	AP Switches Addressed	Dosage Included	Major covariates addressed
Lambert et al, 2003 ¹¹ Bristol-Myers Squibb; Otsuka America Pharma- ceutical, Inc.	Scientific meeting poster presentation	Case control	California Medicaid 1997 – 2000	Schizophrenia	≥12 weeks	Dx	No	No	Race, age, sex, diabetogenic drugs
Lee et al, 2002 ¹⁷ Eli Lilly and Company	Journal article; not peer reviewed	Cohort	US MCO; Sept 1997 - Dec 1999; age <65 years	Schizophrenia, bipolar disorder, depression, other	Mean 126.10 days atypical 108.3 days conventional AP	Dx or Rx	No, patients who switched retained in index group (ITT)	No	Age, sex, geographic region, mental health dx, hypertension, heart disease, duration of AP
Leslie and Rosenheck, 2003 ²² Bristol-Myers Squibb	Scientific meeting poster presentation	Cohort	56,849 VA patients from June 99 through Sept 02	Schizophrenia	Required all patients to have at least 90 days; mean = unknown	Dx	No	No	Sociodemographic and diagnostic characteristics, disability and service use
L'Italien et al, 2002 ¹² Bristol-Myers Squibb	Scientific meeting poster presentation	Case control	Regenstrief Record System -Indianapolis healthcare provider database	Schizophrenia	Approximately 2.2 yrs atypical AP, 5.6 yrs conventional	Dx	NR	No	Age, sex, comorbidities, healthcare use, benztropine, obesity

AP = antipsychotic; Dx = diagnosis; ITT = intent to treat; MCO = managed care organization; PPO = preferred provider organization; Rx = prescription;

VA = Veterans Administration; VISN = Veteran's Integrated Service Network; NR = not reported

^aExcess risk defined as increased risk of diabetes compared with patients with major psychiatric illness not taking an antipsychotic.

^bRelative risk of diabetes associated with an individual or grouped atypical antipsychotics compared with another individual or grouped antipsychotics.

(Continued)

Risperidone and Glucose Metabolism: Executive Summary

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Study author; Industry support	Publication type	Study design	Sample population Source	Psychiatric diagnosis (results)	Duration of AP exposure	Diabetes criteria	AP Switches Addressed	Dosage included	Major covariates addressed
L'Italien et al, 2003 ²³	Scientific meeting poster presentation	Cohort	UK General Practice Research Data-base, June 1987 – Sept. 2000	Schizophrenia	Mean follow-up 4.2±2 years	Dx	NR	No	Unknown
Moisan et al, 2001 ³ Janssen-Ortho, Inc.	Scientific meeting poster presentation	Cohort	Seniors, welfare, uninsured; government Rx claims database, Quebec; Jan 1997 – Aug 2000	Unspecified	Varied	Rx	Yes, data censored upon switch- ing	No	Age, sex
Sernyak et al, 2002 ⁵ none	Peer- reviewed journal article	Preva- lence	VA workload database; Oct 1998 – Sept, 1999	Schizophrenia	Varied, point prevalence estimate only	Dx	No	No	Age, sex, race, comorbid psychiatric Dx, days psychiatric hospitalization, degree of dis- ability, travel

AP = antipsychotic; Dx = diagnosis; ITT = intent to treat; MCO = managed care organization; PPO = preferred provider organization; Rx = prescription;
VA = Veterans Administration; VISN = Veteran's Integrated Service Network; NR = not reported

^aExcess risk defined as increased risk of diabetes compared with patients with major psychiatric illness not taking an antipsychotic.

^bRelative risk of diabetes associated with an individual or grouped atypical antipsychotics compared with another individual or grouped antipsychotics.

Risperidone and Glucose Metabolism: Executive Summary

Table 2: Excess Risk of Diabetes Associated With Atypical Antipsychotic Treatment Compared With Major Psychiatric Illness Without Antipsychotic Treatment

Study	Untreated patients (n)	Antipsychotic	Treated patients (n)	Odds ratio	95% confidence interval
Gianfrancesco et al, 2002 ⁸	1738	risperidone	994	0.88	0.372 - 2.070
		clozapine	39	7.44	1.603 - 34.751 ^a
		olanzapine	986	3.10	1.620 - 5.934 ^a
Gianfrancesco et al, 2003 ⁹	2644	risperidone	849	1.024	0.351 - 3.015
		olanzapine	656	4.289	2.102 - 8.827 ^a
Gianfrancesco et al, 2003 ¹⁰	10,296	risperidone	2860 ^b	0.660	0.311 - 1.408
		olanzapine	2703 ^b	1.426	1.046 - 1.955 ^a
		quetiapine	922 ^b	0.976	0.422 - 2.271
Koro et al, 2002 ⁷	NR	risperidone	1683 ^c	2.2	0.9 - 5.2
		olanzapine	970 ^c	5.8	2.0 - 16.7 ^a
Wang et al, 2002 ¹⁸	NR	clozapine	NR	0.98	0.74 - 1.31

NR = not reported

^a Statistically significant at $P < 0.05$ level.

^b Reported as treatment episodes only; total treated patients = 6582.

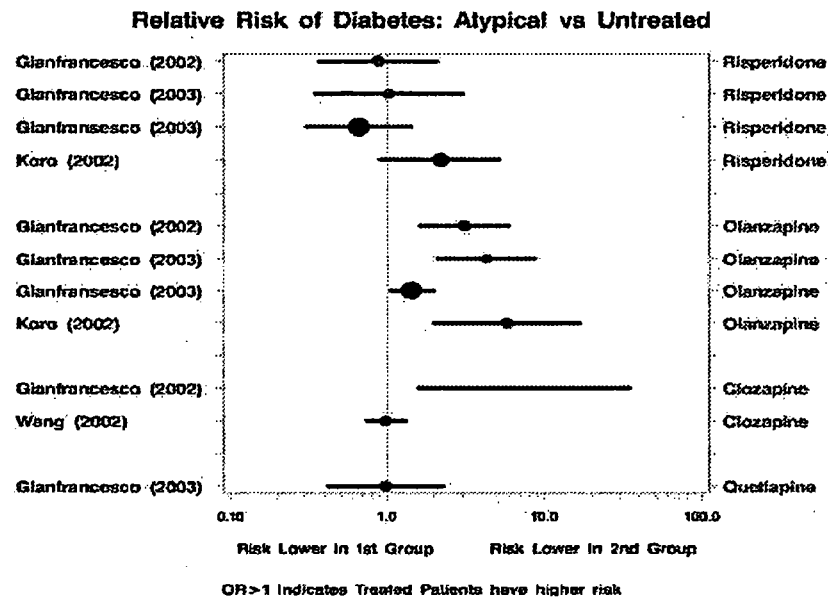
^c Derived from case-control data; case-control n's are smaller than cohort n's.

Figure for Table 2: Relative Risk of Diabetes: Atypical Versus Untreated (Odds Ratios)

1st Group = Specific atypical antipsychotic

2nd Group = No treatment

Size of point estimate represents size of population studied



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Table 3: Relative Risk of Diabetes Associated With Atypical Antipsychotics Versus Conventional Antipsychotics

Studies comparing ATYP to CONV	Medication	n	Reference Medication	n	Risk ratio ATYP vs. CONV	95% CI
Buse et al, 2003 ¹³	risperidone	20,633	haloperidol	8476	1.23 ^b	1.01 - 1.50 ^a
	olanzapine	13,863	haloperidol	8476	1.09 ^b	0.86 - 1.37
	clozapine	277	haloperidol	8476	1.31 ^b	0.60 - 2.86
	quetiapine	4196	haloperidol	8476	0.67 ^b	0.46 - 0.97 ^a
	All ATYP	38,869	All CONV	8476	0.97 ^b	0.84 - 1.11
Cunningham et al, 2003 ²⁰	risperidone	5901	All CONV	7009	1.47 ^a	NR
	olanzapine	5981	All CONV	7009	1.50 ^a	NR
	quetiapine	877	All CONV	7009	1.54	NR
Feldman et al, 2002 ¹⁵	risperidone	12,244	haloperidol	6481	1.295	1.05 - 1.60 ^c
	clozapine	117	haloperidol	6481	1.403	0.57 - 3.47
	olanzapine	5382	haloperidol	6481	1.172	0.92 - 1.50
	quetiapine	1664	haloperidol	6481	0.732	0.49 - 1.10
	All ATYP	19,407	All CONV	11,546	1.071	0.92 - 1.25
Kennedy et al, 2002 ²¹	risperidone	NR	All CONV	NR	1.331	NR; NS
	olanzapine	NR	All CONV	NR	1.084	NR; NS
	haloperidol	NR	All ATYP	NR	0.981	NR; NS
Koro et al, 2002 ⁷	risperidone	970	All CONV	18,443	1.6 ^a	0.7 - 3.8
	olanzapine	1638	All CONV	18,443	4.2	1.5 - 12.2 ^a
Lage et al, 2001 ¹⁶	risperidone	1598	All CONV	3208	1.453	0.972 - 2.173
	olanzapine	1530	All CONV	3208	1.136	0.727 - 1.775
	All ATYP	3,232	All CONV	3208	1.228	0.869 - 1.736
Lee et al, 2002 ¹⁷	risperidone	750	All CONV	981	1.074	0.612 - 1.885
	olanzapine	513	All CONV	981	0.864	0.431 - 1.732
	All ATYP	1334	All CONV	981	1.010	0.612 - 1.668

ATYP = atypical antipsychotic; CONV = conventional antipsychotic; NR = not reported; NS = not significant.

^a Statistically significant at $P < 0.05$ level.

^b Reported as hazard ratio; all others reported as odds ratio or unspecified (risk ratio).

^c Significant at $P < 0.05$ level for all patients & for patients aged ≥ 75 years; NS for subgroup aged 60-74 years.

^d Derived from case-control data; case-control n's are smaller than cohort n's.

^e Prevalence study; patients with preexisting diabetes not excluded.

^f Some patients received prescriptions for more than one atypical antipsychotic.

^g The total number of patients who received the drug during the study, either at the index date or subsequently.

Table 3: Relative Risk of Diabetes Associated With Atypical Antipsychotics Versus Conventional Antipsychotics

Studies comparing ATYP to CONV	Medication	n	Reference Medication	n	Risk ratio ATYP vs. CONV	95% CI
Leslie and Rosenheck, 2003 ²²	risperidone	14,012	All CONV	23,809	1.01 ^b	NR
	olanzapine	16,068			1.15 ^a	
	clozapine	1,260			1.57 ^a	
	quetiapine	1,700			1.20	
L'Italien et al, 2002 ¹²	risperidone	150	All CONV	482	2.22 ^a	0.5 - 10.6
	olanzapine	112	All CONV	482	3.92	1.0 - 15.6
Studies comparing ATYP to CONV	Medication	n	Reference Medication	n	Risk ratio ATYP vs. CONV	95% CI
Lambert et al, 2002 ¹¹	risperidone	2483	ALL CONV	NR	1.06 ^d	0.94 - 1.19
	clozapine	861	ALL CONV		1.35	1.14 - 1.60 ^a
	olanzapine	3177	ALL CONV		1.30	1.16 - 1.44 ^a
	quetiapine	348	ALL CONV		1.22	0.95 - 1.58
Sernyak et al, 2002 ^{5c}	risperidone	9903	ALL CONV	15,984	1.05	0.98 - 1.12
	clozapine	1207	ALL CONV	15,984	1.25	1.07 - 1.46 ^a
	olanzapine	10,970	ALL CONV	15,984	1.11	1.04 - 1.18 ^a
	quetiapine	955	ALL CONV	15,984	1.31	1.11 - 1.55 ^a
	All ATYP	22,648 ^f	ALL CONV	15,984	1.09	1.03 - 1.15 ^a
Gianfrancesco et al, 2002 ⁸	low potency	307	risperidone	994	3.93	NR; <i>P</i> < 0.05 ^a
	high potency	915	risperidone	994	2.42	NR; NS
Fuller et al, 2003 ⁶	fluphenazine	428 ^g	risperidone	2493 ^g	1.11 ^b	0.68 - 1.79
	haloperidol	1790 ^g	risperidone	2493 ^g	0.89 ^b	0.67 - 1.17

ATYP = atypical antipsychotic; CONV = conventional antipsychotic; NR = not reported; NS = not significant.

^a Statistically significant at *P* < 0.05 level.^b Reported as hazard ratio; all others reported as odds ratio or unspecified (risk ratio).^c Significant at *P* < 0.05 level for all patients & for patients aged ≥ 75 years; NS for subgroup aged 60-74 years.^d Derived from case-control data; case-control n's are smaller than cohort n's.^e Prevalence study; patients with preexisting diabetes not excluded.^f Some patients received prescriptions for more than one atypical antipsychotic.^g The total number of patients who received the drug during the study, either at the index date or subsequently.

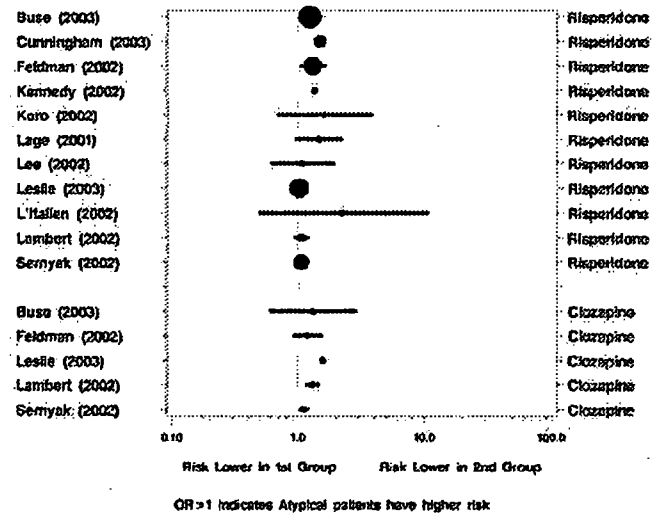
Figures A and B for Table 3: Relative Risk of Diabetes: Atypical Versus Conventional Antipsychotics (Odds Ratios)

1st Group = Specific atypical antipsychotic

2nd Group = Conventional antipsychotic

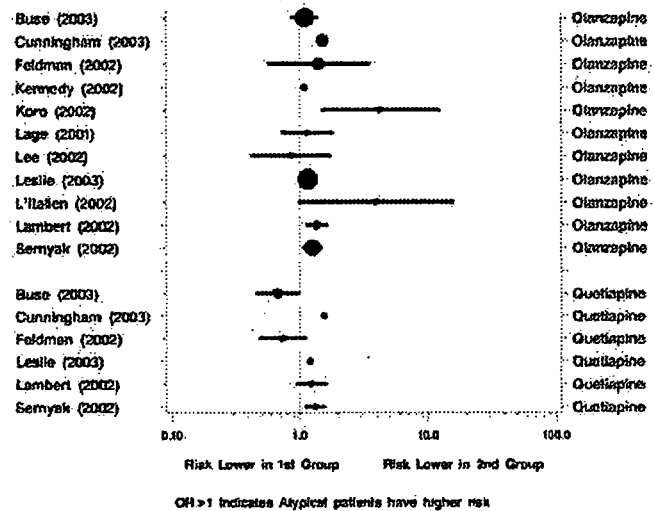
Size of point estimate represents size of population studied.

Relative Risk of Diabetes: Atypical vs Conventional APS (Figure A)



Size of point estimate represents size of population studied.

Relative Risk of Diabetes: Atypical vs Conventional APS (Figure B)



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Table 4: Relative Risk of Diabetes Associated With Olanzapine Compared With Risperidone

Study	Olanzapine (n)	Risperidone (n)	Risk Ratio	95% CI
Buse et al, 2002 ¹³	13,863	20,633	HR = 0.90	0.76 - 1.07
Caro et al, 2002 ⁴	17,142	12,259	RR = 1.2	1.00 - 1.43
			RR = 1.90 ^c	1.40 - 2.57 ^a
			RR = 1.30 ^d	1.05 - 1.65 ^a
Fuller et al, 2000 ⁶	3056 ^f	2493 ^f	RR = 1.37	1.06 - 1.76 ^a
Gianfrancesco et al, 2002 ⁸	986	994	OR = 3.53	NR; <i>P</i> < 0.05 ^a
Gianfrancesco et al, 2003 ⁹	656	849	OR = 4.189	NR; <i>P</i> = 0.0296 ^a
Grogg et al, 2003 ^{19 a}	8550	7895	OR = 1.30	1.05 - 1.62 ^a
Lage et al, 2001 ¹⁶	1530	1598	OR = 0.752	0.471 - 1.201
Lee et al, 2002 ¹⁷	513	750	OR = 0.786	0.384 - 1.610
L'Italien et al, 2003 ²³	- ^b	- ^b	RR = 2.23	1.35-3.7 ^a
Moisan et al, 2000 ³	12,945	15,197	IRR = 1.209	1.001 - 1.460

HR= hazard ratio; IRR= incidence rate ratio; RR = relative risk; OR = odds ratio; NR = not reported

^a Statistically significant at *P* < 0.05 level.

^b Only total sample size available (n=19,637).

^c First 3 months of treatment; RR at 3 to 6, 6 to 12, and >12 months not significant.

^d Females only.

^e This study also reported no statistically significant difference in risk between quetiapine (n = 1578) and risperidone (OR = 0.72; 95% CI = 0.46 - 1.12).

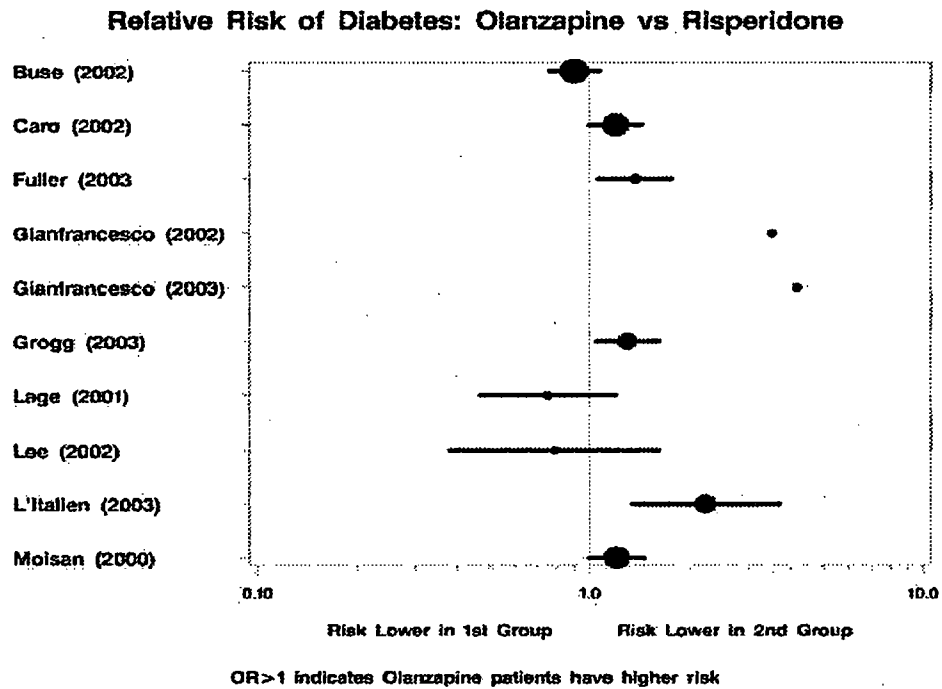
^f The total number of patients who received the drug during the study, either at the index date or subsequently.

Figure for Table 4: Relative Risk of Diabetes: Olanzapine Versus Risperidone (Odds Ratios)

1st Group = Olanzapine

2nd Group = Risperidone

Size of point estimate represents size of population studied.



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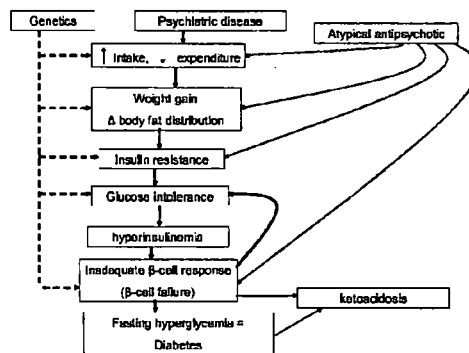
3. PHYSIOLOGY

3.1. Introduction

Given the complexity of the pathogenesis of diabetes, the role that antipsychotics may play in the development of hyperglycemia is not straightforward. The potential pathways that may be affected by atypical antipsychotic medications are illustrated in Figure 2. Certain antipsychotic medications may cause increased food intake and/or decreased energy expenditure, leading to weight gain and changes in body fat distribution, and this is well correlated with insulin resistance. In addition to these indirect effects through weight gain, particular medications may also directly impair insulin sensitivity or damage beta-cell function.

To investigate these complicated issues, several studies have been conducted to evaluate the potential diabetogenic effects of the 6 commonly used atypical antipsychotics. The results consistently show that some of these drugs are diabetogenic, and that benzisoxazoles (e.g., risperidone) are associated with significantly less risk of hyperglycemia than the chemically distinct dibenzodiazepines (e.g., olanzapine, clozapine). Further, preliminary data have suggested one mechanism by which olanzapine may contribute to glucose dysregulation, based on a pharmacodynamic property that has not been observed for risperidone.

Figure 2: Possible Pathways by Which Atypical Antipsychotic Treatment May Result in Diabetes



3.2. Diabetes Pathophysiology

In healthy individuals, the fasting glucose concentration ranges between 80 mg/dL (4.4 mmol/L) and 110 mg/dL (6.1 mmol/L). Overt diabetes mellitus is defined by the American Diabetes Association (ADA) as fasting glucose concentration in excess of 126 mg/dL (7.0 mmol/L).

Type 1 diabetes is caused by autoimmune destruction of the beta-cells of the pancreatic islets. Approximately 0.5% of the U.S. population is diagnosed with Type 1 diabetes, which has a rapid onset and must be treated by insulin therapy. Inappropriate therapy can result in diabetic ketoacidosis, which is associated with overproduction of ketoacids by the liver in the absence of sufficient insulin. The appearance of fasting hyperglycemia is associated with destruction of 80-90% of the beta-cells, and untreated Type 1 diabetics have nearly undetectable levels of insulin.¹

Type 2 diabetes is much more prevalent in westernized societies. Type 2 diabetes was previously known as "adult-onset," because of the prevalence of the diagnosis in adults. Since Type 2 diabetes is now being diagnosed in prepubertal children, this term is no longer appropriate.

The precise etiology of Type 2 diabetes is considerably less well understood than that of Type 1. Obesity is a major cause of resistance to the actions of insulin, but it is neither sufficient nor required for disease.² Although the exact relationship between obesity and insulin resistance has not been elucidated, many factors have been investigated, including the effects of certain proteins secreted by adipocytes on insulin sensitive tissues (liver and muscle), and the effects of free fatty acids (FFA) released by adipose cells under fasting conditions and present at higher levels in diabetic patients.³ FFA are known to induce insulin resistance in liver as well as skeletal muscle.^{4,5} It is possible that the release of FFA from adipocytes, which are naturally insulin resistant, may cause accumulation of triglycerides in liver and skeletal muscle and result in whole-body insulin resistance.

Unlike Type 1 diabetes, insulin levels are not zero in Type 2 diabetes; in fact, the concentrations are commonly normal and often above normal. Reduction in insulin sensitivity in normal individuals elicits a compensatory increase in insulin secretion. Eventually, beta-cell function is no longer able to compensate for progressive insulin resistance, and hyperglycemia ensues. Type 2 diabetes can be understood as a disease in which insulin resistance is

associated with a later beta-cell defect; this only becomes obvious after beta-cell function diminishes to approximately 20% of normal. Therefore, most cases of Type 2 diabetes reflect a "2-hit" phenomenon: insulin resistance followed by progressive beta-cell defect.⁶⁻⁹

The events that occur during the use of certain atypical antipsychotic medications result in a metabolic profile with many characteristics in common with Type 2 diabetes. There are, however, important features of the profile that are very rare in cases of Type 2 diabetes. Not the least of these is the occurrence of diabetic ketoacidosis. Thus, the glucose intolerance, which has been associated with atypical antipsychotic therapy must be understood in the context of the pathogenesis of both Type 1 *and* Type 2 diabetes, since the profile of events associated with this therapy has elements of both.

3.3. The Effect of Atypical Antipsychotics on Glucose Homeostasis

3.3.1. Schizophrenic Patients as an At-Risk Population

Patients with schizophrenia, even when untreated, are more likely to develop diabetes than normal healthy individuals in the general population. An association between schizophrenia and diabetes was detected as early as the 1920's.¹⁰ Psychiatric disease can lead to changes in energy intake and expenditure. There is some evidence that patients with schizophrenia have greater visceral adiposity than healthy individuals.¹¹ Based on a significant body of evidence from the general population, the correlation between visceral fat depot and insulin resistance is high.^{12,13} Smoking, which is very common among patients with schizophrenia,¹⁴ is an additional factor which exacerbates increased insulin resistance. Given this background, it is predicted that, with an increase in weight/adiposity in this at-risk population, beta-cells will mount a greater than normal insulin response, and as discussed above, beta-cells will eventually fail to mount a supranormal insulin response, with a result of hyperglycemia.

Since there is underlying pathology in the glucose metabolism of at least some patients with schizophrenia, the metabolic response of any individual schizophrenic to an atypical antipsychotic is determined by the environmental factors (i.e., food intake, smoking, etc.), as well as by genetic predisposition for weight maintenance,^{15,16} insulin resistance,^{17,18} and pancreatic function.^{19,20}

Because multiple interacting factors are involved in an individual patient's response to antipsychotic treatment, it is imperative to fully evaluate and recognize the documented differences among various antipsychotic medications. This will provide invaluable assistance to prescribers when choosing the antipsychotic treatment most suitable for each patient.

3.4. Adiposity as the Precursor to Diabetes

Many antipsychotic medications are associated with increased body weight, albeit to different degrees.²¹ Among the commonly used atypical agents, clozapine is reported to have the largest effect, followed by olanzapine and quetiapine. A smaller effect has been associated with risperidone; aripiprazole and ziprasidone have little overall effect on body weight.^{21,22}

To compare the mechanisms of action related to glucose dysregulation exerted by different atypical antipsychotics, it is important to evaluate changes in both weight gain and fat deposition, since a significant body of evidence has implicated the intra-abdominal fat depot as the greatest contributor to insulin resistance. However, the relationship between weight gain and body fat distribution with these drugs is less clear.

3.4.1. Body Weight

Very little is known about the causes of weight increase or change in the distribution of fat in the body associated with antipsychotics. In rodents, clozapine and olanzapine increase food intake;²⁰ little data are available for the effect of risperidone in rodents.^{21,23} However rodents have not been considered a good model for antipsychotic-induced weight gain because of extensive sedation that results from treatment, and this affects both food intake and energy expenditure.²⁴ In a prospective study evaluating food intake and activity levels in schizophrenic males treated with olanzapine and haloperidol over 4 weeks, Gothelf et al. found body mass index (BMI) increased in the olanzapine group, but not in the haloperidol group.²⁵ The observed change in BMI was attributed to an increase in caloric intake.

While weight gain associated with atypical antipsychotic drugs is likely a result of increased food intake, the data about changes in energy expenditure are less clear. It is very difficult to measure food intake and energy expenditure accurately in schizophrenic patients. To evaluate this parameter and the potential effects of each medication, it is important to measure the relative effects on energy expenditure and food intake under controlled

conditions that account for changes in body weight. In the study by Gothelf et al, neither antipsychotic had a significant effect on resting energy expenditure. Additional studies in energy balance need to be conducted.

3.4.2. Weight Gain and Body Fat Distribution

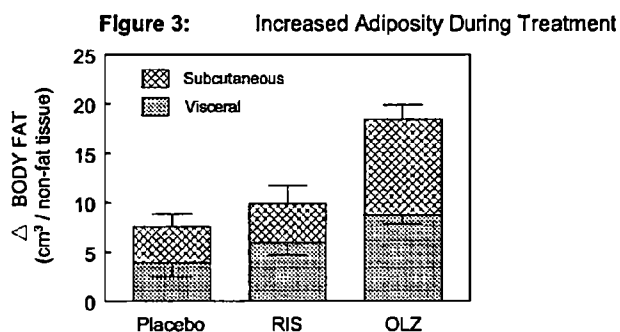
An additional issue of concern is the distribution of increased fat storage in patients taking these medications. Use of dual-energy X-ray absorptiometry (DEXA) allows for excellent estimation of total fat as a percentage of body weight.²⁶ Such an approach allows for comparison of lean versus fat body mass in the presence of drug therapy. The use of imaging techniques such as computer tomography (CT) scans or MRI can also be used to quantify distribution of body fat in the visceral versus the subcutaneous compartments. Preferential distribution of fat in the visceral compartment would account for greater risk of insulin resistance, and hence for diabetes itself.

Thakore et al report on CT scans in schizophrenics not on drug (naïve or off drug) versus normal but lean patients.¹¹ Strikingly, abdominal fat in these schizophrenic subjects was 3-fold that in the normal lean patients. In another study using abdominal CT, Ryan and Thakore corroborated this finding; significantly greater visceral fat (mean value) was present in the schizophrenic group versus healthy controls (subjects with schizophrenia, 116.8 cm² [SD=20.2] versus healthy subjects, 38.3 cm² [SD=4.8]; $p < 0.0001$).²⁷ After 6 months of olanzapine (n=6) or risperidone (n=10) treatment in the schizophrenic subjects, a nonsignificant mean increase from baseline in visceral fat was measured for both treatment groups. A numerical, but not statistically significant, difference in the mean increase was observed between the 2 groups (olanzapine, 26.9 cm² [SD=12.1] versus risperidone, 18.24 cm² [SD=11.44]; $p < 0.63$, favoring risperidone treatment).

In a comparative study of the diabetogenic effects of antipsychotic drugs, Bergman and Ader treated mongrel dogs (10 risperidone, 10 olanzapine, and 6 placebo) and found modest changes in body weight in all groups.²⁸ Overall, these data show that weight gain during olanzapine may be explained, at least in part, by increased food intake; dogs consumed a statistically significant excess of calories during the entire treatment period. Risperidone-treated dogs showed a marginal, nonsignificant upward trend in weight, and food intake was not appreciably altered by risperidone.

Placebo- treated dogs exhibited a steady upward trend in body weight with a trend toward increased food intake.

In contrast to very modest changes in body weight, abdominal MRI revealed that adiposity was increased differently in the 3 treatment groups (Figure 3). Placebo- and risperidone-treated dogs exhibited modest and comparable increases in adiposity. In contrast, fat deposition was dramatic in olanzapine-treated dogs; total trunk fat nearly doubled in all dogs, from $24.9 \pm 3.2 \text{ cm}^3$ to $43.4 \pm 3.9 \text{ cm}^3$ ($p < 0.001$). Fat accumulation from olanzapine was 2-fold greater than that observed with risperidone treatment in total ($p = 0.018$) and subcutaneous ($p = 0.024$) compartments, and tended to statistical significance in visceral fat accumulation (olanzapine, $8.7 \pm 0.9 \text{ cm}^3$; risperidone, $5.9 \pm 1.3 \text{ cm}^3$; $p = 0.091$).²⁸



Gene expression (messenger RNA levels) of key factors involved in lipid turnover and fat accumulation were also measured. In suggestive data from 4 randomly chosen dogs from each treatment group, adipose tissue from olanzapine-treated dogs exhibited approximately 50% higher expression of the gene for nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR γ) when compared to either risperidone- or placebo-treated animals. PPAR γ has been implicated in a wide array of physiological and pathological processes ranging from adipocyte differentiation to lipid trafficking to insulin resistance. Although very preliminary, these data raise the possibility that the increase of body fat deposition observed in the olanzapine-treated animals may be associated with an increase in fat cell accumulation mediated by genetic factors including PPAR γ . PPAR γ was not different between risperidone- and placebo-treated animals, groups that also did not differ in the degree of fat deposition.²⁹

3.5. Pathways to Diabetes With Antipsychotic Medication

Changes in weight gain and adiposity suggest possible indirect explanations for the insulin resistance observed in antipsychotic-treated patients. To assess the more direct effects of atypical antipsychotics on glucose metabolism, however, additional measures of insulin secretion and resistance are necessary. The following methodologies have been employed to make these direct measurements: (1) the Euglycemic Insulin Clamp, (2) the FSIVGTT, and (3) the HOMA.

Insulin Clamp: The euglycemic clamp is a highly reliable and most frequently recommended methodology for the measurement of insulin sensitivity. This method assesses beta-cell sensitivity by quantifying the amount of glucose metabolized by the body following a controlled hyperglycemic infusion. Two insulin clamp methodologies have been used in studies evaluating antipsychotic-induced diabetes: the euglycemic clamp and the hyperglycemic clamp. The euglycemic clamp is a technique used to assess insulin sensitivity. The hyperglycemic clamp is used primarily to measure beta-cell secretory function. Insulin acts on the liver to reduce gluconeogenesis and glycogenolysis, which normally occurs during periods of fasting. Radiologic tracers are employed to distinguish changes in the liver's response to insulin from those in the periphery, where glucose is utilized for energy.

FSIVGTT with Minimal Model Analysis: The Minimal Model is a complex set of calculations that uses individual patient data from the FSIVGTT. Since insulin causes glucose to fall and glucose causes insulin to rise, the complete feedback loop can be mathematically analyzed from frequently-obtained blood samples to quantify numerous glucoregulatory parameters. In contrast to clamps, this technique allows for the simultaneous assessment of insulin secretion and insulin sensitivity in a single individual, which is important when quantifying their relative role in the evolution of diabetes.

HOMA: HOMA analysis can estimate insulin sensitivity (IR) without employing complex procedures. HOMA-IR relies on the use of fasting insulin and glucose levels to calculate insulin resistance [insulin resistance = (fasting glucose x fasting insulin)/ 22.5]. Although correlations between HOMA-IR and measures of insulin resistance by FSIVGTT and clamps are good, this methodology does not produce results as reliable as the 2 previous complex models described. Also, HOMA gives an estimate only of basal

insulin resistance; in contrast, insulin clamps and FSIVGTT provide estimates of stimulated insulin resistance.

3.5.1. Fasting Values

Insulin resistance is often estimated from fasting glucose and insulin concentrations. Many reports on hyperglycemia in schizophrenics treated with antipsychotics have reported fasting insulin levels to be higher than those in lean normal subjects; this is not unexpected for obese subjects on atypical antipsychotics who are likely to be insulin resistant. For example, Melkersson and Dahl³⁰ report hyperinsulinemia in over half of the obese subjects on clozapine or olanzapine. In contrast, subjects on risperidone did not display elevated fasting insulin.³¹

From Melkersson's data,³⁰ the HOMA-IR index may be calculated; for patients on classical antipsychotics, the index is 3.97 versus 4.26 for the patients on clozapine. A greater difference in the HOMA-IR values was reported by Cohn;³² values were 3.1 for patients on clozapine or olanzapine, versus 2.0 for those on risperidone, quetiapine or typical antipsychotics grouped together.

Using HOMA-IR, Ebenbichler calculated insulin resistance at baseline and after 8 weeks of treatment in patients treated with olanzapine (n=10) versus healthy controls (n=10). In the olanzapine-treated patients, the index increased significantly (p=0.006); in contrast, the control groups were stable. These findings corresponded to significant increases in weight and body fat in the olanzapine-treated patients, but not in the control subjects. There were no changes in HOMA-insulin secretion for either group.³³

Numerous other cross-sectional and prospective studies support the consistent pattern that olanzapine and clozapine are associated with elevations in fasting glucose and insulin levels. These studies reported that this is not observed for risperidone, other atypical, and conventional antipsychotic medications.

- Hagg et al reported the prevalence of Type 2 diabetes and Impaired Glucose Tolerance (IGT) among clozapine patients to be 22% compared with 10% in the control group (p=0.06).³⁴
- Chue and Welch reported a higher incidence of diabetes (fasting glucose > 126 mg/dL) among clozapine- (15%) and olanzapine-treated

(11%) patients versus those using conventional agents (6%) or risperidone (0%).³⁵

- During a 14-week trial, Lindenmayer found significant glucose elevations at 6 weeks for clozapine and haloperidol and at 14 weeks for olanzapine; in contrast, risperidone did not have an effect at either timepoint.³⁶ (It should be noted that other studies have reported no significant glucose elevations associated with haloperidol treatment. The reason for the disparity in the results of Lindenmayer is not clear.)
- Glick measured HOMA-IR in 268 schizophrenic patients randomly assigned to receive olanzapine or ziprasidone. A significant increase in insulin resistance (HOMA-IR) between baseline and Week 6 was observed in the olanzapine group ($p=0.0002$), but not in the ziprasidone group.³⁷

Taken together, these data indicate that clozapine and olanzapine may induce greater insulin resistance than other agents. However, fasting insulin is not a direct measure of insulin resistance. Reports of fasting-based measures of insulin resistance and/or insulin secretory function can only be regarded as suggestive of mechanistic changes. To identify and compare mechanisms of action by which different antipsychotic agents affect glucose metabolism, additional studies are needed.

3.5.2. Glucose Tolerance Tests

The oral glucose tolerance test (OGTT) has long been available as a diagnostic test for various "pre-diabetic" states.^{38,39} In this test, a specified dose of glucose (usually 75 g) is given orally, and plasma glucose and insulin are measured over 2 or more hours after administration; the results represent a qualitative measure of an individual's ability to respond to carbohydrate. If the glucose pattern is elevated, this ability is considered to be diminished. When both the glucose pattern and the insulin pattern are elevated, this is compelling evidence of the reduced ability of insulin to affect glucose disposal, i.e., insulin resistance.

Newcomer et al measured insulin resistance using a modified OGTT in treated schizophrenic and healthy volunteer subjects with matching groups for BMI and age.⁴⁰ Postload glucose was significantly elevated in clozapine- and olanzapine-treated subjects compared to subjects treated with typical agents and to untreated healthy control subjects. Elevations in fasting and postload glucose levels were also observed in risperidone-treated subjects, but they differed significantly only in comparison with untreated healthy control subjects, and not with typical agents. Modest increases in fasting

insulin levels were observed in all treatment groups, but occurred at a greater degree with olanzapine or clozapine treatment. Further, increases in HOMA-IR values were detected only in subjects treated with olanzapine and clozapine compared to patients taking typical antipsychotics.

In studies by Chue, Kurt, and Smith, OGTT was also performed in schizophrenic patients treated with atypical and conventional antipsychotics. Although no differences in HOMA values were observed, numerous significant changes in a variety of glucoregulatory parameters were evident. These differences confirm and extend previous observations of dissimilarities between olanzapine and clozapine compared to other antipsychotics.

In a separate study, Chue et al evaluated patients treated with clozapine (n=51), olanzapine (n=35), risperidone (n=33), or conventional antipsychotics (n=36) and found that the prevalence of diabetes was greatest with clozapine (15%), followed by olanzapine (12%), conventional antipsychotics (6%), and risperidone (0%).⁴¹ Elevated fasting serum insulin, elevated plasma glucose, obesity and hypertriglyceridemia were significantly more prevalent in olanzapine- and clozapine-treated patients compared to patients on risperidone. Olanzapine and clozapine resembled each other most closely on the 3 largest discriminant function coefficients – fasting plasma glucose, BMI, triglycerides — while risperidone was most similar to conventionals on these factors. Although in the first study performed by Chue et al and in that published by Prior, clozapine was associated with the highest glucose elevations, followed by risperidone and then olanzapine, these results must be interpreted with caution due to small numbers (10 or fewer subjects) in each treatment arm.⁴²

Kurt et al reported that clozapine was associated with significantly increased fasting glucose levels ($p=0.04$).⁴³ In a cross-sectional study in patients treated with risperidone, olanzapine, clozapine, or conventional antipsychotics, Smith et al observed no differences in fasting glucose, insulin or HgbA1c (results controlled for demographic factors).⁴⁴ The nonrandom assignment of drugs must be considered in the interpretation of this and all cross-sectional studies. Physicians may not readily prescribe olanzapine to patients at risk for diabetes (e.g., obesity or strong family history), and therefore, the risperidone sample may potentially be enriched with prediabetic patients.

Taken together, OGTT data suggest that certain atypical antipsychotics (e.g., olanzapine and clozapine) reduce glucose tolerance, while others do not (e.g., risperidone, conventional). The elevations of glucose observed suggest insulin resistance, which may be due to increases in weight or body fat mass. However, other physiological changes that affect insulin sensitivity, beta-cell function, and glucose effectiveness could account for the altered tolerance observed with some of these agents.

3.5.3. Direct Measures of Metabolic Processes-Minimal Model Analysis

Using FSIVGTT (see Section 3.5), Cagliero and Henderson conducted a cross-sectional study in non-obese schizophrenic patients treated either with clozapine, olanzapine or risperidone.³¹ Results showed a pronounced insulin resistance in non-obese patients taking clozapine or olanzapine (insulin sensitivity index, $S_I = 2.4 \pm 0.7$ vs. $4.2 \pm 0.8 \text{ min}^{-1} \text{ per } \mu\text{U/mL} \times 10^{-4}$). In contrast, risperidone was not associated with insulin resistance ($11.0 \pm 2.2 \text{ min}^{-1} \text{ per } \mu\text{U/mL} \times 10^{-4}$). Analysis of other parameters in this study that were consistent with these results provide supportive evidence, including insulin levels and HOMA-IR values that were elevated with clozapine and olanzapine, but not risperidone. In these lean patients, no differences in diet, activity level, or energy expenditure among the 3 drugs were noted, suggesting that the differences with treatment were directly related to insulin sensitivity. Beta-cell function was also assessed by measuring 20-minute insulin levels; no differences were found between the agents. This report is 1 of the few available studies in which insulin resistance that could not have been mediated by obesity could be quantitatively assessed. In this non-obese schizophrenic population, a substantial difference among the tested drugs in terms of relative effects on insulin resistance was clearly documented.

3.5.4. Direct Measures of Metabolic Processes-Insulin Clamp Studies

In two insulin clamp studies, Sowell, Beasely, and colleagues studied the effects of risperidone, olanzapine, and placebo on insulin sensitivity and beta-cell function.^{45,46} The euglycemic clamp was used in one study to measure insulin sensitivity and, in a second study, the hyperglycemic clamp was used to measure beta-cell function.

Sowell performed hyperglycemic clamps in normal volunteers, tested at baseline and after administration of olanzapine, risperidone, or placebo. The hyperglycemic clamp was used to measure beta-cell function as well as an index of insulin resistance (glucose infusion/change in insulin at hyperglycemic steady-state). The clamps were performed after diet stabilization. Following baseline measurement, subjects were put on medication and counseled to maintain an isocaloric diet throughout the 15-17 days of therapy. Within-group comparison of olanzapine subjects from baseline to endpoint showed development of statistically significant increases in insulin resistance ($p=0.038$) and compensatory insulin secretion ($p<0.01$). Compared to placebo-treated subjects, increases in insulin secretion in the olanzapine group were statistically significantly higher ($p<0.001$), while decreases in sensitivity were not. In contrast, from baseline to endpoint, risperidone subjects experienced neither significantly increased resistance nor secretion ($p=0.157$ and $p=0.054$, respectively). Compared to placebo, there were no statistically significant differences in insulin sensitivity, although the increase in insulin secretion represented a significant increase versus placebo ($p=0.014$). The reason for this rise is not clear, since it did not represent a compensatory response to worsening insulin resistance, as was observed in olanzapine subjects. This observation requires further investigation.

The authors performed multivariate regression analysis to adjust the changes in insulin sensitivity and secretion for weight gain. With this reanalysis, the effect of olanzapine treatment on insulin secretion or sensitivity did not persist. As described above in the study in dogs, olanzapine was associated with increases in visceral adiposity, which play an important role in the pathogenesis of insulin resistance. It should therefore be noted that, since this adjustment was performed for weight gain rather than adiposity, the finding of "equivalent drug effect" may be unsubstantiated when the parameter is adiposity.

The greatest methodological limitation of this study is the method chosen to measure insulin secretion (the objective of this study). Both insulin secretion and insulin sensitivity must be assessed concurrently. The authors understood the need for assessing insulin secretion with insulin sensitivity, but employed a poor means of measuring it: the hyperglycemic clamp. During hyperglycemic clamps, both glucose and insulin are elevated. Since

both glucose and insulin exert similar actions to increase glucose uptake into tissues and to suppress glucose production by the liver, measurement of glucose uptake or production during hyperglycemic clamps cannot be assumed to reflect insulin sensitivity alone. Without an accurate sensitivity assessment, the secretion results are not interpretable. If drugs *only reduce insulin sensitivity*, insulin secretion increases to compensate for the reduced action of the insulin. If drugs *reduce both insulin sensitivity and insulin secretion*, one may observe no change in secretion from predrug baseline. This scenario would lead to a false interpretation that the drugs did not impair the pancreas, when in fact they did, because a "healthy" pancreas would have increased secretion to compensate for reduced sensitivity.

To assess insulin sensitivity more accurately, Beasley performed euglycemic clamps in a separate group of volunteers with methods similar to the hyperglycemic clamp protocol.⁴⁵ Weight gain was reported for olanzapine and risperidone over the 3-week period (~1.5 kg over 3 weeks), with no change in weight in the placebo group. No difference between agents was reported in insulin sensitivity (glucose infusion rate during clamps divided by change in insulin) at low or high insulin infusion rates. The reason for the absence of change in glucose infusion during clamps despite the weight gain should be investigated further since the correlation between BMI and insulin resistance from clamps in non-obese individuals is strong.⁴⁷ Specific changes in insulin sensitivity of muscle or liver may have occurred, but were masked because the specific effects of insulin on these separate components were not assessed.

There are some further methodological problems common to both studies. In these non-obese volunteers, caloric restriction would limit drug-induced weight and adiposity gain, minimizing the true metabolic response to these drugs. Also, epidemiology data suggests that the 2- to 3-week exposure time may be inadequate for the onset of detectable drug effects. Additionally, patients at greatest risk for developing glucose dysregulation (e.g., schizophrenics or patients with a family history of diabetes) were excluded from both trials, decreasing the likelihood that beta-cell function defect and ensuing hyperglycemia would be observed in the subjects. Finally, insulin data are sometimes extremely variable, and may drastically limit statistical power to detect differential treatment effects. The standard deviations for insulin measurements are large in these studies, especially in the olanzapine

group using the hyperglycemic clamp. It is doubtful the study possessed the sufficient statistical power to detect differences between drugs or between drugs and placebo.

In summary, these limitations emphasize that it cannot be concluded on the basis of these studies that olanzapine and risperidone have comparable effects.

3.5.5. Mechanistic Studies in Dogs

While the results from all of the previously described studies have suggested a link between some atypical antipsychotics and the development of diabetes, there are significant obstacles to proving causation for any. Most notably, schizophrenics have an increased predisposition to diabetes^{48,49} and no studies on drug effects have been performed in drug-naïve individuals. Since it is not known whether the diabetogenic agents cause reversible or irreversible effects, prior treatments can be confounding. Also, polypharmacy is common in schizophrenia, making it difficult to determine the direct effect of atypical medications from those of co-medications such as valproate, which itself has been associated with pronounced weight gain and fasting hyperinsulinemia.^{50,51} Furthermore, substance abuse (e.g., nicotine, cannabis, cocaine) is extremely common in patients with schizophrenia and bipolar disorder, and can affect glucose metabolism. Such use will obscure the assessment of the metabolic effects of antipsychotics.^{14,52} Finally, most studies have been conducted on an outpatient basis, making it difficult to ensure compliance in taking medications and maintaining adequate records of food intake and activity.

Therefore, Ader and Bergman have examined the metabolic effects of olanzapine, risperidone, and placebo in mongrel dogs.²⁸ An animal model permits the use of radiolabeled glucose tracer dilution methods to assess insulin sensitivity directly in skeletal muscle versus liver and the ability to perform more invasive investigations (e.g., complete autopsy with brain, adipose tissue and pancreatic histopathology). Based on the results of this study, the authors have elucidated a plausible mechanism of action for olanzapine-induced glucose dysregulation, not shared by risperidone: severe impairment of hepatic insulin resistance and the disposition index.

The study was divided into 2 phases: 1) baseline (predrug) testing, and 2) "postdrug" period. Prior to study entry, dogs were randomly assigned to

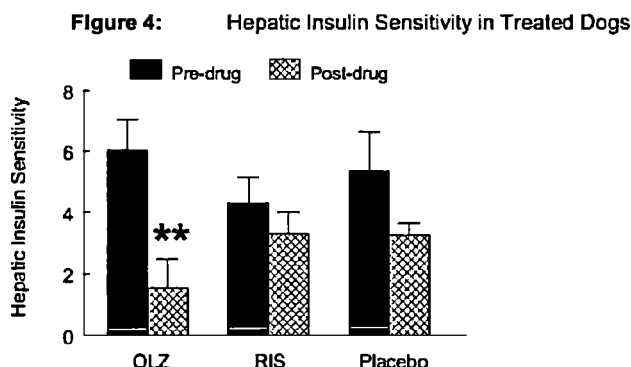
1 of 3 treatment arms: olanzapine (15 mg), risperidone (5 mg), or placebo. Predrug testing was performed to quantify insulin sensitivity and trunk adiposity. The order of experiments was randomized, and studies were performed in each animal over a 10-day period, with at least 2 days between experiments. After predrug testing, dogs were placed on drug or placebo regimen for 4 to 6 weeks, after which all procedures performed during predrug phase were repeated ("postdrug") under conditions identical to predrug testing. Drug treatment was continued during the entire postdrug testing period. Body weight was measured twice weekly between pre- and postdrug testing.

During predrug and postdrug periods, all animals underwent 3 procedures, performed in random order: (1) the euglycemic hyperinsulinemic clamp (EGC), to quantify hepatic and peripheral insulin sensitivity, (2) beta-cell stepwise stimulation test (STEP test), to quantify glucose-stimulated insulin secretion, and (3) abdominal MRI, to assess treatment-induced changes in adiposity.

As described above, olanzapine administration was associated with profound increases in adiposity and total fat, reflecting marked increases in both subcutaneous and adipose stores. Olanzapine-associated increase in total adiposity greatly exceeded the observed increase in fat deposition in risperidone-treated animals ($p=0.018$). In contrast to olanzapine, changes in adiposity with risperidone administration were not different from that observed in placebo animals ($p>0.33$).

While peripheral insulin sensitivity was similar before treatment and not significantly altered by treatment in any group, there were differences between drugs on alterations in hepatic insulin sensitivity. Insulin-mediated suppression of glucose production from the liver was significantly affected by olanzapine (Figure 4). All 10 olanzapine-treated dogs were affected. Prior to olanzapine treatment, hepatic glucose output was appropriately suppressed ($>90\%$) during the clamp studies, but olanzapine exposure caused hepatic insulin sensitivity to decline from 6.1 ± 1.0 to 1.5 ± 0.9 dL/min per kg per $\mu\text{U/mL}$ ($p=0.009$; Figure 4). A significant reduction in liver insulin sensitivity with risperidone was not observed (pre: 4.3 ± 0.8 , post: 3.0 ± 0.9 dL/min per kg per $\mu\text{U/mL}$; $p=0.35$), although the mean was reduced. Also, there was no significant change in hepatic insulin sensitivity in

placebo-treated dogs (pre: 5.4 ± 1.3 , post: 3.3 ± 0.4 dL/min per kg per $\mu\text{U/mL}$; $p=0.12$).⁵⁴



As discussed earlier, reduction in insulin sensitivity elicits a compensatory increase in insulin secretion. Thus, a given reduction in insulin sensitivity elicits a proportionately equal, but opposite, change in insulin secretion; in fact the product of insulin secretion times insulin sensitivity is a constant, which has been defined as the disposition index (DI).⁵³ Because the disposition index is a measure of the *ability* of the beta-cells to compensate for insulin resistance, and thus maintain glucose tolerance within normal bounds, it is an excellent marker for beta-cell health.

In this study, a significant reduction in the DI after 4 weeks of treatment with olanzapine was observed (pre: 28.5 vs. post 22.1; $p=0.021$). In contrast, the DI was not altered by either risperidone (pre: 22.7 vs. post: 21.8; $p=0.45$) or placebo (pre: 28.8 vs. post: 40.3; $p=0.80$).⁵⁴ This study emphasizes the need to assess insulin secretory function in the context of concomitant quantitative measures of insulin sensitivity, as the present secretory defects were only manifest when secretion was observed to be inadequate for the prevailing degree of insulin resistance.

It is unknown whether changes in hepatic insulin sensitivity and the DI are due to effects on the central nervous system (CNS) or whether these drugs act directly on the liver, pancreas or peripheral tissues. Indeed there is some evidence that the CNS plays a contributory role in glucose homeostasis.⁵⁵ Further research is required to reveal the extent to which metabolic effects are mediated by direct neural actions. In summary:

- Olanzapine causes substantial increases in adiposity – both in visceral and subcutaneous fat depots. In contrast, risperidone did not increase adiposity beyond that observed in placebo animals.
- Olanzapine and risperidone had different effects on insulin action in dogs. Olanzapine caused a statistically significant reduction in hepatic insulin sensitivity, i.e., insulin could no longer suppress glucose production. Little net effect of risperidone on hepatic insulin sensitivity was observed.
- Finally, and most significantly, the insulin resistance due to olanzapine was not adequately compensated for by the expected increase in insulin secretion. Therefore, olanzapine, but not risperidone or placebo treatment, caused a significant reduction in pancreatic beta-cell function.

3.5.6. Life-Threatening Complications: Diabetic Ketoacidosis

There have been numerous reports of atypical antipsychotic-related diabetic ketoacidosis, a condition that is seen more frequently in Type 1 than in Type 2 diabetes. For DKA to occur, there must be a near complete absence of insulin or severe glucose toxicity. To understand how certain agents could so severely impair beta-cell function, insulin secretion must be accurately quantified using clamps in predisposed individuals. Given the rarity and unpredictability of this phenomenon, such prospective studies are impossible to perform. However, retrospectively studying individuals with antipsychotic-induced DKA for assessment of insulin secretory function provides very useful data in further understanding these very disturbing events.

Avram reported a case of a 33-year-old man treated with clozapine for 5 months who developed DKA.⁵⁶ After resolution of his acute illness and discontinuation of clozapine, an OGTT, FSIVGTT, and euglycemic clamp were performed at different times. Despite a normal OGTT, he was shown to have both impaired sensitivity and secretion by the more sophisticated methods.

The authors hypothesized that the mechanism by which clozapine may produce glucose intolerance may require a preexisting latent defect in insulin secretion and insulin action. With the administration of clozapine, the subject may have developed worsening insulin resistance and failed to mount an appropriate compensatory insulin secretion for the degree of insulin resistance. As a consequence, hyperglycemia developed and its persistence resulted in glucose toxicity, further suppressing secretion. The synergistic

defects in secretion and sensitivity lead to the development of abnormal glucose tolerance, which can be clinically manifested as a spectrum ranging from impaired glucose tolerance through severe hyperglycemia to DKA.⁵⁶

Except for the preliminary work by Avram, there exist very few other physiology studies in patients experiencing DKA.

3.5.7. Hyperlipidemia

Given the known causal relationship between weight gain, adiposity, and insulin resistance with elevations in lipid levels, it is not surprising that there have been numerous reports and a few studies demonstrating antipsychotic-associated hyperlipidemia, particularly hypertriglyceridemia. The mechanism of action for these observed changes is not clear. Consistent with the body of evidence that demonstrates greater weight gain and diabetes risk associated with olanzapine and clozapine, hyperlipidemia has been linked more strongly to these medications than to other atypical antipsychotics.^{36,41,57-60} Furthermore, a recent report demonstrated differences among atypical antipsychotics in relation to the risk for pancreatitis, which could possibly be related to the observed differences in effect on triglycerides.⁶¹ At this time, the data on hyperlipidemia is preliminary, and while patterns are emerging, significantly more research is required to understand how atypical antipsychotic exert effects on lipid metabolism.

3.6. Conclusion

There have been significant advances over the past 6 years in the understanding of glucose dysregulation in patients treated with atypical antipsychotics, including early reports to the FDA, retrospective epidemiology studies, and the sophisticated and well-validated assessments of insulin sensitivity and beta-cell function that are currently available today.

Since patients with schizophrenia have increased risk of developing diabetes, patients on any antipsychotic, including risperidone, will inevitably develop hyperglycemia. However, no study specifically designed to evaluate the diabetogenic risk of risperidone has documented any significant association. While acknowledging methodological limitations, studies that evaluate elevations of fasting insulin, glucose, or HOMA-IR values failed to demonstrate risk associated with risperidone. Further, numerous OGTT studies showed that risperidone does not impair the body's ability to dispose

of carbohydrates. A cross-sectional study employing the minimal model detected reduced insulin sensitivity associated in patients treated with certain other atypical antipsychotics, but did not detect abnormalities in risperidone-treated patients. Finally, a well-designed study employing an animal model found marked abnormalities associated with olanzapine, but failed to distinguish between risperidone and placebo on all parameters tested.

Two small insulin clamp studies failed to differentiate an effect between risperidone and olanzapine on insulin resistance, but this likely represents a "false negative" due to flaws in the study design and data interpretation. Overall, the weight of evidence from the available physiological data support that significant differences exist among atypical antipsychotics, particularly between risperidone, a benzisoxazole, and the chemically distinct dibenzodiazepines (e.g., olanzapine) for risk of glucose dysregulation. The increased risk associated with olanzapine and clozapine may be due to their greater propensity for inducing weight gain, and more importantly fat deposition. The study in dogs has raised the possibility that, for olanzapine, one mechanism of action in the development of insulin resistance and beta-cell impairment is mediated at the genetic level, resulting in markedly increased visceral fat stores, which is documented to impair hepatic insulin resistance. This abnormality was not observed for risperidone.

In summary, the available physiologic studies strongly suggest that a "class effect" on glucose homeostasis among these chemically distinct compounds does not exist a priori, but rather that certain antipsychotics (e.g., clozapine or olanzapine) have diabetogenic potential, whereas others (e.g., risperidone) do not. Clearly more research into this issue using sophisticated and well-validated tools, such as the clamp, minimal model and imaging techniques, will provide more compelling data and understanding.

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4. CLINICAL TRIALS

The data from over 12,000 subjects treated in short-term (≤ 3 months) and over 7500 treated in long-term (≥ 6 months) Phase 2, 3 and 4 trials conducted and analyzed by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (formerly Janssen Research Foundation) were collected for a review of adverse events associated with abnormalities in glucose metabolism. The program consisted of trials with all formulations of risperidone. The trials were not specifically designed to measure the impact of risperidone on glucose metabolism. Information was derived from adverse event reports.

Indications studied included schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar mania, dementia and behavioral disturbances (mainly in elderly subjects), and conduct or other disruptive behavior disorders (mainly in children and adolescents). Trial medication doses given for indications other than schizophrenia and bipolar disorder were generally lower.

The data presented in this section are provided in further detail in the Clinical Trials Appendix to this report; this includes a detailed listing of the specific clinical studies from which data were pooled for the in-text tables, and additional data for and discussion of subgroup analyses.

4.1. Adverse Events

The following were considered glucose-related adverse events: metabolic acidosis, decreased blood sugar, increased blood sugar, diabetic coma, hyperosmolar, diabetes mellitus, diabetes mellitus aggravated, diabetes mellitus deteriorated, new onset diabetes mellitus, diabetes mellitus precipitated, diabetes mellitus reactivated, diabetic ketoacidosis, abnormal glucose tolerance, glucose tolerance decreased, abnormal glucose tolerance test, glycosuria, hyperglycemia, hypoglycemia, hypoglycemic reaction, ketoacidosis, and ketonuria. For all age groups combined, in short-term trials (≤ 3 months) the incidence of reported glucose-related adverse events was low among risperidone-treated subjects (0.72% of 8458 subjects) and comparable to the incidence among placebo-treated subjects (0.88% of 1825 subjects) and olanzapine-treated subjects (0.93% of 536 subjects). In the long-term trials (≥ 6 months), the incidence of glucose-related adverse events was comparable between risperidone treatment (1.49% of 6590

subjects) and the typical agent, haloperidol (1.55% of 579 subjects), and tended to be lower than in olanzapine-treated subjects (1.66% of 300 subjects). There were no placebo-controlled long-term trials.

Table 5 shows the incidence of glucose-related adverse events in short-term trials only. In these trials, no glucose-related adverse events were reported in the pediatric population. In adults, the incidence of glucose-related adverse events was very low with risperidone treatment (0.72% of 8558 subjects) and comparable to placebo (0.88% of 1825 subjects). The incidence in olanzapine-treated subjects was 0.93% of 536 subjects. Disturbances in glucose metabolism appeared to be age-dependent regardless of study treatment. The incidence of glucose-related adverse events was slightly higher with risperidone treatment (2.17% of 1105 subjects) than with placebo (1.70% of 707 subjects) among the elderly. In short-term trials, elderly subjects had a higher incidence of glucose-related adverse events (2.7%) compared to adult subjects (0.52%; see Clinical Trials Appendix).

Table 5: Incidence (Number of Subjects and %) of Adverse Events Related to Abnormalities in Glucose Metabolism in Short-Term Trials

Adverse event preferred term	Placebo N=1825	Risperidone N=8458	Haloperidol N=920	Olanzapine N=536	Other Neuroleptics ^a N=293
Any glucose-related adverse event	16 (0.88%)	61 (0.72%)	3 (0.33%)	5 (0.93%)	1 (0.34%)
Acidosis	0	1 (0.01%)	0	0	0
Blood sugar increased	0	2 (0.03%)	0	0	0
Coma diabetic	0	1 ^b (0.01%)	0	0	0
Diabetes mellitus	3 (0.16%)	9 (0.11%)	0	2 (0.37%)	1 (0.34%)
Diabetes mellitus aggravated	0	2 (0.03%)	0	0	0
Glycosuria	1 (0.07%)	6 (0.07%)	0	1 (0.19%)	0
Hyperglycemia	10 (0.55%)	40 (0.47%)	3 (0.33%)	3 (0.56%)	0
Hypoglycemia	3 (0.21%)	7 (0.10%)	0	0	0
Ketosis	0	1 (0.01%)	0	0	0
Plasma osmolality increased	0	1 (0.01%)	0	0	0

^a Other neuroleptics include: zuclopenthixol, perphenazine, remoxipride, clozapine, methotrimeprazine.

^b Although originally coded as "coma diabetic", one elderly subject experienced hyperglycemia with a hyperosmolar nonketotic state as a complication of urinary sepsis and acute renal failure and died one day later.

Cross-reference: Clinical Trials Appendix.

In long-term trials, there was a comparable incidence of glucose-related adverse events with risperidone treatment (1.49 % of 6590 subjects) and with both haloperidol treatment (1.55% of 579 subjects) and olanzapine treatment

(1.66% of 300 subjects) (Table 6). No glucose-related adverse events were reported for other neuroleptics (0% of 234 subjects). No glucose-related adverse events were reported in placebo-treated subjects in long-term, double-blind trials.

Table 6: Incidence (Number of Subjects and %) of Adverse Events Related to Abnormalities in Glucose Metabolism in Long-Term Trials

Adverse event preferred term	Risperidone N=6590	Haloperidol N=579	Olanzapine N=300	Other neuroleptics ^a N=234
Any glucose-related adverse event	98 (1.49%)	9 (1.55%)	5 (1.66%)	0
Acidosis	1 (0.02%)	0		0
Diabetes mellitus	32 (0.049%)	5 (0.86%)	1 (0.33%)	0
Diabetes mellitus aggravated	2 (0.03%)	0		0
Glycosuria	22 (0.33%)	0		0
Hyperglycemia	48 (0.73%)	5 (1.66%)	4 (1.33%)	0
Hypoglycemia	5 (0.11%)	1 (0.17%)		0
Ketosis	1 (0.02%)	0		0

^a Conventional neuroleptics, not specified.

Cross-reference: Clinical Trials Appendix.

Among risperidone-treated subjects in these trials, the incidence of glucose-related adverse events was 0.13% in 782 pediatric subjects, 1.51% in 4982 adults, and 2.66% in 826 elderly. The incidence was 1.58% among 569 haloperidol-treated adults and 1.68% among olanzapine-treated adults (Clinical Trials Appendix).

4.2. Serious Adverse Events

Among all risperidone-treated subjects, there was 1 fatal case in which, among other symptoms, a glucose-related adverse event was reported. This was an elderly subject with hyperglycemia and hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

The incidences of glucose-related serious adverse events and deaths are summarized in Table 7 for short-term trials and in Table 8 for long-term trials. Among the 26 risperidone-treated subjects who had a serious adverse event, 11 subjects experienced hyperglycemia, 10 subjects experienced diabetes mellitus (worsening or new onset), 4 subjects experienced hypoglycemia, and 1 experienced glucosuria. The subject who died had a serious adverse event listed as diabetic coma (described above). Fourteen of

the risperidone-treated subjects with a serious glucose-related adverse event had a pre-existing glucose-related condition; an additional risperidone-treated subject had a history of diabetes documented only in the report from the Council for International Organizations of Medical Sciences (CIOMS). Among haloperidol-treated subjects, serious adverse events included diabetes mellitus, hypoglycemia, and hyperglycemia. Serious adverse events among placebo subjects were uncontrolled diabetes, hypoglycemia, and hyperglycemia.

Table 7: Incidence of Deaths, Serious Adverse Events and Discontinuations Due to Adverse Events Related to Abnormalities in Glucose Metabolism in Short-Term Trials

	Placebo N=1825	Risperidone N=8458	Haloperidol N=920
Deaths ^a	0	1 ^b (0.01%)	0
Serious adverse events	4 (0.22%)	9 (0.11%)	0
Discontinuations due to adverse events	1 (0.05%)	2 (0.02%)	0

^a One subject died from non glucose-related adverse events but did report a glucose-related adverse event during treatment; the subject is not included in this table.

^b Although originally coded as "coma diabetic", this elderly subject experienced hyperglycemia with a hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

No deaths, discontinuations or serious adverse events related to abnormalities of glucose metabolism were reported with olanzapine (N=536) or other neuroleptic treatment; not shown in the table.

Cross-reference: Clinical Trials Appendix.

The incidence of serious adverse events with long-term risperidone treatment (0.26% of 6590 subjects) was lower than with long-term haloperidol treatment (0.52% of 579 subjects).

Table 8: Incidence of Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events Related to Abnormalities in Glucose Metabolism in Long-Term Trials

	Placebo N=0	Risperidone N=6590	Haloperidol N=579
Deaths ^a	--	0	0
Serious adverse events	--	17 (0.26%)	3 (0.52%)
Discontinuations due to adverse events	--	3 (0.05%)	1 (0.17%)

^a Two subjects died from non glucose-related adverse events but did report a glucose-related adverse event during treatment; these subjects are not included in this table.

No deaths, discontinuations or serious adverse events related to abnormalities of glucose metabolism were reported with olanzapine (N=300) or other neuroleptic treatment; not shown in the table.

Cross-reference: Clinical Trials Appendix.

The incidence of serious adverse events related to abnormalities in glucose metabolism with short-term (0.11% of 8458 subjects) or long-term (0.26% of 6590 subjects) risperidone treatment was comparable to short-term placebo (0.22% of 1825 subjects) or short-term haloperidol treatment (0% of 920 subjects), and lower than with long-term haloperidol treatment (0.52% of 579 subjects). No serious glucose-related adverse events were reported in subjects treated with olanzapine (536 and 300 subjects in short-term and long-term trials, respectively).

4.3. Discontinuations Due to Adverse Events

The incidences of discontinuations due to adverse events related to abnormalities in glucose metabolism with risperidone treatment in short- and long-term trials are summarized in Tables 7 and 8. In short-term trials, the incidence of discontinuation in risperidone-treated (0.02%) was comparable to that in placebo-treated (0.05%) subjects. The incidence of discontinuations in long-term trials was lower in subjects receiving risperidone (0.05%) than in those receiving haloperidol (0.17%). No discontinuations were related to abnormalities of glucose metabolism with short-term haloperidol treatment, or in a smaller group with olanzapine.

4.4. Other Safety Observations

4.4.1. Glucose Levels

Because fasting conditions were not required in the trials, results were treated according to the status of the subject at the sampling time. Samples obtained from subjects not known to be fasting were considered random

samples. Random glucose levels of ≥ 11.1 mmol/L were categorized as suggestive of diabetes; levels ≥ 7.8 and < 11.1 mmol/L were characterized as suggestive of impaired glucose tolerance in subjects with random glucose levels < 7.8 mmol/L at baseline. These criteria were based on recommendations of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus according to which random levels ≥ 11.1 mmol/L are diagnostic for diabetes in the presence of clinical symptoms; results of oral glucose tolerance tests 2 hours post-load (75 g glucose) or fasting plasma glucose levels ≥ 7.8 and < 11.1 mmol/L are diagnostic of impaired glucose tolerance. Fasting glucose levels were categorized as follows: normal (< 6.1 mmol/L), suggestive of impaired glucose tolerance (≥ 6.1 mmol/L but < 7 mmol/L), or suggestive of diabetes (≥ 7 mmol/L). Glucose was not typically measured in the pediatric trials. Among risperidone-treated adults with normal baseline glucose levels in short-term trials, the incidences of glucose levels suggestive of diabetes or impaired glucose tolerance during treatment (0.4% and 3.1% of 3131 subjects, respectively) were comparable to those with placebo (0.5% and 6.4% of 598 subjects), haloperidol (0% and 5.7% of 158), and other antipsychotic treatments (0.2% and 2.8% of 464 subjects). Elderly subjects had slightly higher incidences of glucose levels suggestive of diabetes or impaired glucose tolerance (6.5% and 15.6% of 743 subjects) with risperidone relative to placebo (6.9% and 10.8% of 464 subjects) and other antipsychotic treatments (2.1% and 8.5% of 142 subjects). Among risperidone-treated adults with normal baseline in long-term trials (1424 subjects), 1.6% had levels suggestive of diabetes and 7.3% suggestive of impaired glucose tolerance, lower than the 2.4% and 12.7% of 245 olanzapine-treated subjects, and 3.0% and 8.3% (of 230 subjects) incidences of diabetic and hyperglycemic levels observed for subjects who received other antipsychotic treatments in the long-term trials. Among elderly subjects with normal baseline in the long-term trials, 4.1% of 292 had levels suggestive of diabetes, and 25.0% of 292 had levels suggestive of impaired glucose tolerance. There were only 2 elderly subjects in comparator groups in the long-term trials.

In a trial in which fasting laboratory tests were recommended, among fasting subjects with normal glucose levels at baseline, glucose levels at endpoint were suggestive of diabetes for 2.9% of 136 subjects on olanzapine

compared to 1.9% of 106 subjects on risperidone long-acting injectable formulation, and 9.6% of olanzapine-treated subjects compared to 8.5% of risperidone-treated subjects had endpoint glucose levels suggestive of impaired glucose tolerance.

4.4.2. Body Weight

Weight gain is associated with antipsychotic treatment. A widely referenced study on antipsychotic-induced weight gain (Allison et al)¹ categorizes olanzapine and clozapine as being associated with the highest weight gain among the antipsychotics, risperidone as associated with moderate weight gain and haloperidol as associated with low weight gain. Since weight gain and changes in body composition are associated with glucose-related metabolic disorders², the J&JPRD clinical database was explored to assess if the rank order of antipsychotic-induced weight gain reported by Allison was confirmed by the J&JPRD clinical database. In addition, weight gain data for both elderly and pediatric populations were examined.

Mean change $\pm$ SD in body weight from baseline to study endpoint was analyzed using pooled data from subjects in 76 risperidone clinical studies (Phases 2 through 4). This analysis uses the baseline and last postbaseline weight measurements from subjects in short term (12 weeks or less) or long-term (6 months or longer) studies.

Table 9 summarizes the mean weight changes in short- and long-term trials in pediatric/adolescent (less than 18 years of age), adult (18 to 65 years), and elderly (>65 years) subjects. The mean weight gain ($\pm$ SD) in adults in short-term trials was greater in the risperidone group (1.2 ± 3.64 kg) than in the placebo group (-0.1 ± 3.38 kg). In comparison, mean weight change at endpoint was 0.4 ± 3.66 kg in the haloperidol, and 0.7 ± 3.19 kg treatment group in the other neuroleptics treatment group. In contrast, weight gain was 3.2 ± 4.53 kg in the olanzapine group. In general, weight increases were lower in elderly subjects in all treatment groups in short-term trials, but the trends in weight gain with treatment type were the same as those for adult subjects; mean weight change was lowest in elderly subjects receiving placebo or haloperidol (-0.6 ± 3.07 kg and -1.3 ± 3.62 kg, respectively), was slightly higher for risperidone (0.3 ± 3.16 kg), and highest with olanzapine treatment (1.5 ± 3.73 kg).

In long-term trials, the incidence of weight increase in adults taking risperidone or haloperidol was similar (2.3 ± 6.86 kg or 2.9 ± 8.46 kg, respectively), and was greater in those taking olanzapine (4.0 ± 6.59 kg). Insufficient data are available for treatments other than risperidone in elderly subjects in long-term trials. The incidence of weight change observed for risperidone in the elderly in long-term trials (0.2 ± 4.61 kg) is consistent, however, with that observed for risperidone in elderly subjects in short-term trials (0.3 ± 3.16 kg).

Table 9: Mean $\pm$ SD Weight Change (kg) From Baseline to Endpoint

Trial term						
Treatment	N	<18years	N	18-65 years	N	>65 years
Short-term trials						
Placebo	142	0.6 ± 1.67	833	-0.1 ± 3.38	602	-0.6 ± 3.07
Risperidone	139	2.2 ± 1.78	4874	1.2 ± 3.64	964	0.3 ± 3.16
Haloperidol		-	651	0.4 ± 3.66	90	-1.3 ± 3.62
Olanzapine		-	412	3.2 ± 4.53	72	1.5 ± 3.73
Other neuroleptics ^a		-	256	0.7 ± 3.19		-
Long-term trials						
Risperidone	680	7.4 ± 5.8	3914	2.3 ± 6.86	660	0.2 ± 4.61
Haloperidol		-	484	2.9 ± 8.46		-
Olanzapine		-	294	4.0 ± 6.59		-

^a Other neuroleptics included zuclopenthixol, perphenazine, remoxipride, clozapine, thioridazine, levomepromazine, divalproex.

Cross-reference: Clinical Trials Appendix.

Body weight changes were also analyzed by the percentages of subjects with body weight increases at endpoint of $>7\%$ of baseline weight in short- and long-term trials. A 7% weight gain is the equivalent to a gain of approximately 5 kg in a 70 kg individual, and is a commonly quoted standard for clinically meaningful weight gain in adults. Since growth and weight gain would be expected in subjects younger than 18 years, any discussion of this age group should take into account the natural weight gain. According to the National Center for Health Statistics (NCHS) percentiles³, the annual expected weight gain for an 8-year-old male of 34.6 kg is 5.1 kg. Since this normal weight change corresponds to a weight gain of 14.7%, the standard of 7% as the definition for clinically meaningful weight gain is therefore not appropriate for children. It should be noted that the average weight change for risperidone-treated pediatric/adolescent subjects in long-term trials (680 subjects, with the mean age = 9.6 years, mean baseline weight = 36.3 kg) was 7.4 kg or 20.4%.

Table 10 summarizes the percentages of subjects with clinically significant weight gain in short- and long-term trials in adults and elderly populations only. In short-term trials, incidence of weight gain >7% was greater in the risperidone group (11.9%) than in the placebo group (5.4%), but similar to that in the haloperidol (10.4%) and other neuroleptics (11.3%) treatment groups. In contrast, the incidence of clinically significant weight gain with olanzapine treatment was greater than 2-fold higher (26.9%) than that with risperidone.

In long-term trials, the incidence of clinically significant weight increase was 24.1% for adult subjects in the risperidone treatment group, and slightly higher (28.1%) in the haloperidol treatment group. The percentage of adult subjects with body weight increases at endpoint of >7% of baseline weight was highest in the olanzapine treatment group (35.7%).

In placebo- and risperidone-treated elderly subjects, results were similar (4.7% and 9.9%, respectively) to those in short-term trials. Weight data from long-term trials was not available for other neuroleptics.

Table 10: Incidence of Body Weight Increase >7% in Subjects >18 Years

Trial term Treatment	% subjects with increase of >7% of baseline weight			
	N	18-65 years	N	>65 years
Short-term trials				
Placebo	833	5.4%	602	4.7%
Risperidone	4874	11.9%	964	9.9%
Haloperidol	651	10.4%	90	4.4%
Olanzapine	412	26.9%	72	13.9%
Other neuroleptics ^a	256	11.3%		-
Long-term trials				
Risperidone	3914	24.1%	660	16.4%
Haloperidol	484	28.1%		-
Olanzapine	294	35.7%		-

^a Other neuroleptics included zuclopenthixol, perphenazine, remoxipride, clozapine, thioridazine, levomepromazine, divalproex.

Cross-reference: Clinical Trials Appendix.

The J&JPRD clinical database reflects the rank-order of antipsychotic weight gain reported by Allison in the American Journal of Psychiatry.¹ That is, in the J&JPRD database, olanzapine was associated with the highest weight gain, risperidone with moderate weight gain, and haloperidol with low weight gain. This rank order (olanzapine>risperidone>haloperidol) was generally true in each analysis of weight gain including short-term and

long-term trials, elderly population, pediatric population, and in the percentage of subjects gaining a clinically significant amount of weight.

4.4.3. Subgroup Analysis by Prior History of Diabetes

Analysis of the subgroup of subjects in which presence or absence of prior diabetes was clinically determined (5298 in short-term trials, 2572 in long-term trials) suggests that abnormalities of glucose metabolism in this clinical database (as reflected in adverse event reports) mainly represented poorly controlled existing diabetes rather than new-onset diabetes. In the short-term trials, among subjects without pre-existing diabetes, 0.5% of the risperidone-treated and 0.5% of the placebo-treated subjects had glucose-related adverse events. Among subjects with no prior history of diabetes in long-term trials, 0.7% of risperidone-treated and 1.4% of olanzapine-treated subjects had glucose-related adverse events. Among subjects with pre-existing diabetes, in the short-term trials the rates of glucose-related adverse events were 6.2% of risperidone subjects and 6.5% of the placebo subjects. Among subjects with pre-existing diabetes in the long-term trials, 14.3% of risperidone-treated subjects had glucose-related adverse events.

4.5. Conclusion

The information derived from a large number of clinical trials reporting on more than 12,000 subjects in short-term trials and over 7500 subjects in long-term trials supports the conclusion that disturbances of glucose metabolism during risperidone treatment are not very common. Overall, the incidence of glucose-related adverse events was lower with risperidone than placebo or olanzapine. Serious glucose-related adverse events were rare and were not more frequent with risperidone than with placebo. One fatal case resulted from urosepsis. In the pediatric and adult populations, risperidone was similar to, if not lower than, placebo, and lower than olanzapine in terms of percentage of individuals with abnormalities in glucose metabolism. Elderly subjects showed a higher incidence than adults of abnormalities in glucose metabolism and had a slightly higher incidence with risperidone compared to placebo in short-term trials. Most observations in this database were hyperglycemia in subjects with a history of diabetes; new-onset diabetes was infrequent among subjects with no prior history of diabetes.

4.6. References

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5. PHARMACOVIGILANCE

5.1. Sponsor's Pharmacovigilance Database

A complete review was conducted of worldwide reports of adverse drug experiences involving terms related to glucose metabolism in patients taking risperidone captured in the Johnson & Johnson pharmacovigilance database over life of product. Total patient exposure for life of product is currently estimated to be more than 17,200,000 patient-years. Only 375 reports of adverse drug events were identified. Diabetes mellitus is the most frequently reported term, followed by hyperglycemia, diabetes mellitus aggravated, and hypoglycemia. The majority of reports cite multiple concomitant medications, many of which are known to be associated with disorders in glucose homeostasis. In addition, many of these patients have previously diagnosed diabetes (some revealing noncompliance with diabetic diet or therapy), positive family history, and/or co-morbid medical conditions. The documented duration of therapy from initial treatment to onset of adverse event varies widely, from 1 day to several years, with no clear pattern identified. Review of cases for suggestive evidence of causal drug association shows isolated instances of positive rechallenge as well as some cases demonstrating positive dechallenge. Scrutiny of fatal outcomes suggests that deaths are infrequent and often do not appear to be related to therapy. Overall, adverse events involving glucose metabolism are relatively rare in patients receiving risperidone. The pharmacovigilance database provides no evidence to suggest an increased risk of diabetes or related events in association with risperidone treatment.

5.2. Published Summaries of Spontaneous Reports

The sponsor's pharmacovigilance database is limited to cases involving the sponsor's drug, and a summary of those data can only characterize those cases. Comparisons between drugs can be made based on searches of inclusive databases such as MedWatch or the World Health Organization (WHO).

Three similar summaries, by Koller and colleagues have reported diabetes-related adverse events with atypical antipsychotic treatments primarily identified with the United States Food and Drug Administration's MedWatch program and published case reports.¹⁻³ Although results of these publications should be interpreted with caution, they can be a signal of a

potential association between a specific medication and diabetes-related diagnoses or events.

The first of these¹ examined 384 cases associated with clozapine, which included 323 cases of new-onset hyperglycemia or diabetes, 54 cases of exacerbation of pre-existing diabetes and 7 cases unknown as to new-onset or pre-existing diabetes-related disease. Among the 384 cases, 80 had a diagnosis of metabolic acidosis or ketosis and 25 resulted in death. The mean age of all patients was 40 ± 12 years with a male to female ratio of 2:1 and an average dose of clozapine of 362 ± 208 mg. Of those definitively identified with diabetes through laboratory values ($n=171/323$), 56% were diagnosed within the first 3 months of therapy. Exacerbation of diabetes in patients with pre-existing disease was observed in 64% within the first 3 months of treatment. Clozapine was discontinued in 110 of the 384 cases and where follow-up data was available, a large majority (42/54) of patients improved. In the 5 cases with a reduction in the clozapine dose and with follow-up data available, 4 patients improved. In the few patients ($n=12$) where clozapine was re-initiated, 9 developed a deterioration of glycemic control. Many of these findings suggest a relationship between clozapine use and diabetes including the number of cases, the severity of the cases, the temporal relationship to the initiation of clozapine therapy and the reversibility upon withdrawal of the drug.

A similar review of 289 diabetes-related cases associated with olanzapine use² identified 225 with new-onset diabetes, 57 with exacerbations of pre-existing diabetes and 7 cases that could not be classified. In addition, there were 100 cases of acidosis or ketosis and 25 deaths. Mean patient age was approximately 43 years with a male to female ratio of 1.8 to 1 and an average daily dose of olanzapine of 15.6 ± 7 mg in the original sample population. Approximately 73% of all cases occurred within 6 months of the start of olanzapine therapy. When olanzapine was discontinued or the dosage decreased, 78% of patients had improved glycemic control. In 8 of 10 cases of rechallenge with olanzapine, hyperglycemia occurred. The authors concluded that the number of cases, rapid onset, resolution upon withdrawal, and re-emergence upon re-challenge suggested that olanzapine was causally related to these adverse events.

The final review³ of a similar type examined 131 cases associated with risperidone monotherapy use, including 78 new-onset cases,

46 exacerbations of pre-existing disease and 7 that could not be classified. There were 26 cases of acidosis or ketosis and 4 deaths. Mean patient age was approximately 40 years with a male to female ratio of 1.5 to 1 and an average daily dose of 4.7 ± 2.5 mg. As compared to the review of clozapine and olanzapine cases, less information is known regarding discontinuation, reduction in dosage, and rechallenge with these risperidone users. The authors conclude that although cases of diabetes-related events attributed to clozapine or olanzapine are more numerous than those associated with risperidone, the number for risperidone-associated hyperglycemia is relatively higher than that observed with haloperidol.

To provide a context for these three summaries, Table 11 presents an estimate of the total exposure for clozapine, olanzapine and risperidone since their market introduction in the U.S. through the time period of each study and a summary of the cases in the reviews described above. Risperidone has 1.5 times the potential exposure of olanzapine and 2.4 times that of clozapine but had less than half the number of cases of diabetes or hyperglycemia associated as compared to olanzapine and almost two-thirds less than clozapine. With respect to serious, life-threatening reports and deaths, risperidone also demonstrated much less event reporting.

Table 11: Summary of Published FDA Pharmacovigilance

	Total prescriptions (x 10 ³) ^a	Total cases diabetes or hyperglycemia	Reports of acidosis or ketosis	Deaths
Clozapine	17,962	384	80	25
Olanzapine	29,220	289	100	25
Risperidone	43,232	131	26	4

^a IMS Health, NPA Plus, Total Prescriptions.

The Koller publications/posters refer to an international literature survey. Since international total prescriptions are unavailable, the total prescriptions in the United States are being used even though the article reflects international case reports as early as 1990. Olanzapine search dates: 1996-February 2002; Risperidone search dates: 1994-2001; Clozapine search dates: 1991-February 2002.

In a fourth report, Hedenmalm et al,⁴ of the Medical Products Agency in Sweden, examined the WHO database for the association between impaired glucose tolerance and diabetes and clozapine, olanzapine and risperidone. Using the Bayesian Confidence Propagation Neural Network method, atypical antipsychotics (clozapine, olanzapine and risperidone) were significantly associated with glucose intolerance. In contrast, conventional antipsychotics (chlorpromazine and haloperidol) were not associated with glucose intolerance. For atypical antipsychotics, the following potential risk

factors for glucose intolerance were identified: an underlying diabetic condition (odds ratio 10.22, 95% CI 8.20- 12.73), an increase in weight gain (OR 2.36, 95% CI 1.76-3.17), male gender (OR 1.27, 95% CI 1.11- 1.47), and concomitant use of valproic acid (OR 1.97, 95% CI 1.61-2.40), selective serotonin reuptake inhibitors (OR 1.63, 95% CI 1.33-1.99) or buspirone (OR 2.24, 95% CI 1.33-3.77). In summary, the suggestion that some antipsychotics, such as clozapine and olanzapine, may be associated with greater disruption of normal glucose metabolism than other antipsychotics is supported by the preponderance of published case reports and review of MedWatch and WHO reports. All of these publications are based entirely on spontaneous adverse event reporting. These spontaneously reported pharmacovigilance reviews should be interpreted with caution. Spontaneous events are significantly under-reported, no control population is available for comparison, case reports are often incomplete with respect to important information regarding confounding concomitant medications or risk factors, and assessment of exposure (an accurate population denominator) is difficult. Population-based epidemiologic studies offer a variety of advantages over evaluation of spontaneous reports. Further, these reports – notably Hedenmalm et al - group all “glucose-related” events together, and may obscure differences in risk for the most serious events (e.g., DKA). Such grouping may also produce misleading results if drugs are used in populations with differing underlying risk for glucose-related diagnoses or, even if overall risk is comparable, differing proportional risk for various diabetes-related events (e.g., hyperglycemia).

5.3. References

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6. SUMMARY AND CONCLUSIONS

In summary, the weight of evidence demonstrates that risperidone-treated patients do not have an increased risk of glucose-related adverse events compared to untreated patients. The class label now in effect fails to provide adequate information to guide the physician in determining differential risks among atypical antipsychotics with respect to glucose-related adverse events, although the data clearly support a reduced risk with risperidone relative to olanzapine and clozapine. It is crucial to emphasize the clinically important risk differences for the atypical antipsychotics, especially risk of life-threatening events, since these are critical aids to the clinician in determining the highest quality of medical care for each patient. Recommendations applied identically to diverse antipsychotics obscure documented differences among treatment options, rather than providing clarity about these issues. In addition, because patient exposure for the more recently introduced antipsychotics is not comparable to that for risperidone, the large cumulative clinical and preclinical experience that documents the relative safety of risperidone should be evaluated in assessing the use of a broad "class effect" statement on the label to address this important clinical concern.

**Antipsychotics and Glycemic side-effects:
A Bayesian data-mining analysis of the AERS database
(1968- 2002)**

Report Prepared For Janssen Pharmaceutica Products L.P.
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Antipsychotics and Glycemic side-effects: A Bayesian data-mining analysis of the AERS database (1968- 2002)

Background and Objectives

Some of the drugs known as atypical antipsychotics have been suspected of being linked to increased risk of diabetes. The objective of this study was to examine the association strength between antipsychotic usage and reports of glycemic side effects using a Bayesian data mining analysis of spontaneous post-marketing adverse events

Methods

An empirical Bayes data mining technique was employed in conjunction with an analysis database which was derived from the database of post-marketing adverse event reports maintained by the US Food and Drug Administration.

Post-marketing adverse event reports are submitted to the FDA in one of the following ways:

- By drug manufacturers, according to regulations
- By health care professionals and consumers who voluntarily report through the MedWatch program

From the first month of 1968 through the end of June 1998, the name of the database was the Spontaneous Reporting System (SRS). The SRS database was maintained by the FDA's Center for Drug Evaluation and Research (CDER). From the beginning of November 1997 through the present, the name of the database has been the Adverse Event Reporting System (AERS). The AERS database is maintained by CDER and the FDA's Center for Biologics and Research (CBER). The SRS and AERS databases, covered by the Freedom of Information (FOI) Act, are available through the National Technical Information Services (NTIS), which is part of the U.S. Department of Commerce.

This public safety data has been collected over many years from many different sources. As a result, it contains a number of inconsistencies, errors, and duplications. The data must be cleaned and transformed before it can be used meaningfully for data mining analysis.

For a number of fields in the database, SRS utilized different coding conventions than AERS. The most significant difference was the use in SRS of the COSTART terminology (Coding Symbols for a Thesaurus of Adverse Reaction Terms) for the coding of adverse events. AERS uses a version of the MedDRA dictionary (Medical Dictionary for Regulatory Activities), which was developed under the auspices of the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) and is now maintained by the MedDRA Maintenance and Support Services Organization (MSSO) at Northrop Grumman Mission Systems (formerly TRW Inc.). There are only 1,180 distinct adverse reaction terms in COSTART, while the latest version of MedDRA has over 15,000 distinct "Primary Terms" (MedDRA Primary Terms are intended to represent distinct medical concepts).

The following list highlights the major data cleaning and transformation tasks that were undertaken to prepare the FOI data for data mining:

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- (a) Transform COSTART terms in SRS to MedDRA
- (b) Select latest follow-up report if both initial and follow-up reports are present
- (c) Clean and code the verbatim drug names supplied in the FOI data in order to extract standardized trade and generic names
- (d) Identify and merge any remaining duplicate reports. (Even after accounting for the issue of follow-up reports, both SRS data and AERS data contain numerous instances of adverse reaction cases for which there are duplicate reports. These duplicates result from several possible sources; e.g., multiple manufacturers reporting a case that involved several drugs, reporting directly to the FDA and also to the company, dual electronic and paper reporting requested by the FDA during pilot tests of electronic reporting.)

The resulting analysis database used for this study was current as of the 3rd quarter of 2002 and contained approximately 2.2 million reports. Adverse events were represented as MedDRA Primary Terms in MedDRA Version 4.0. As a result of the drug name cleaning/coding process (item (c), above), the analysis database contained references to approximately 2500 distinct generic drug names.

For the remainder of this report, the term "AERS" will be used informally to refer to the analysis database just described.

The set of drugs selected for study consisted of five atypical antipsychotics - Clozapine (CLO), Olanzapine (OLA), Quetiapine (QUE), Risperidone (RIS), and Ziprasidone (ZIP) and one older antipsychotic - Haloperidol (HAL).

The adverse reaction terms selected for study consisted of 15 MedDRA Primary Terms (PT's) which were judged to be highly related to diabetes. These terms, along with a count of the total number of reports mentioning each term, are given below:

TABLE 1

MedDRA PT	Reports
Blood glucose abnormal	301
Blood glucose increased	3652
Diabetes mellitus NOS	4457
Diabetes mellitus aggravated	2398
Diabetes mellitus inadequate control	1926
Diabetes mellitus insulin-dependent	196
Diabetes mellitus non insulin-dependent	324
Diabetic coma NOS	384
Diabetic hyperglycemic coma	38
Diabetic hyperosmolar coma	25
Diabetic ketoacidosis	925
Glucose tolerance decreased	274
Glucose tolerance impaired	94
Glycosylated hemoglobin increased	374
Hyperglycemia NOS	20106

The empirical Bayes data mining algorithm known as the Multi-Item Gamma Poisson Shrinker (MGPS) was used to obtain quantitative measures of association strength ("signal scores") between drugs and adverse event terms. For each drug-event combination, the algorithm

computes a statistic known as EBGM ("empirical Bayes geometric mean") along with its lower 5% (EB05) and upper 95% (EB95) confidence limits. EBGM is a stable estimate of the relative reporting ratio for the given drug-event combination (observed count divided by expected count). As an example, an EBGM value of 5 for a given drug-event combination is interpretable as indicating that, as a best estimate, the drug-event combination is being reported 5 times more frequently than would be expected if there were no association between the reporting of that drug to AERS and of that event to AERS. An EB05 value of 5 for a given drug-event combination is interpretable as indicating that, with 95% confidence, one can say that the drug-event combination is being reported *at least* 5 times more frequently than expected. Full details on the mathematical formulas used to derive EBGM, EB05, and EB95 can be found in reference [1].

Comparison of signal scores between drugs is inherently problematic, as there may certainly be differences in reporting rates between different drugs. However, so long as the actual reporting rates vary essentially only as a function of the drug or the event—and not as a function of drug-event combination—one may with care interpret differences in signal score (for a given adverse reaction term) between two drugs as reflecting differences in risk. This issue of comparison in the presence of differential reporting rates is discussed at some length in reference [2]. One phenomenon that might produce reporting rates that vary as a function of the specific drug-event combination would be media coverage of a newsworthy safety issue ("publicity effect"). To guard against this type of effect influencing our analysis, we studied the progression of signals over time to see whether there had been any telltale reporting "spikes" for a particular drug-event combination at a particular point in time (see further discussion below).

In making comparisons of signal scores, the criterion used for declaring that two drugs have different association strengths with a given adverse reaction term is that the corresponding two [EB05, EB95] confidence intervals do not overlap.

The calculation of "expected counts" within MGPS includes a provision for stratification. Stratifying makes sense as it guards against concluding that a drug and a reaction are associated simply because the drug and the reaction both occur preferentially in some sub-population ("stratum") of the database. The MGPS analyses for the present study were carried out using strata formed from the following three stratification variables: Gender, Age Group, and FDA Receipt Year. The values that these three variables can assume are depicted below:

Gender (3 values): F, M, and Unknown

Age Group (9 values): 0-1, 2-4, 5-12, 13-16, 17-45, 46-75, 76-85, >85, Unknown

FDA Receipt Year (35 values): 1968, 1969, 1970, 1971, . . . , 2001, 2002

The total number of strata (all combinations of Gender, Age Group, and FDA Receipt Year) is therefore 945 ($3 \times 9 \times 35$).

Stratification could not be carried out based on indication, since the indication associated with an adverse event report has only been made available as part of the FOI version of AERS beginning in 2nd quarter 2002.

It is often advisable to examine, retrospectively, the progression of MGPS signal scores over time, in order to see whether there are any surprising secular changes (e.g., a large spike in a signal score related perhaps to a "publicity effect"). This can be done by creating a series of

cumulative subsets of the database (e.g., 1968-1990, 1968-1991, 1968-1992, etc.) and carrying out separate MGPS analyses on each of them.

The MGPS analyses for this study were carried out without regard to the reporter-assigned role code (primary suspect, secondary suspect, concomitant, interacting); i.e., *all* reported drugs were included in the analyses. This approach seems desirable as a way of eliminating any reporter-introduced biases concerning assignment of "causality". On the other hand, the approach increases the possibility that the results will include "innocent bystander" effects, in which a drug's apparent signal score for some adverse reaction is elevated because the drug is frequently co-prescribed with another drug that is actually the true causal agent. Another possibility for misinterpretation is the case of a true drug-drug interaction. If the adverse reaction Event E only occurs when Drug A and Drug B are present simultaneously, a simple pairwise (drug-event) analysis will tend to generate elevated signal scores for both pairwise combinations Drug A-Event E and Drug B-Event E.

In the present study, one of whose purposes was to compare signal scores for diabetes-related events between different atypical antipsychotics, it was felt to be important to explore whether there might be "innocent bystander" effects occurring as a result of co-administration of multiple atypical antipsychotics. Accordingly, additional analyses were carried out in which the drug name of each atypical antipsychotic was recoded into two "pseudo-drugnames" according to whether the case report included mention of a second atypical antipsychotic or not. Thus, "Clozapine" became "Clozapine_alone" or "Clozapine_other", depending on the absence/presence of other atypical antipsychotics in the case report. Once this recoding was done, separate signal scores could be generated (for each adverse reaction) for each atypical antipsychotic both *alone* ("monotherapy") and *with other atypical antipsychotics* ("polytherapy").

Results

Results are summarized in the accompanying set of spreadsheets and graphical displays.

Table 2 presents N (report count), EBGM, EB05, and EB95 for each combination of antipsychotic and diabetes-related MedDRA PT.

TABLE 2

Drug	PT	N	EB04	EB05	EB95
Clozapine	Blood glucose abnormal	3	0.878	0.375	1.811
Haloperidol	Blood glucose abnormal	3	1.256	0.537	2.593
Olanzapine	Blood glucose abnormal	6	1.384	0.727	2.444
Clozapine	Blood glucose increased	37	1.005	0.765	1.301
Haloperidol	Blood glucose increased	27	1.281	0.931	1.728
Olanzapine	Blood glucose increased	118	2.681	2.301	3.11
Quetiapine	Blood glucose increased	13	0.838	0.533	1.769
Risperidone	Blood glucose increased	25	0.679	0.488	0.926
Clozapine	Diabetes mellitus aggravated	34	1.283	0.965	1.678
Haloperidol	Diabetes mellitus aggravated	12	0.855	0.534	1.313
Olanzapine	Diabetes mellitus aggravated	32	1.099	0.819	1.449
Quetiapine	Diabetes mellitus aggravated	7	0.734	0.402	1.253
Risperidone	Diabetes mellitus aggravated	25	1.113	0.802	1.529
Ziprasidone	Diabetes mellitus aggravated	7	1.235	0.676	2.21
Clozapine	Diabetes mellitus inadequate control	8	0.434	0.246	0.721
Haloperidol	Diabetes mellitus inadequate control	4	0.421	0.197	0.814
Olanzapine	Diabetes mellitus inadequate control	24	1.051	0.749	1.44
Quetiapine	Diabetes mellitus inadequate control	3	0.488	0.208	1.007
Risperidone	Diabetes mellitus inadequate control	8	0.463	0.263	0.77
Clozapine	Diabetes mellitus insulin-dependent	26	5.771	4.036	8.504
Haloperidol	Diabetes mellitus insulin-dependent	5	1.936	0.965	3.561
Olanzapine	Diabetes mellitus insulin-dependent	16	3.119	2.066	4.562
Quetiapine	Diabetes mellitus insulin-dependent	4	1.951	0.864	3.581
Risperidone	Diabetes mellitus insulin-dependent	3	0.827	0.353	1.706
Clozapine	Diabetes mellitus non insulin-dependent	50	9.678	7.175	12.513
Haloperidol	Diabetes mellitus non insulin-dependent	8	2.387	1.352	3.971
Olanzapine	Diabetes mellitus non insulin-dependent	28	4.327	3.156	5.836
Quetiapine	Diabetes mellitus non insulin-dependent	5	1.811	0.903	3.329
Risperidone	Diabetes mellitus non insulin-dependent	9	1.882	1.099	3.054
Clozapine	Diabetes mellitus NOS	275	4.429	4.008	4.885
Haloperidol	Diabetes mellitus NOS	51	1.524	1.208	1.903
Olanzapine	Diabetes mellitus NOS	137	3.387	2.939	3.888
Quetiapine	Diabetes mellitus NOS	26	2.206	1.652	3.099
Risperidone	Diabetes mellitus NOS	97	2.27	1.833	2.554
Clozapine	Diabetic coma NOS	24	4.014	2.858	5.523
Haloperidol	Diabetic coma NOS	5	1.369	0.683	2.516
Olanzapine	Diabetic coma NOS	20	4.476	3.067	6.426
Quetiapine	Diabetic coma NOS	3	1.723	0.736	3.56
Risperidone	Diabetic coma NOS	4	1.053	0.491	2.034
Clozapine	Diabetic hyperglycemic coma	5	2.843	1.403	5.344
Olanzapine	Diabetic hyperglycemic coma	6	3.198	1.651	5.866
Olanzapine	Diabetic hyperosmolar coma	5	3.085	1.498	6.043
Clozapine	Diabetic ketoacidosis	61	3.849	3.11	6.721
Haloperidol	Diabetic ketoacidosis	23	2.688	1.904	3.788
Olanzapine	Diabetic ketoacidosis	113	9.131	7.661	10.76
Quetiapine	Diabetic ketoacidosis	23	4.681	3.291	6.574
Risperidone	Diabetic ketoacidosis	28	2.37	1.733	3.18
Haloperidol	Glucose tolerance decreased	3	1.288	0.551	2.659
Risperidone	Glucose tolerance decreased	3	1.194	0.51	2.463
Clozapine	Glucose tolerance impaired	7	3.077	1.676	5.326
Olanzapine	Glucose tolerance impaired	4	1.859	0.867	3.596
Risperidone	Glucose tolerance impaired	3	1.601	0.684	3.306
Clozapine	Glycosylated hemoglobin increased	11	1.844	1.129	2.879
Haloperidol	Glycosylated hemoglobin increased	4	1.299	0.606	2.51
Olanzapine	Glycosylated hemoglobin increased	24	3.671	2.615	5.043
Quetiapine	Glycosylated hemoglobin increased	6	2.231	1.17	3.942
Risperidone	Glycosylated hemoglobin increased	4	0.892	0.416	1.724
Clozapine	Hyperglycemia NOS	265	1.156	1.044	1.277
Haloperidol	Hyperglycemia NOS	90	0.674	0.566	0.798
Olanzapine	Hyperglycemia NOS	245	2.289	2.068	2.539
Quetiapine	Hyperglycemia NOS	26	1.441	1.041	1.953
Risperidone	Hyperglycemia NOS	116	0.781	0.669	0.906

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Figure 1 presents an overall summary of the report counts and association strengths for the 6 antipsychotic drugs and 15 diabetes-related MedDRA PT's. Clozapine, Olanzapine, and Quetiapine exhibit the strongest signal scores (exhibiting EBGM signal scores >4 for four, three, and one of the 15 MedDRA PT's, respectively). Risperidone and the older antipsychotic Haloperidol appear to have significantly weaker associations with the diabetes-related MedDRA terms. For 14 of the 15 PT's, Ziprasidone has fewer than 3 reports and thus no signal scores were obtained (a threshold of 3 or more reports was used during the MGPS analysis). For Diabetes mellitus aggravated, Ziprasidone has a weakly positive signals score based on a case count of N=7.

Figures 2a-2f show the progression of counts and signal scores over time (yearly cumulative subsets) for each of the 6 antipsychotic drugs and the 15 MedDRA PT's. The earliest yearly cumulative subset shown is 1968-1985, and the only drug that shows reports this far back is Haloperidol. The following table summarizes when the count of reports mentioning any one of the 15 diabetes-related MedDRA terms first exceeded the threshold of 3 for each of the 6 antipsychotic drugs:

TABLE 3

Antipsychotic	Year number of reports exceeded threshold of 3 for diabetes-related PT
Clozapine	1991
Haloperidol	1985
Olanzapine	1997
Quetiapine	1999
Risperidone	1994
Ziprasidone	2002

By and large, the counts and signal scores progress smoothly over time (both counts and signal scores typically rising smoothly and steadily), giving us confidence that there are no significant "publicity effects" or other secular artifacts. A notable exception is the progression of scores for Diabetes mellitus aggravated, which appears to go through cycles of increasing and decreasing for both Clozapine and Risperidone. This suggests that the MedDRA Primary Term Diabetes mellitus aggravated is less reliable (as compared to other terms selected) for the purposes of this study.

Figure 3 compares the signal score confidence intervals of the 6 antipsychotic drugs for each of the 15 diabetes-related MedDRA PT's. For 6 of the PT's (Blood glucose abnormal, Diabetes mellitus aggravated, Diabetes mellitus inadequate control, Diabetic hyperglycemic coma, Glucose tolerance decreased, Glucose tolerance impaired), the confidence intervals of the drugs are completely mutually overlapping; thus based on these PT's there is no reason to conclude that there are any association strength differences among the drugs. One PT (i.e., Diabetic hyperosmolar coma) was reported only in OLA.

For the remaining 8 PT's, there are 34 non-overlapping confidence intervals in which the EB05 value of Drug1 exceeds the EB95 value of Drug2 and the EB05 of Drug1 is greater than 1.5:

TABLE 4

	Based on PT -	Drug1 [EB05, EB95]		Drug2 [EB05, EB95]
1	Blood glucose increased	OLA [2.301,3.11]	>	CLO [0.765,1.30]
2	Blood glucose increased	OLA [2.301,3.11]	>	HAL [0.931,1.728]
3	Blood glucose increased	OLA [2.301,3.11]	>	QUE [0.533,1.269]
4	Blood glucose increased	OLA [2.301,3.11]	>	RIS [0.488,0.926]
5	Diabetes mellitus NOS	CLO [4.008,4.885]	>	HAL [1.208,1.903]
6	Diabetes mellitus NOS	CLO [4.008,4.885]	>	OLA [2.939,3.888]
7	Diabetes mellitus NOS	CLO [4.008,4.885]	>	QUE [1.652,3.099]
8	Diabetes mellitus NOS	CLO [4.008,4.885]	>	RIS [1.833,2.554]
9	Diabetes mellitus NOS	OLA [2.939,3.888]	>	HAL [1.208,1.903]
10	Diabetes mellitus NOS	OLA [2.939,3.888]	>	RIS [1.833,2.554]
11	Diabetes mellitus insulin-dependent	CLO [4.036,8.504]	>	HAL [0.965,3.561]
12	Diabetes mellitus insulin-dependent	CLO [4.036,8.504]	>	QUE [0.864,3.581]
13	Diabetes mellitus insulin-dependent	CLO [4.036,8.504]	>	RIS [0.353,1.706]
14	Diabetes mellitus insulin-dependent	OLA [2.066,4.562]	>	RIS [0.353,1.706]
15	Diabetes mellitus non insulin-dependent	CLO [7.175,12.51]	>	HAL [1.352,3.971]
16	Diabetes mellitus non insulin-dependent	CLO [7.175,12.51]	>	OLA [3.156,5.836]
17	Diabetes mellitus non insulin-dependent	CLO [7.175,12.51]	>	QUE [0.903,3.329]
18	Diabetes mellitus non insulin-dependent	CLO [7.175,12.51]	>	RIS [1.099,3.054]
19	Diabetes mellitus non insulin-dependent	OLA [3.156,5.836]	>	RIS [1.099,3.054]
20	Diabetic coma NOS	CLO [2.858,5.523]	>	HAL [0.683,2.516]
21	Diabetic coma NOS	CLO [2.858,5.523]	>	RIS [0.491,2.034]
22	Diabetic coma NOS	OLA [3.067,6.426]	>	HAL [0.683,2.516]
23	Diabetic coma NOS	OLA [3.067,6.426]	>	RIS [0.491,2.034]
24	Diabetic ketoacidosis	OLA [7.661,10.76]	>	CLO [3.11,4.721]
25	Diabetic ketoacidosis	OLA [7.661,10.76]	>	HAL [1.904,3.708]
26	Diabetic ketoacidosis	OLA [7.661,10.76]	>	QUE [3.291,6.574]
27	Diabetic ketoacidosis	OLA [7.661,10.76]	>	RIS [1.733,3.18]
28	Diabetic ketoacidosis	QUE [3.291,6.574]	>	RIS [1.733,3.18]
29	Glycosylated hemoglobin increased	OLA [2.616,5.043]	>	HAL [0.606,2.51]
30	Glycosylated hemoglobin increased	OLA [2.616,5.043]	>	RIS [0.416,1.724]
31	Hyperglycemia NOS	OLA [2.059,2.539]	>	CLO [1.044,1.277]
32	Hyperglycemia NOS	OLA [2.059,2.539]	>	HAL [0.566,0.798]
33	Hyperglycemia NOS	OLA [2.059,2.539]	>	QUE [1.041,1.953]
34	Hyperglycemia NOS	OLA [2.059,2.539]	>	RIS [0.669,0.905]

TABLE 5: Sorting by Drug1, then Drug2, then by PT produces the following summary:

	Drug1 [EB05, EB95]	>	Drug2 [EB05, EB95]	Based on PT =
1	CLO [4.036, 8.504]	>	HAL [0.965, 3.561]	Diabetes mellitus insulin-dependent
2	CLO [7.175, 12.51]	>	HAL [1.352, 3.971]	Diabetes mellitus non insulin-dependent
3	CLO [4.008, 4.885]	>	HAL [1.208, 1.903]	Diabetes mellitus NOS
4	CLO [2.858, 5.523]	>	HAL [0.683, 2.516]	Diabetic coma NOS
5	CLO [7.175, 12.51]	>	OLA [3.156, 5.836]	Diabetes mellitus non insulin-dependent
6	CLO [4.008, 4.885]	>	OLA [2.939, 3.888]	Diabetes mellitus NOS
7	CLO [4.036, 8.504]	>	QUE [0.864, 3.581]	Diabetes mellitus insulin-dependent
8	CLO [7.175, 12.51]	>	QUE [0.903, 3.329]	Diabetes mellitus non insulin-dependent
9	CLO [4.008, 4.885]	>	QUE [1.652, 3.099]	Diabetes mellitus NOS
10	CLO [4.036, 8.504]	>	RIS [0.353, 1.706]	Diabetes mellitus insulin-dependent
11	CLO [7.175, 12.51]	>	RIS [1.099, 3.054]	Diabetes mellitus non insulin-dependent
12	CLO [4.008, 4.885]	>	RIS [1.833, 2.554]	Diabetes mellitus NOS
13	CLO [2.858, 5.523]	>	RIS [0.491, 2.034]	Diabetic coma NOS
14	OLA [2.301, 3.11]	>	CLO [0.765, 1.30]	Blood glucose increased
15	OLA [7.661, 10.76]	>	CLO [3.11, 4.721]	Diabetic ketoacidosis
16	OLA [2.059, 2.539]	>	CLO [1.044, 1.277]	Hyperglycemia NOS
17	OLA [2.301, 3.11]	>	HAL [0.931, 1.728]	Blood glucose increased
18	OLA [2.939, 3.888]	>	HAL [1.208, 1.903]	Diabetes mellitus NOS
19	OLA [3.067, 6.426]	>	HAL [0.683, 2.516]	Diabetic coma NOS
20	OLA [7.661, 10.76]	>	HAL [1.804, 3.708]	Diabetic ketoacidosis
21	OLA [2.616, 5.043]	>	HAL [0.606, 2.51]	Glycosylated hemoglobin increased
22	OLA [2.059, 2.539]	>	HAL [0.566, 0.798]	Hyperglycemia NOS
23	OLA [2.301, 3.11]	>	QUE [0.533, 1.269]	Blood glucose increased
24	OLA [7.661, 10.76]	>	QUE [3.291, 6.574]	Diabetic ketoacidosis
25	OLA [2.059, 2.539]	>	QUE [1.041, 1.953]	Hyperglycemia NOS
26	OLA [2.301, 3.11]	>	RIS [0.488, 0.926]	Blood glucose increased
27	OLA [2.066, 4.562]	>	RIS [0.353, 1.706]	Diabetes mellitus insulin-dependent
28	OLA [3.156, 5.836]	>	RIS [1.099, 3.054]	Diabetes mellitus non insulin-dependent
29	OLA [2.939, 3.888]	>	RIS [1.833, 2.554]	Diabetes mellitus NOS
30	OLA [3.067, 6.426]	>	RIS [0.491, 2.034]	Diabetic coma NOS
31	OLA [7.661, 10.76]	>	RIS [1.733, 3.18]	Diabetic ketoacidosis
32	OLA [2.616, 5.043]	>	RIS [0.416, 1.724]	Glycosylated hemoglobin increased
33	OLA [2.059, 2.539]	>	RIS [0.669, 0.906]	Hyperglycemia NOS
34	QUE [3.291, 6.574]	>	RIS [1.733, 3.18]	Diabetic ketoacidosis

OLA had a higher, non-overlapping signal score for "Diabetic ketoacidosis", "Blood glucose increased" and "Hyperglycemia NOS" compared to either RIS, QUE, HAL or CLO. Additionally, OLA had higher EBGM scores for "Diabetes mellitus NOS", "Diabetic coma NOS", and "Glycosylated hemoglobin increased" than either RIS or HAL. Also, OLA had higher EBGM scores for "Diabetes mellitus insulin-dependent" and "Diabetes mellitus non insulin-dependent" compared to RIS.

Similarly, CLO had higher, non-overlapping signal scores for "Diabetes mellitus non insulin-dependent" and "Diabetes mellitus NOS" compared to RIS, QUE, HAL, or OLA; for "Diabetes mellitus insulin-dependent" compared to RIS, QUE, or HAL; and for "Diabetic coma NOS" compared to either RIS or HAL.

Finally, QUE had a higher, non-overlapping EBGM score for "Diabetic Ketoacidosis" compared to RIS.

RIS and HAL did not have higher, non-overlapping EBGm scores for any of the 15 MPTs compared to any other agent.

There did not appear to be any "publicity effects" or unexpected spikes in the signal strengths over time, and APS monotherapy EBGm scores were in keeping with the results reported above.

Figures 4a-4d and Figures 5a-5b show the results of the polytherapy-versus-monotherapy analysis for the four atypical antipsychotics Clozapine, Olanzapine, Quetiapine, and Risperidone (there was insufficient data to perform the analysis for Ziprasidone).

In Figure 4a (Clozapine), the instances of non-overlapping confidence intervals (between MONO and POLY: Diabetes mellitus NOS, Diabetes mellitus non insulin-dependent) indicate that monotherapy with Clozapine tends to have a higher signal score than polytherapy with Clozapine.

In Figure 4b (Olanzapine), the instances of non-overlapping confidence intervals (Diabetic ketoacidosis, Hyperglycemia NOS) indicate that monotherapy has a higher signal score than polytherapy.

In Figure 4c (Quetiapine), there is a single instance of non-overlapping confidence intervals (Diabetes mellitus NOS), and it points in the direction of a higher signal score for polytherapy as compared to monotherapy.

In Figure 4d (Risperidone), the instances of non-overlapping confidence intervals (Blood glucose increased, Diabetic ketoacidosis) indicate that polytherapy has a higher signal score than monotherapy.

The results contained in Figures 4c and 4d may be interpreted to mean that some of the initially computed association strengths between Quetiapine and diabetes-related PT's and between Risperidone and diabetes-related PT's may be due to concomitant use of other atypical antipsychotics.

The monotherapy-versus-polytherapy results shown in Figures 4a (Clozapine) are consistent with what one would expect if Clozapine were causally associated with Diabetes mellitus NOS and Diabetes mellitus non insulin-dependent but there is also another causally associated agent which is sometimes given concomitantly (in such a case one would expect the polytherapy signal score for Clozapine to be weakened relative to the monotherapy signal score, since the monotherapy analysis provides a sharper "contrast").

Similarly the monotherapy-versus-polytherapy results shown in Figures 4b (Olanzapine) are consistent with what one would expect if Olanzapine were causally associated with Diabetic ketoacidosis and Hyperglycemia NOS but there is also another causally associated agent which is sometimes given concomitantly.

Review of Figure 5b (monotherapy signal scores) indicates that, overall, the comparison of signal strengths between antipsychotic drugs is not affected significantly by restricting attention to monotherapy cases (no concomitant use of another atypical antipsychotic). Whatever "innocent bystander" effects may be present appear to be quite small.

Figures in Appendix C depict, for each of the 15 MedDRA PT's, the distribution of reports in FOI AERS (1968 to 3rd quarter 2002) by the variables used for stratification (Gender, Age Group, FDA Receipt Year) in carrying out the MGPS analyses. Review of age group

distribution indicates that most of the reports of diabetes-related MedDRA terms cluster in the two age groups 17-45 and 46-75 (there is also a cluster for the age group "unknown"). This suggests that our age-related stratification was not optimal; it would probably have been better to choose age cutpoints that produced more and finer divisions within the broad 17-75 age range. To determine how large an effect, if any, the choice of finer-grained stratification within the 17-75 age range would have on the final results, we reran one of the original analyses changing only the choice of age cutpoints (establishing age groups of 0-18, 19-30, 31-50, 51-60, 61-70, >71 and "unknown"). For all the drug-event combinations of interest (6 drugs, 15 MedDRA terms), the EBGM [EB05, EB95] obtained with the new stratification were virtually identical with those obtained with the original stratification (Not Shown).

Conclusions

For each of the glycemic MPTs studied, the association strengths of Risperidone and Haloperidol are essentially indistinguishable. In each case, the association strength for Risperidone/Haloperidol appears to be smaller than, or no different from, that of any other antipsychotic studied. Olanzapine and risperidone, which have fairly similar rates of exposure in the population, generate substantially differing signal scores, and the strength of signal association is greater for Olanzapine compared to Risperidone, Haloperidol and other antipsychotics on MPTs ranging from the rare (e.g. Diabetic ketoacidosis, Diabetic coma NOS) to the commonly reported (e.g., Hyperglycemia NOS). Clozapine also shows a more prominent signal association on several of the glycemia-related MPTs than most other antipsychotics studied.

The data do not support the hypothesis that glycemic disturbances may be produced to the same extent by all atypicals (i.e., as a class effect of atypical antipsychotic therapy). Indeed the signals clearly provide suggestive evidence that the glycemic side-effect profiles of the various antipsychotics examined may be very different, and that prudence would dictate that this should be the initial hypothesis for further research or monitoring programs designed to gather data.

Limitations

The methodology provides information about the relative reporting of adverse events in the post-marketing setting. The analysis does not provide estimates of the absolute incidence of adverse events.

Given that the extent of exposure to these drugs is varied, ranging from many years and patient-lives of exposure for some agents (RIS, OLA) to fewer patients exposed over shorter periods of time for other agents (QUE, ZIP), caution must be exercised in drawing conclusions from these data. Moreover, numerous confounders and covariates beyond age and gender such as basal BMI, weight-gain, dose of antipsychotic, family history of predisposition, and other diabetogenic medicines taken concomitantly were not examinable in a study of this nature. Thus, a high reporting rate does not necessarily indicate a high incidence of the event or a causal relationship between the drug and the event. Nevertheless the results provide evidence for directional hypothesis generation that needs to be tested via prospective studies or through epidemiological studies wherein the extent of exposure in a population and numerous covariates and confounders are identified and controlled.

Reporting rates may vary for specific drug-event combinations and may be affected by many different factors, including publicity (e.g., media attention, class-action lawsuits, Dear Doctor

letters). However, from the histograms of the distribution of PT over time and the plots of signal score progression over time, there was no evidence of any unusual spikes in reporting. Also given that significant publicity has been accorded over the years to the theory that glycemic side effects are a class effect of all atypical antipsychotics, one may expect this to mitigate against the reporting of only certain drug-event combinations. Nevertheless, caution should be used in comparing signal scores, as they may reflect biases due to differential reporting of certain drug-event combinations.

ADDENDUM 1:

Within the group of 15 MedDRA Primary Terms used in this study, there are several subgroups of highly interrelated, nearly synonymous terms that may not be well differentiated in real-life coding practice (i.e., different reporters might well select different terms within these subgroups to describe essentially the same medical condition). Thus an alternate approach to the analysis is to begin by "lumping" the terms within each subgroup, creating a smaller number of distinct categories with correspondingly larger reporting frequencies. We explored this approach by recoding the database of adverse event reports according to the term mapping indicated in the table below, and then re-running the same data mining analyses as before.

TABLE 6

Original PT	Subgroup Category
Blood glucose abnormal	Blood glucose abnormal
Blood glucose increased	Blood glucose abnormal
Glucose tolerance decreased	Blood glucose abnormal
Glucose tolerance impaired	Blood glucose abnormal
Glycosylated hemoglobin increased	Blood glucose abnormal
Hyperglycemia NOS	Blood glucose abnormal
Diabetes mellitus NOS	Diabetes mellitus
Diabetes mellitus insulin-dependent	Diabetes mellitus
Diabetes mellitus non insulin-dependent	Diabetes mellitus
Diabetes mellitus aggravated	Diabetes mellitus inadequate control
Diabetes mellitus inadequate control	Diabetes mellitus inadequate control
Diabetic coma NOS	Diabetic life-threatening terms
Diabetic hyperglycemic coma	Diabetic life-threatening terms
Diabetic hyperosmolar coma	Diabetic life-threatening terms
Diabetic ketoacidosis	Diabetic life-threatening terms

The mapping reduced the original 15 diabetes-related MedDRA PT's to 4 broader categories of diabetes-related conditions (Blood glucose abnormal, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetic life-threatening terms). The results obtained with this mapping were quite consistent with those obtained from the original analysis (see figure 6 in Addendum). Clozapine had a higher EBGM estimate and a non-overlapping confidence interval (with respect to all 5 other antipsychotics) for the lumped category of "Diabetes mellitus". Olanzapine had higher EBGM estimates and non-overlapping confidence intervals (with respect to all 5 other antipsychotics) for the lumped categories of "Diabetic life-threatening terms" and "Blood glucose abnormal". For "Diabetes mellitus", olanzapine had a higher EBGM estimate and non-overlapping confidence interval with respect to haloperidol, quetiapine, and risperidone. For "Diabetic life-threatening terms", quetiapine showed a higher EBGM and non-overlapping CI compared to both haloperidol and risperidone, but overlapping with the CI for clozapine. The

findings do not support the hypothesis that diabetes-related adverse events (especially life-threatening events) are a class effect of atypical antipsychotic therapy but suggest that there may be important differences in the adverse-event profiles of atypical agents.

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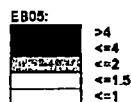
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	EBGM:	>4	Clozapine	Haloperidol	Olanzapine	Quetiapine	Risperidone	Ziprasidone	PT totals
		≤4							
		≤2							
		≤1.5							
		≤1							
Blood glucose abnormal			3	3	6				301
Blood glucose increased			37	27		13	25		3652
Diabetes mellitus NOS				51					4457
Diabetes mellitus aggravated			34	12	32	7	25	7	2398
Diabetes mellitus inadequate control			8	4	24	3	8		1926
Diabetes mellitus insulin-dependent				5		4	3		196
Diabetes mellitus non insulin-dependent						5	9		324
Diabetic coma NOS				5		3	4		384
Diabetic hyperglycaemic coma									38
Diabetic hyperosmolar coma									25
Diabetic ketoacidosis									925
Glucose tolerance decreased				3			3		274
Glucose tolerance impaired					4		3		94
Glycosylated haemoglobin increased			11	4			4		374
Hyperglycaemia NOS			265	90		26	116		20106
Drug Totals			22341	13869	10643	2450	15993	1282	

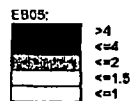
Clozapine	1968-1985	1968-1986	1968-1987	1968-1988	1968-1989	1968-1990	1968-1991	1968-1992	1968-1993	1968-1994	1968-1995	1968-1996	1968-1997	1968-1998	1968-1999	1968-2000	1968-2001	1968-2002
Blood glucose abnormal																		3
Blood glucose increased														4	9	14	26	37
Diabetes mellitus NOS								11	22	30	42	55	65					
Diabetes mellitus aggravated														4	11	16	31	34
Diabetes mellitus inadequate control																3	5	8
Diabetes mellitus insulin-dependent														5				
Diabetes mellitus non insulin-dependent																		
Diabetic coma NOS									4	4	6	9	11	12				
Diabetic hyperglycaemic coma															3	4	5	5
Diabetic hyperosmolar coma																		
Diabetic ketoacidosis									3	6	6	6	8	16	15	16		
Glucose tolerance decreased																		
Glucose tolerance impaired															3	3		
Glycosylated haemoglobin increased																7	8	
Hyperglycaemia NOS							14	32	54	70	90	120	144	163	191	236	218	255
Drug Totals							3621	5748	8672	10611	12322	14304	15892	16821	18049	19647	21028	22341



Graphical spreadsheet showing progression of counts and signal scores over time for the specified anti-psychotic drug and 15 diabetes-related MedDRA Primary Terms (PTs). Rows represent the different PTs, columns represent cumulative time periods. Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. The number in each cell gives the count of reports in AERS (as of the end of the indicated cumulative time period) that mention the specified drug and corresponding PT. The color of each cell encodes the value of the EBGM statistic (see key), which serves as a measure of the strength of association between the drug and the PT (as of the corresponding point in time). EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). The bottom-most row presents the total number of reports in AERS for the specified drug as of the corresponding point in time. [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 2a

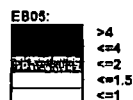
Haloperidol	1968-1985	1968-1986	1968-1987	1968-1988	1968-1989	1968-1990	1968-1991	1968-1992	1968-1993	1968-1994	1968-1995	1968-1996	1968-1997	1968-1998	1968-1999	1968-2000	1968-2001	1968-2002
Blood glucose abnormal																		3
Blood glucose increased														6	10	12	17	27
Diabetes mellitus NOS						7	7	12	13	16	18	21	24	32	35	39	46	51
Diabetes mellitus aggravated															3	6	9	12
Diabetes mellitus inadequate control																	3	4
Diabetes mellitus insulin-dependent																3	4	5
Diabetes mellitus non insulin-dependent															3	5	6	8
Diabetic coma NOS											4	4	4	4	4	4	5	5
Diabetic hyperglycaemic coma																		
Diabetic hyperosmolar coma																		
Diabetic ketoacidosis														4	4	7	17	24
Glucose tolerance decreased									3	3	3	3	3	3	3	3	3	3
Glucose tolerance impaired																		
Glycosylated haemoglobin increased																3	3	4
Hyperglycaemia NOS	3	3	4	7	10	13	14	18	24	27	33	39	46	55	66	78	85	90
Drug Totals	1910	2159	2531	2925	3331	3916	4560	5236	6162	7141	8085	9039	10016	10849	11739	12519	13295	13869



Graphical spreadsheet showing progression of counts and signal scores over time for the specified anti-psychotic drug and 15 diabetes-related MedDRA Primary Terms (PT's). Rows represent the different PT's, columns represent cumulative time periods. Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. The number in each cell gives the count of reports in AERS (as of the end of the indicated cumulative time period) that mention the specified drug and corresponding PT. The color of each cell encodes the value of the EBGM statistic (see key), which serves as a measure of the strength of association between the drug and the PT (as of the corresponding point in time). EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). The bottom-most row presents the total number of reports in AERS for the specified drug as of the corresponding point in time. [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 2b

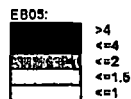
Olanzapine	1968-1985	1968-1986	1968-1987	1968-1988	1968-1989	1968-1990	1968-1991	1968-1992	1968-1993	1968-1994	1968-1995	1968-1996	1968-1997	1968-1998	1968-1999	1968-2000	1968-2001	1968-2002
Blood glucose abnormal																	3	6
Blood glucose increased													4	11	30			
Diabetes mellitus NOS														22				
Diabetes mellitus aggravated															3	10	18	32
Diabetes mellitus inadequate control															4	8	12	24
Diabetes mellitus insulin-dependent														5	6	8		
Diabetes mellitus non insulin-dependent																7		
Diabetic coma NOS														3	4			
Diabetic hyperglycaemic coma																	4	
Diabetic hyperosmolar coma																	4	5
Diabetic ketoacidosis													4					
Glucose tolerance decreased																		
Glucose tolerance impaired																		4
Glycosylated haemoglobin increased															4	9	12	
Hyperglycaemia NOS													55	96	125	191		
Drug Totals													2766	4187	5730	7363	9366	10643



Graphical spreadsheet showing progression of counts and signal scores over time for the specified anti-psychotic drug and 15 diabetes-related MedDRA Primary Terms (PT's). Rows represent the different PT's, columns represent cumulative time periods. Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. The number in each cell gives the count of reports in AERS (as of the end of the indicated cumulative time period) that mention the specified drug and corresponding PT. The color of each cell encodes the value of the EBGM statistic (see key), which serves as a measure of the strength of association between the drug and the PT (as of the corresponding point in time). EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). The bottom-most row presents the total number of reports in AERS for the specified drug as of the corresponding point in time. [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 2c

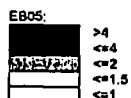
Quetiapine	1968-1985	1968-1986	1968-1987	1968-1988	1968-1989	1968-1990	1968-1991	1968-1992	1968-1993	1968-1994	1968-1995	1968-1996	1968-1997	1968-1998	1968-1999	1968-2000	1968-2001	1968-2002
Blood glucose abnormal																		
Blood glucose increased																4	7	13
Diabetes mellitus NOS															3	9	17	26
Diabetes mellitus aggravated																	4	7
Diabetes mellitus inadequate control																		3
Diabetes mellitus insulin-dependent																		4
Diabetes mellitus non insulin-dependent																		5
Diabetic coma NOS																		3
Diabetic hyperglycaemic coma																		
Diabetic hyperosmolar coma																		
Diabetic ketoacidosis																		
Glucose tolerance decreased																		
Glucose tolerance impaired																		
Glycosylated haemoglobin increased																		6
Hyperglycaemia NOS																12	19	26
Drug Totals															635	1064	1762	2450



Graphical spreadsheet showing progression of counts and signal scores over time for the specified anti-psychotic drug and 15 diabetes-related MedDRA Primary Terms (PTs). Rows represent the different PT's, columns represent cumulative time periods. Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. The number in each cell gives the count of reports in AERS (as of the end of the indicated cumulative time period) that mention the specified drug and corresponding PT. The color of each cell encodes the value of the EBGM statistic (see key), which serves as a measure of the strength of association between the drug and the PT (as of the corresponding point in time). EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). The bottom-most row presents the total number of reports in AERS for the specified drug as of the corresponding point in time. [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 2d

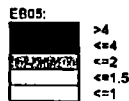
Risperidone	1968-1985	1986-1987	1988-1989	1990-1991	1992-1993	1994-1995	1996-1997	1998-1999	2000-2001	2002-2003
Blood glucose abnormal										
Blood glucose increased								4	6	8
Diabetes mellitus NOS						10	22	32	36	48
Diabetes mellitus aggravated								3	10	15
Diabetes mellitus inadequate control								4	7	7
Diabetes mellitus insulin-dependent									3	3
Diabetes mellitus non insulin-dependent									4	6
Diabetic coma NOS										4
Diabetic hyperglycemic coma										
Diabetic hyperosmolar coma										
Diabetic ketoacidosis								3	5	9
Glucose tolerance decreased							3	3	3	3
Glucose tolerance impaired										3
Glycosylated haemoglobin increased										4
Hyperglycaemia NOS						6	32	54	69	90
Drug Totals						2340	5107	7416	8502	10558



Graphical spreadsheet showing progression of counts and signal scores over time for the specified anti-psychotic drug and 15 diabetes-related MedDRA Primary Terms (PTs). Rows represent the different PTs, columns represent cumulative time periods. Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. The number in each cell gives the count of reports in AERS (as of the end of the indicated cumulative time period) that mention the specified drug and corresponding PT. The color of each cell encodes the value of the EBGM statistic (see key), which serves as a measure of the strength of association between the drug and the PT (as of the corresponding point in time). EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). The bottom-most row presents the total number of reports in AERS for the specified drug as of the corresponding point in time. [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

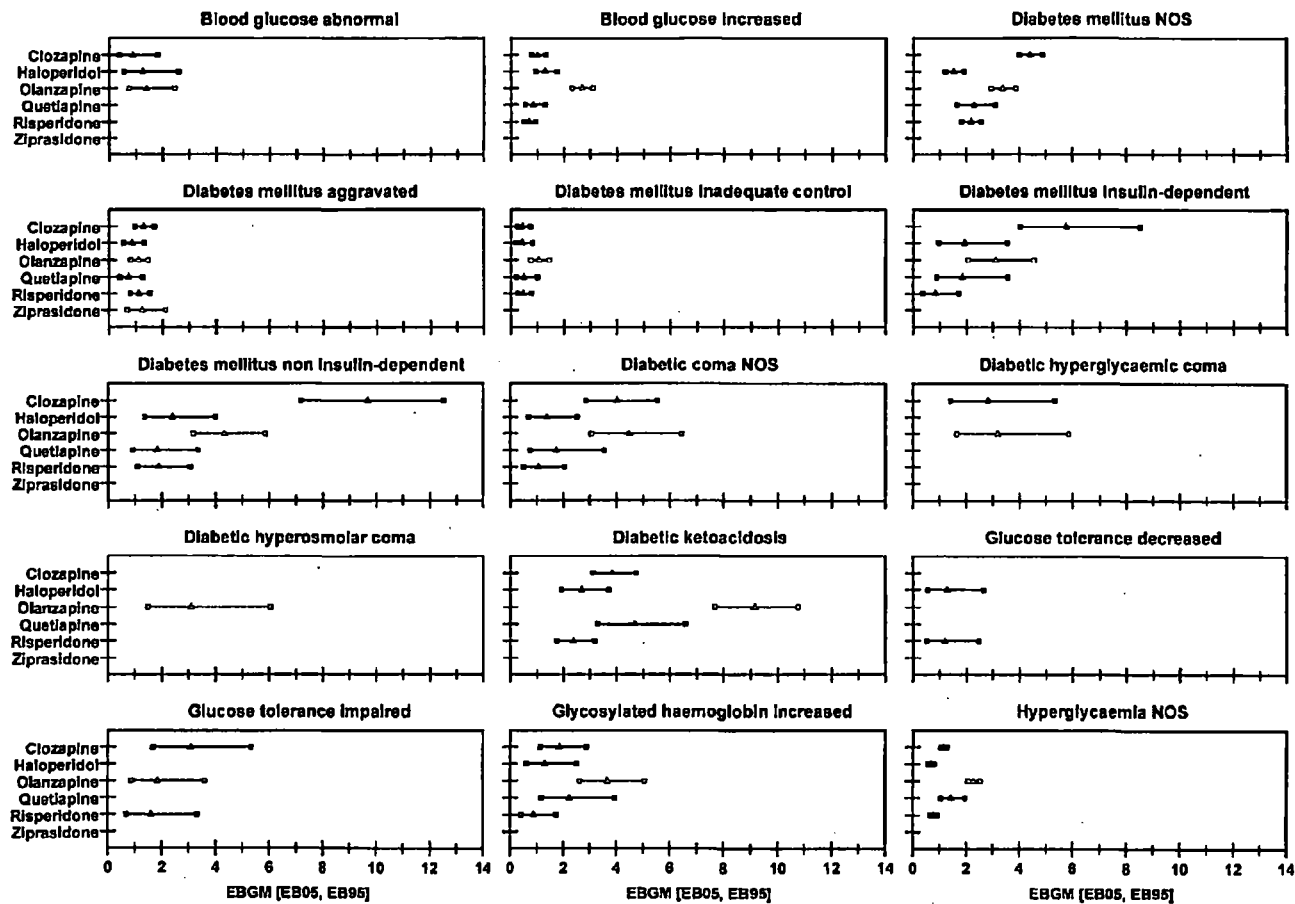
Figure 2e

Ziprasidone	1968-1985	1968-1986	1968-1987	1968-1988	1968-1989	1968-1990	1968-1991	1968-1992	1968-1993	1968-1994	1968-1995	1968-1996	1968-1997	1968-1998	1968-1999	1968-2000	1968-2001	1968-2002
Blood glucose abnormal																		
Blood glucose increased																		
Diabetes mellitus NOS																		
Diabetes mellitus aggravated																		7
Diabetes mellitus inadequate control																		
Diabetes mellitus insulin-dependent																		
Diabetes mellitus non insulin-dependent																		
Diabetic coma NOS																		
Diabetic hyperglycaemic coma																		
Diabetic hyperosmolar coma																		
Diabetic ketoacidosis																		
Glucose tolerance decreased																		
Glucose tolerance impaired																		
Glycosylated haemoglobin increased																		
Hyperglycaemia NOS																		
Drug Totals																		1282



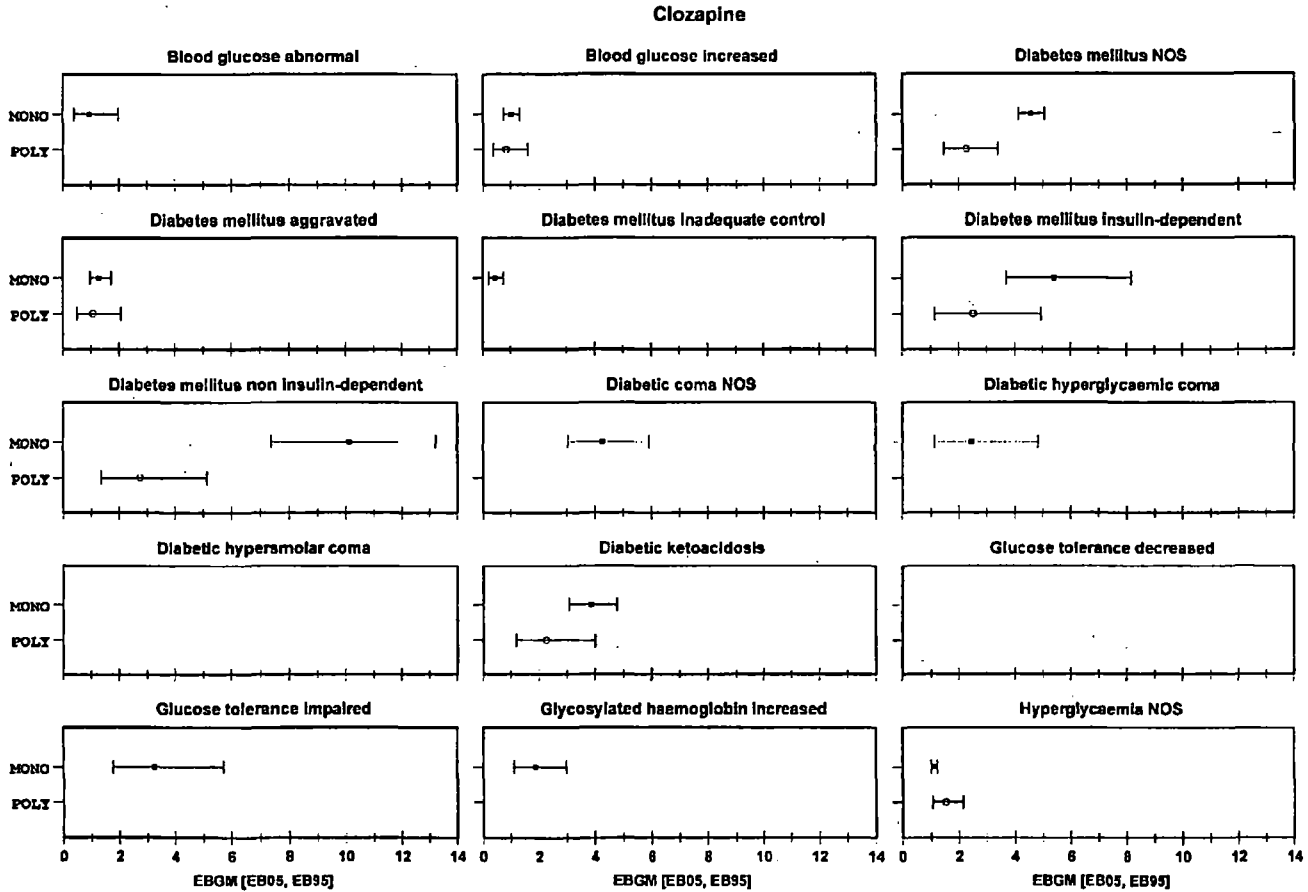
Graphical spreadsheet showing progression of counts and signal scores over time for the specified anti-psychotic drug and 15 diabetes-related MedDRA Primary Terms (PT's). Rows represent the different PT's, columns represent cumulative time periods. Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. The number in each cell gives the count of reports in AERS (as of the end of the indicated cumulative time period) that mention the specified drug and corresponding PT. The color of each cell encodes the value of the EBGM statistic (see key), which serves as a measure of the strength of association between the drug and the PT (as of the corresponding point in time). EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). The bottom-most row presents the total number of reports in AERS for the specified drug as of the corresponding point in time. [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 2f



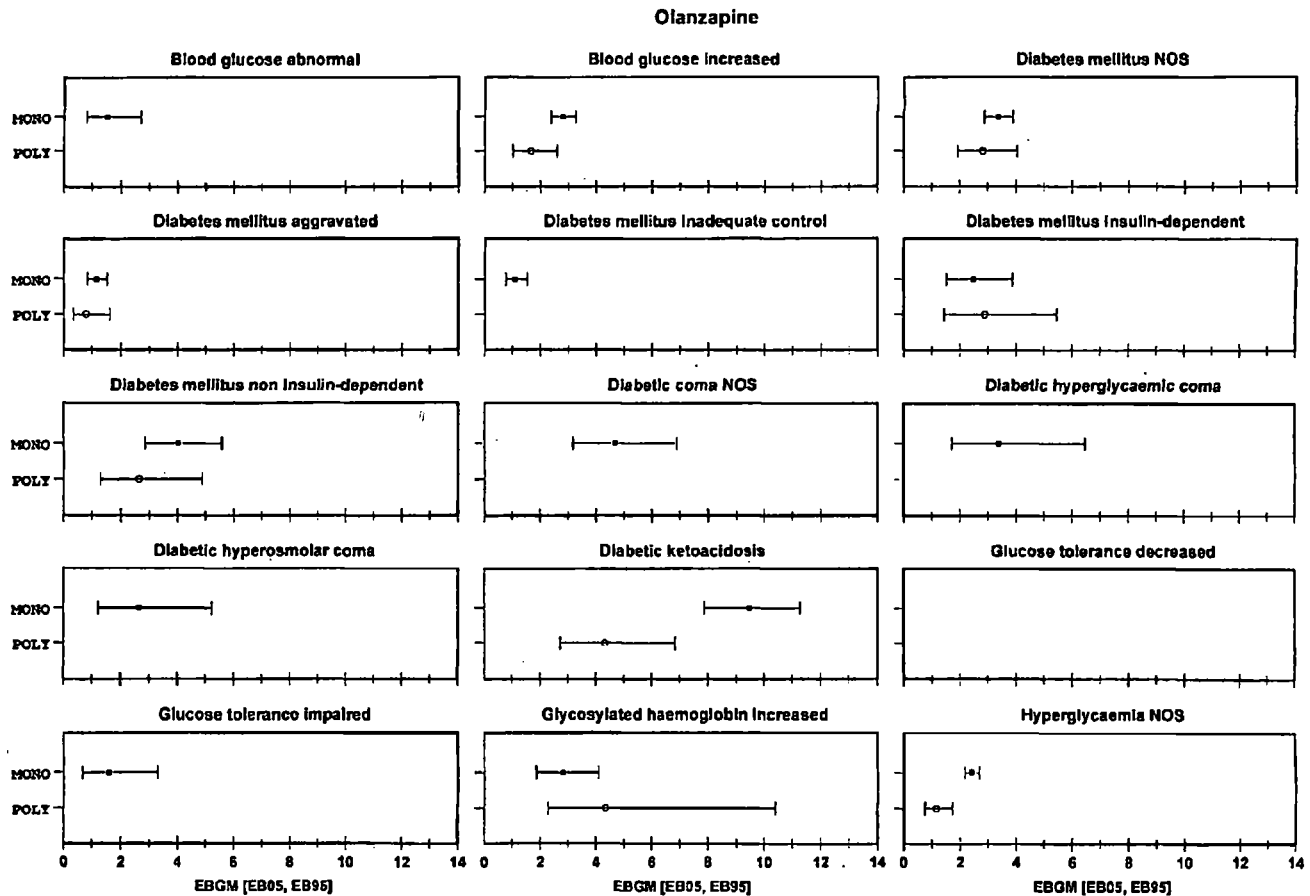
Signal scores for 6 drugs with confidence intervals. Association strength for 15 diabetes-related MedDRA terms with each of 6 anti-psychotic drugs. Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. Association strength is indicated by EBGM statistic along with its lower 5% (EB05) and upper 95% (EB95) confidence limits. EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 3



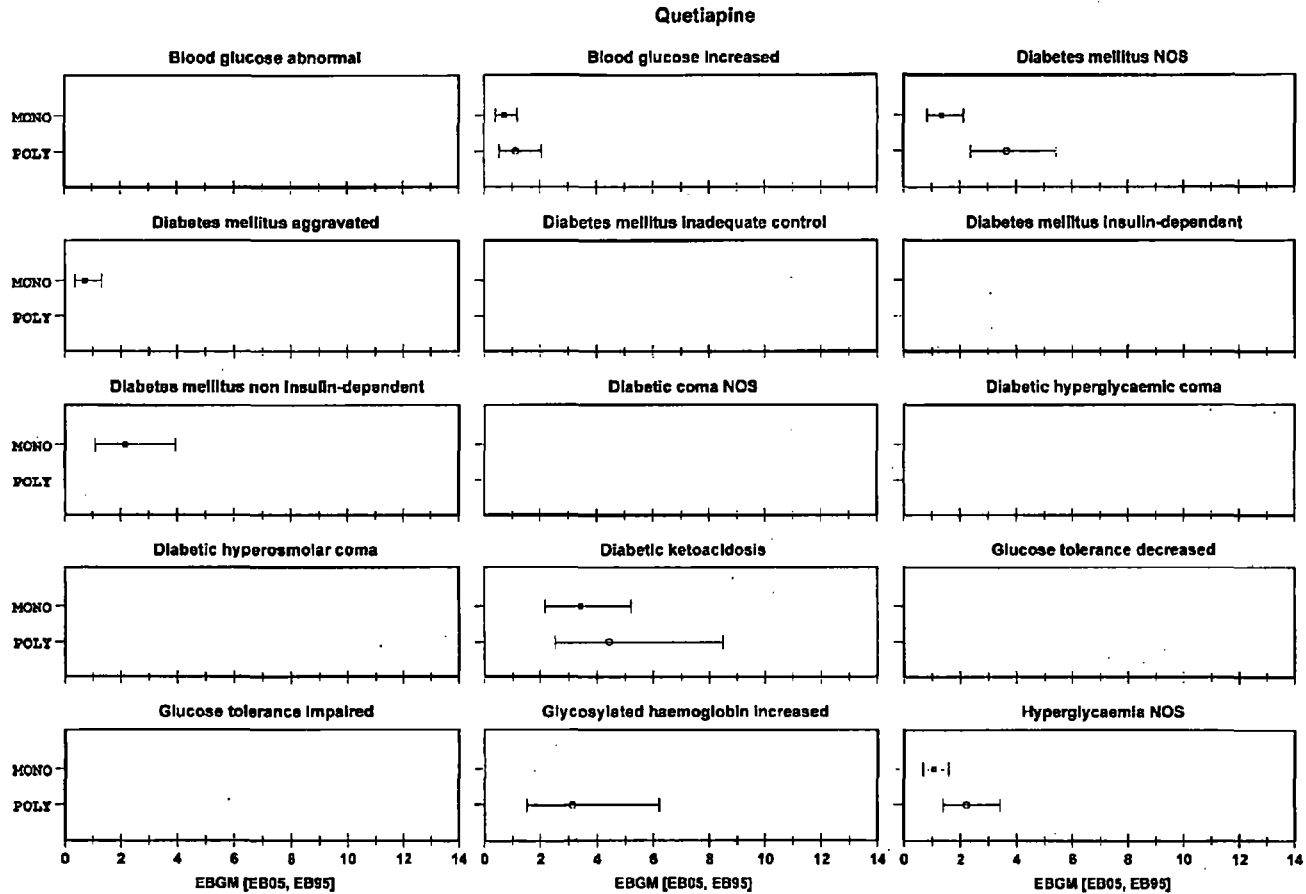
Monotherapy/polytherapy signal scores for Clozapine. Association strength for 15 diabetes-related MedDRA terms with Clozapine without/with ("MONO"/"POLY") concomitant use of one of 4 other atypical anti-psychotics (Olanzapine, Quetiapine, Risperidone, Ziprasidone). Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. Association strength is indicated by EBGM statistic along with its lower 5% (EB05) and upper 95% (EB95) confidence limits. EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 4a



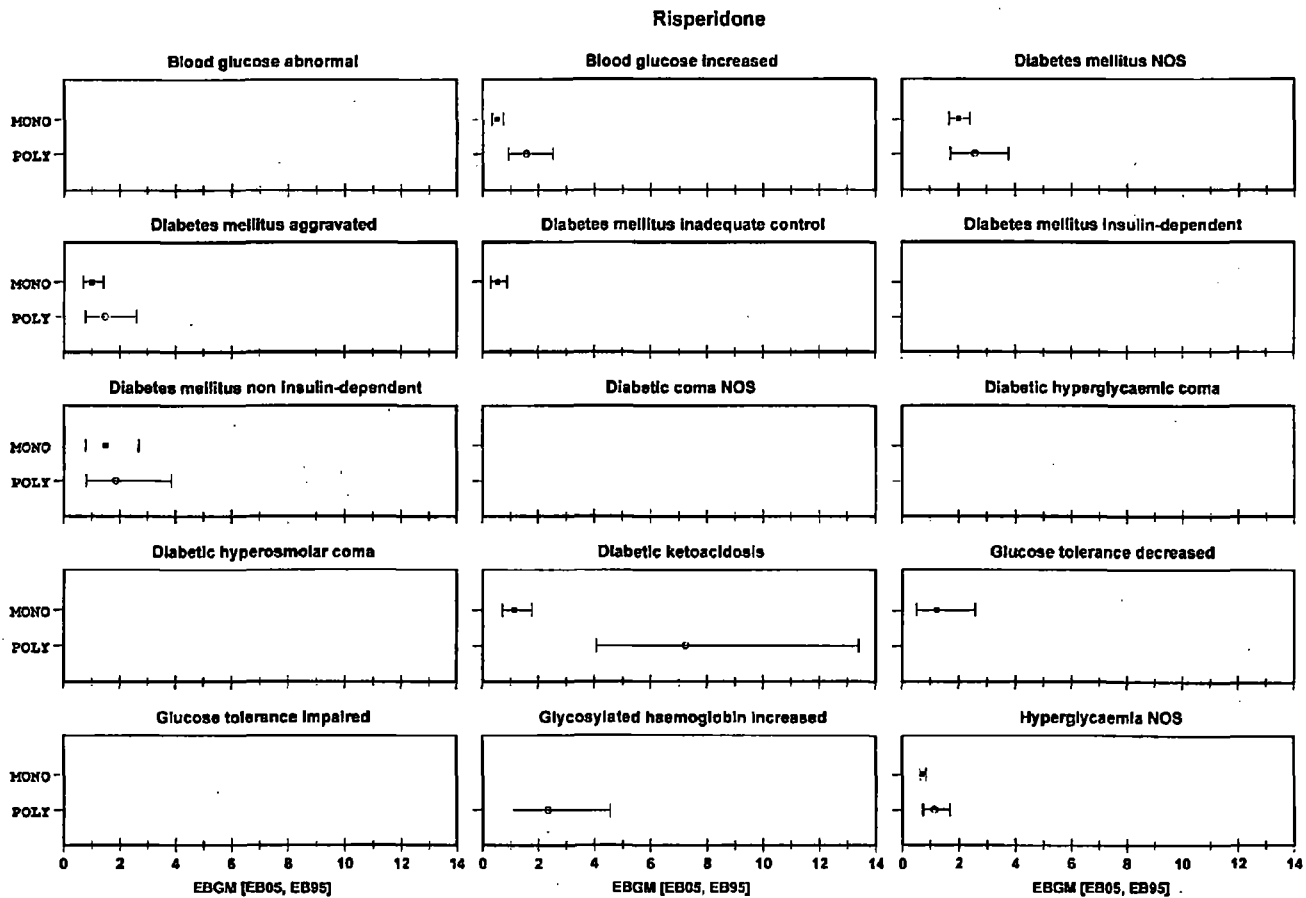
Monotherapy/polytherapy signal scores for Olanzapine. Association strength for 15 diabetes-related MedDRA terms with Olanzapine without/with ("MONO"/"POLY") concomitant use of one of 4 other atypical anti-psychotics (Clozapine, Quetiapine, Risperidone, Ziprasidone). Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. Association strength is indicated by EBGM statistic along with its lower 5% (EB05) and upper 95% (EB95) confidence limits. EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 4b



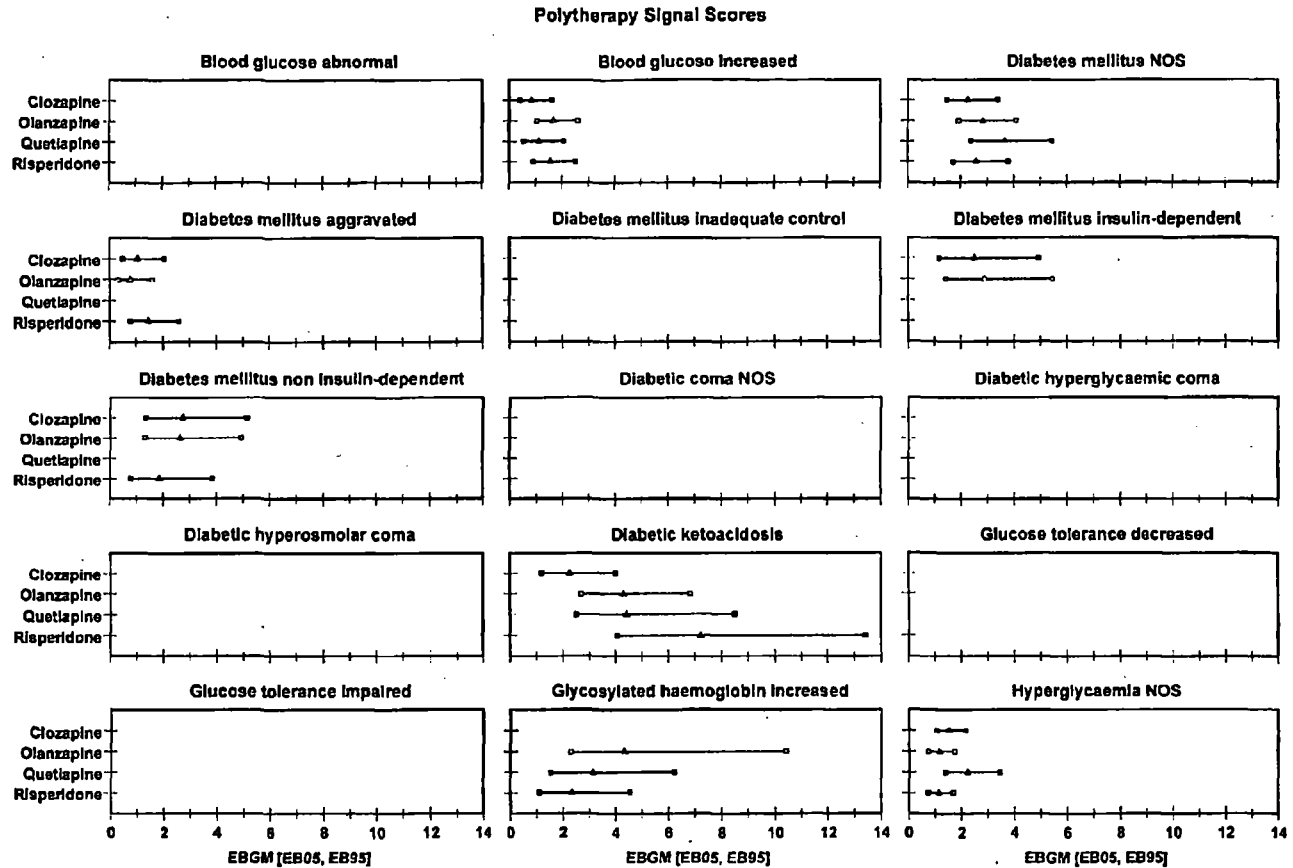
Monotherapy/polytherapy signal scores for Quetiapine. Association strength for 15 diabetes-related MedDRA terms with Quetiapine without/with ("MONO"/"POLY") concomitant use of one of 4 other atypical anti-psychotics (Clozapine, Olanzapine, Risperidone, Ziprasidone). Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. Association strength is indicated by EBGM statistic along with its lower 5% (EB05) and upper 95% (EB95) confidence limits. EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 4c



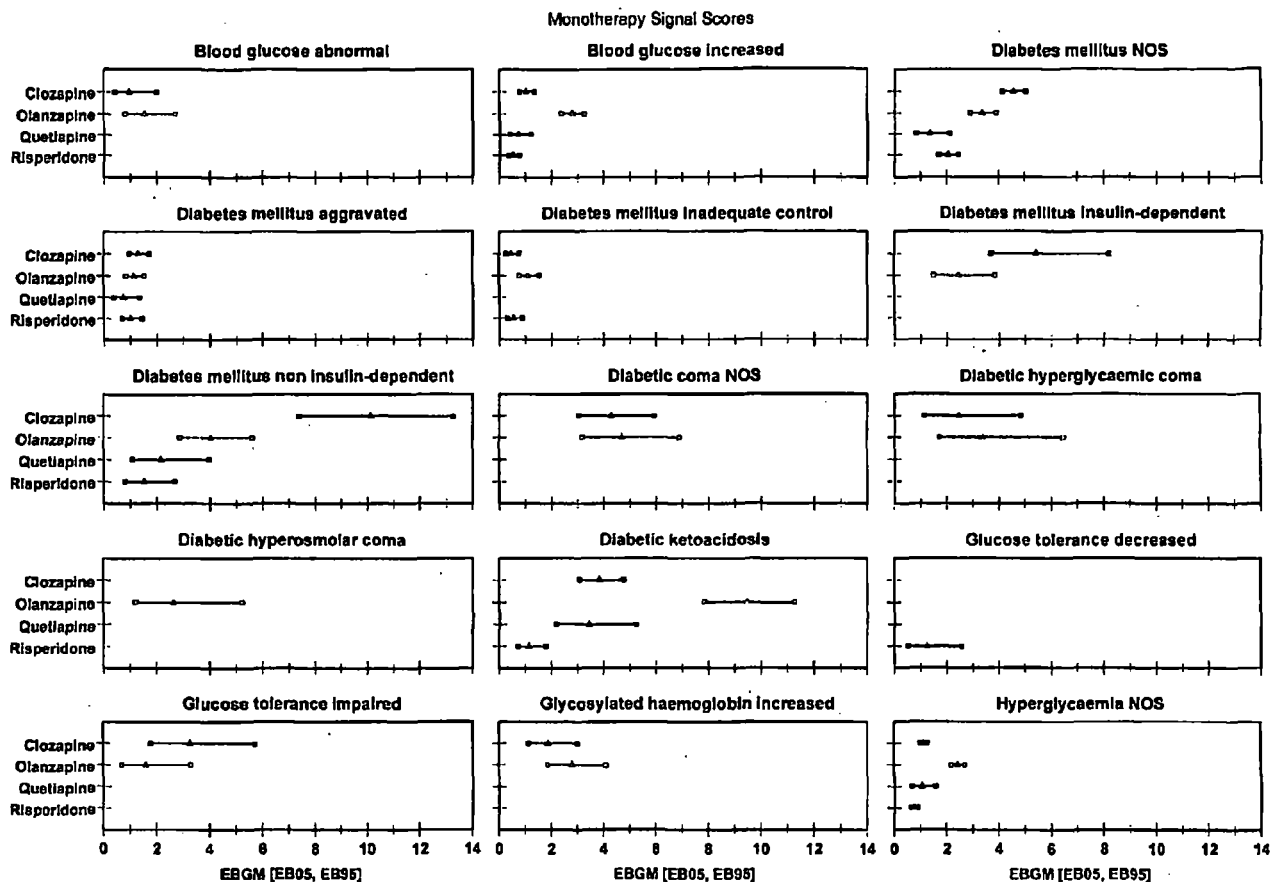
Monotherapy/polytherapy signal scores for Risperidone. Association strength for 15 diabetes-related MedDRA terms with Risperidone without/with ("MONO"/"POLY") concomitant use of one of 4 other atypical anti-psychotics (Clozapine, Olanzapine, Quetiapine, Ziprasidone). Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. Association strength is indicated by EBGM statistic along with its lower 5% (EB05) and upper 95% (EB95) confidence limits. EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). (Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.)

Figure 4d



Comparison of polytherapy signal scores. Association strength for 15 diabetes-related MedDRA terms for each of 4 atypical anti-psychotic drugs (Clozapine, Olanzapine, Quetiapine, Risperidone) WITH concomitant use of one or more of 5 other atypical anti-psychotics (Olanzapine, Quetiapine, Risperidone, Ziprasidone). Results based on MGHS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. Association strength is indicated by EBGM statistic along with its lower 5% (EB05) and upper 95% (EB95) confidence limits. EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 5a



Comparison of monotherapy signal scores. Association strength for 15 diabetes-related MedDRA terms for each of 4 atypical anti-psychotic drugs (Clozapine, Olanzapine, Quetiapine, Risperidone) WITHOUT concomitant use of any of 5 other atypical anti-psychotics (Olanzapine, Quetiapine, Risperidone, Ziprasidone). Results based on MGPS data mining analysis of FOI AERS data for the period 1968 through 3rd quarter 2002. Association strength is indicated by EBGM statistic along with its lower 5% (EB05) and upper 95% (EB95) confidence limits. EBGM is an estimate of the relative reporting ratio for the drug-event combination (observed count divided by expected count). [Data mining run parameters: Stratification by gender, age, and FDA receipt year. Drug references coded to standardized generic names. Events coded using MedDRA 4.0 Primary Terms. Minimum count threshold of 3 for including drug-event combinations. Run performed on September 14, 2003.]

Figure 5b

**Antipsychotics and Glycemic side-effects:
A Bayesian data-mining analysis of the AERS database
(1968- 2002)**

**ADDENDUM to Report Prepared For Janssen Pharmaceutica Products L.P.
by Lincoln Technologies , Wellesly Hills, MA**

Final Report Date: 10/6/03 (revised 10/28/03)

Addendum (Figures) Date: (10/8/03)

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D919.120

ADDENDUM 1: EBGM
Values & CI (DATA
TABLE)

ITEM1	ITEM2	N	E	RR	EBGM	EB05	EB95
Clozapine	Blood glucose abnormal	314	276.08	1.137	1.135	1.034	1.244
Haloperidol	Blood glucose abnormal	124	158.444	0.783	0.783	0.674	0.904
Quetiapine	Blood glucose abnormal	44	34.36	1.281	1.257	0.979	1.595
Ziprasidone	Blood glucose abnormal	5	18.037	0.277	0.32	0.16	0.588
Risperidone	Blood glucose abnormal	150	181.043	0.785	0.785	0.686	0.896
Olanzapine	Blood glucose abnormal	378	154.332	2.449	2.431	2.233	2.644
Clozapine	Diabetes mellitus	351	70.339	4.99	4.894	4.479	5.339
Haloperidol	Diabetes mellitus	64	38.081	1.775	1.731	1.408	2.112
Olanzapine	Diabetes mellitus	181	47.715	3.793	3.692	3.263	4.183
Risperidone	Diabetes mellitus	109	49.461	2.204	2.157	1.84	2.516
Quetiapine	Diabetes mellitus	35	13.241	2.643	2.434	1.839	3.173
Clozapine	Diabetes mellitus inadequate control	40	43.108	0.928	0.922	0.709	1.183
Ziprasidone	Diabetes mellitus inadequate control	7	8.413	0.832	0.824	0.452	1.407
Risperidone	Diabetes mellitus inadequate control	33	38.068	0.867	0.863	0.647	1.133
Haloperidol	Diabetes mellitus inadequate control	16	23.867	0.67	0.678	0.45	0.989
Quetiapine	Diabetes mellitus inadequate control	9	15.463	0.582	0.602	0.352	0.976
Olanzapine	Diabetes mellitus inadequate control	55	47.821	1.15	1.138	0.909	1.409
Clozapine	Diabetic life-threatening terms	85	19.658	4.324	4.048	3.379	4.818
Haloperidol	Diabetic life-threatening terms	27	10.328	2.614	2.359	1.715	3.18
Quetiapine	Diabetic life-threatening terms	27	4.59	5.882	4.552	3.295	6.198
Risperidone	Diabetic life-threatening terms	31	13.987	2.216	2.063	1.532	2.73
Olanzapine	Diabetic life-threatening terms	138	15.615	8.837	8.583	7.336	9.966

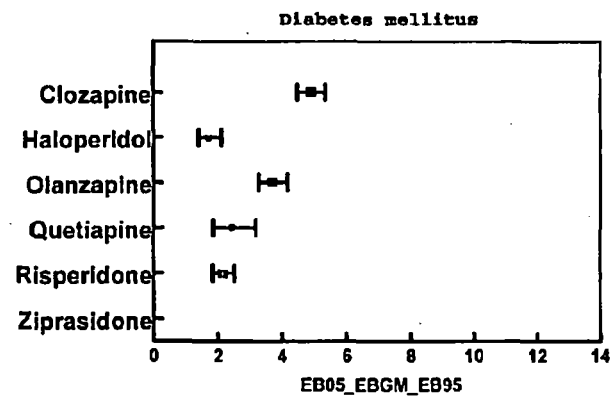
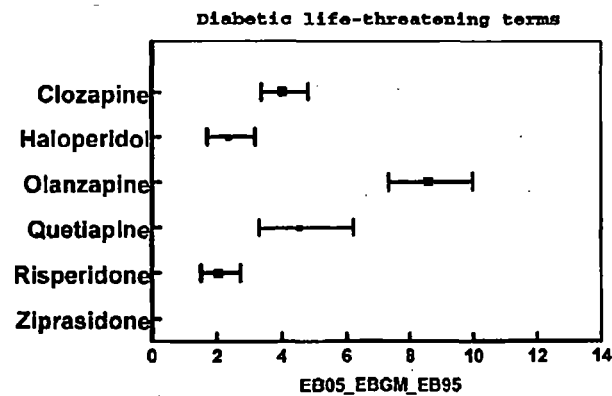
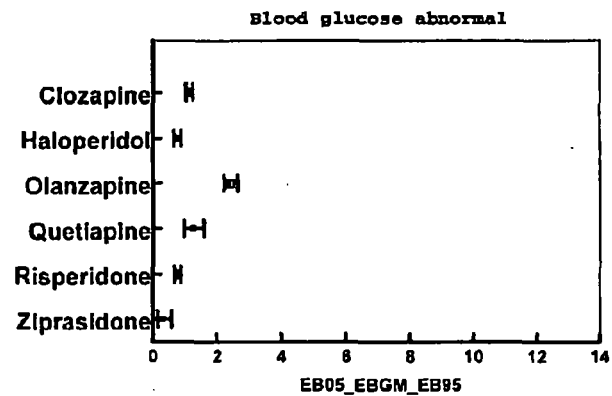
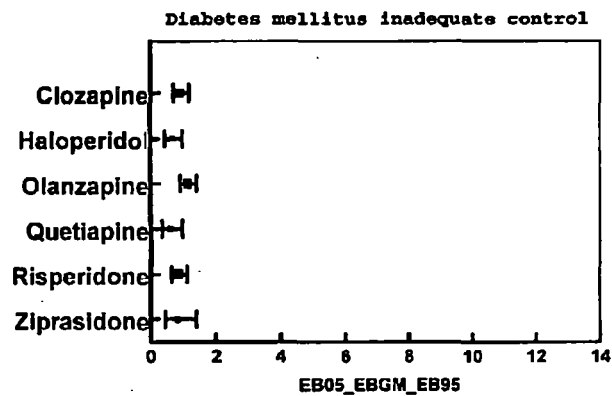


Figure 6. Results (signal scores with confidence intervals for 6 drugs) based on "lumping" of 15 MedDRA PT's into 4 broader categories.

Risk of Diabetes Among Risperidone and Olanzapine Users

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²Unité de recherche en santé des populations, Centre de recherche hospitalier CHU de Québec, Québec, Canada.

INTRODUCTION

Schizophrenia is a major psychotic disorder that can be highly debilitating. The disease most commonly manifests itself in late adolescence to young adulthood with a lifetime prevalence of about 1% throughout the world⁽¹⁾. Schizophrenia is frequently characterized by a chronic recurrent course and consequently significant costs incurred, which are associated with health care and productivity loss^(1, 2). In Canada, in 1996 schizophrenia incurred estimated direct health care and non-health costs of 1.12 billion CAD⁽³⁾. In addition, another 1.23 billion CAD in lost productivity associated with morbidity and premature mortality was attributable to schizophrenia.

Typical antipsychotics, such as chlorpromazine and haloperidol, have revolutionized the treatment of schizophrenia and have contributed substantially to the process of de-institutionalization in the past 20 years⁽⁴⁾. However, their effectiveness in the management of schizophrenia has been compromised by the high incidence of drug-related side effects, especially extra-pyramidal symptoms that often lead to non-compliance and to drug discontinuation^(5, 6). The new atypical antipsychotics exhibit different pharmacological profiles from typical antipsychotics^(7, 8). They have demonstrated a superior efficacy against negative symptoms and they have been associated with a lower risk of extrapyramidal symptoms^(9, 10).

However, emerging evidence suggests that atypical antipsychotics may be associated with the risk of new onset diabetes mellitus on prescription of the drug^(11, 12). For example, cases of new onset diabetes have been reported with clozapine and olanzapine and it has been observed in a cross-sectional study that more clozapine or olanzapine users than haloperidol, risperidone or fluphenazine users were having type II diabetes mellitus.

OBJECTIVE

To compare the incidence of diabetes among first time users of olanzapine and first time users of risperidone treated in an ambulatory setting. (We chose those two drugs because they are the most prescribed atypical antipsychotics in the province of Québec.)

METHODS

Study design

Population-based cohort study using data from the Québec drug benefit plan.

Study population

Inclusion criteria:

- all people who received a first prescription of olanzapine or risperidone between 1/1/1997 and 6/30/1999
- all people who were eligible to the drug plan for the entire 6-month period preceding the first olanzapine or risperidone prescription
- all people who had not been prescribed an antidiabetic drug or any atypical antipsychotic for this same 6-month period

Measurements

Outcomes:

- Having a first prescription of any oral hypoglycemic agent or insulin (those who had a prescription of an antidiabetic drug were considered as having diabetes).
- Person-months of follow-up were figured as the amount of time:

- from the date of the first olanzapine or risperidone prescription
- to the date of one of the following, whichever came first:
 - the first antidiabetic drug prescription
 - the end of olanzapine or risperidone treatment
 - the end of the eligibility to the drug plan
 - the end of the follow-up period (6/31/2000)

Analyses

- A proportional hazard model was used to compute the age and sex adjusted incidence rate ratio (IRR) of developing diabetes, among olanzapine users, compared to risperidone users.

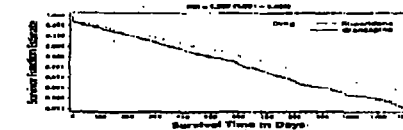
RESULTS

- In all, 28,143 people were included in the cohort.
- 12,945 used olanzapine = 250 (1.9%) of whom had a first prescription of an antidiabetic drug.
- 15,197 used risperidone = 211 (1.4%) of whom had a first prescription of an antidiabetic drug.



- The risk of developing diabetes was slightly higher for those exposed to olanzapine than for those exposed to risperidone.

Figure 1. Survival probabilities of diabetes by drug adjusted for sex and age



CONCLUSION

The results of this study confirm what has been suggested from previous reports: as opposed to risperidone, exposure to olanzapine increases slightly the risk of developing diabetes over a short-term period. There is a need to extend this study over a longer observation period, as the risk of developing diabetes after exposure to antipsychotic drugs is likely to increase with time.

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6. Marder SR, Rothman AW, Kane JM. *Antipsychotic Drugs: A Practical Approach*. London: Taylor & Francis; 1998:1-10.
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8. Marder SR, Rothman AW, Kane JM. *Antipsychotic Drugs: A Practical Approach*. London: Taylor & Francis; 1998:1-10.
9. Marder SR, Rothman AW, Kane JM. *Antipsychotic Drugs: A Practical Approach*. London: Taylor & Francis; 1998:1-10.
10. Marder SR, Rothman AW, Kane JM. *Antipsychotic Drugs: A Practical Approach*. London: Taylor & Francis; 1998:1-10.
11. Marder SR, Rothman AW, Kane JM. *Antipsychotic Drugs: A Practical Approach*. London: Taylor & Francis; 1998:1-10.
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The Risk of Diabetes During Olanzapine Use Compared With Risperidone Use: A Retrospective Database Analysis

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Carey Levinton, Ph.D.; and Kimberly Robinson, M.B.A.B.Sc.

Background: The relative risk of diabetes among patients undergoing risperidone treatment was compared with that of patients receiving olanzapine.

Method: A cohort was formed of 35,946 patients with at least 1 prescription for either olanzapine ($N = 19,153$) or risperidone ($N = 14,793$) between January 1, 1997, and December 31, 1999, recorded in the Régie de l'Assurance Maladie du Québec database. Patients were excluded if clozapine was dispensed to them during the study period or if they were diagnosed with diabetes before beginning antipsychotic therapy. New diabetes diagnoses made after the first antipsychotic prescription during the period were tabulated until December 31, 1999; censoring occurred at this date or at the last service date, if there was no record of using services during the last 6 months of follow-up. Crude hazard ratio and proportional hazard analyses were carried out.

Results: 319 patients developed diabetes on olanzapine treatment, and 217 developed diabetes on risperidone treatment; a crude hazard ratio of 1.08 (95% CI = 0.89 to 1.31, $p = .43$) was determined. When age, gender, and haloperidol use were controlled for using proportional hazard analysis, there was a 20% increased risk of diabetes with olanzapine relative to risperidone (95% CI = 0% to 43%; $p = .05$). Proportional hazard analyses adjusted for duration of olanzapine exposure indicated that the first 3 months of olanzapine treatment was associated with an increased risk of diabetes of 90% (95% CI = 40% to 157%, $p < .0001$), after adjusting for age, gender, and haloperidol use.

Conclusion: Compared with risperidone, olanzapine was associated with an increased risk of developing diabetes. More studies are required to further investigate this association.

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Atypical antipsychotic agents such as risperidone, olanzapine, quetiapine, and clozapine have been a major development in the long-term treatment of psychotic disorders. One major advantage is the lower incidence and severity of extrapyramidal symptoms and tardive dyskinesia compared with conventional antipsychotic agents such as haloperidol.¹ Recently, there have been many case reports associating the atypical antipsychotic agents, especially olanzapine and clozapine, with the development of diabetes.²⁻²⁵ Apparent remission of diabetes after discontinuing olanzapine has also been observed in 9 of the published cases,^{2-6,17,19,24} and 1 patient exhibited a return of hyperglycemia after rechallenge with olanzapine.³ It is unclear whether these cases reflect an incidence of olanzapine-related diabetes in excess of that expected.

Retrospective database analyses have also provided evidence that atypical antipsychotic agents may be associated with development of diabetes by comparison with a general population not receiving any antipsychotic agent.²⁶⁻²⁸ In addition, a study of patients diagnosed with schizophrenia indicated a higher prevalence of diabetes among patients prescribed atypical antipsychotics than among those receiving conventional agents, especially in patients less than 40 years old.²⁹ The studies published have not directly compared the risk of diabetes after initiating olanzapine with that associated with each of the other atypical antipsychotic agents. This study was, therefore, designed to estimate the risk of developing diabetes among patients undergoing treatment with olanzapine compared with risperidone.

METHOD

Data Source

The health care databases managed by the Régie de l'Assurance Maladie du Québec (RAMQ) were used to obtain data for patients who were treated with either olanzapine or risperidone. RAMQ is a provincial government department overseeing health care claims, including those for approximately 3.5 million patients eligible for the drug insurance program. This program covers all residents of Québec, Canada, aged 65 years and older, welfare recipients, and patients without private insurance. The databases contain outpatient prescription claims (including drug code and service date), the primary diagnosis recorded at each outpatient physician visit, dates of service, age, and gender. These databases were linked using unique patient identifiers. Each patient in the database has a unique identification number that is encrypted to protect confidentiality when the files are released for research.

Cohort and Outcome Definition

Patients who received at least 1 prescription for olanzapine or risperidone between January 1, 1997, and December 31, 1999, were identified. The date of the first prescription for one of these drugs was identified as the start date for each patient. Subjects were excluded if a prescription for clozapine was dispensed during the study period, if records were not available for at least 1 year before their start date, or if diabetes had been diagnosed or they were receiving medication for diabetes during the year prior to their start date. The cohort of olanzapine and risperidone users was then divided into 2 groups depending on whether they were dispensed a prescription for olanzapine.

The outcome of interest was whether or not patients received a primary diagnosis of diabetes at a physician visit (4-digit codes 250.0–250.9 in the *International Classification of Diseases*, Ninth Revision [ICD-9])³⁰ or had a first medication claim for insulin or an oral hypoglycemic agent. The date of onset of diabetes was defined as the first date on which the outcome was noted. Patients diagnosed with schizophrenia were identified using ICD-9 codes 295.0 to 295.9.³⁰

The end of follow-up was defined as the date of onset of diabetes; or December 31, 1999; or, among patients with no recorded physician visit or medication claims in the last 6 months of the study, the last service date. For each patient, the observation time was calculated as the number of days between the start and end dates. The duration of exposure to each drug was determined as the time from the first prescription to the end of follow-up, and the total potential exposure time was divided into 4 categories: less than 3 months from index date of prescription, 3 to < 6 months, 6 to < 12 months, and 1 year or more.

Table 1. Patient Demographic Data and Clinical Characteristics*

Characteristic	Olanzapine	Risperidone	p Value
Subjects, N	19,133 (18,763)	14,793 (13,563)	
(person-years)			
Female	9637 (50.3)	8287 (56.0)	< .001
Age			
All patients			< .001
< 45 years	10,967 (57.3)	6096 (41.2)	
45–64 years	4778 (25.0)	2938 (19.9)	
≥ 65 years	3408 (17.8)	5759 (38.9)	
Schizophrenia patients			< .001
< 45 years	7785 (66.0)	3202 (56.0)	
45–64 years	3088 (26.2)	1613 (28.2)	
≥ 65 years	928 (7.9)	905 (15.8)	
Concomitant haloperidol	7293 (38.1)	4832 (32.6)	< .001

*Values shown as N (%) unless otherwise noted.

Analyses

The hazard of diabetes was estimated as the number of cases of diabetes divided by the total observation time. Crude hazard ratios and 95% confidence intervals (CIs) were estimated. Comparisons stratified by age, gender, and treatment exposure duration were also carried out.³¹ A p value ≤ .05 was considered statistically significant. Cox proportional hazard analyses³² were used to adjust for age, gender, diagnosis of schizophrenia, haloperidol use, use of other antipsychotic agents, and duration of exposure.

RESULTS

A total of 34,692 patients had at least 1 prescription for olanzapine or risperidone between January 1, 1997, and December 31, 1999. Clozapine was dispensed to 746 patients (2.2%) who were excluded from the study. The patients receiving either olanzapine or risperidone accumulated 32,328 person-years of follow-up between January 1, 1997, and December 31, 1999. Overall, 4775 (14.1%) of the patients had no evidence of service use in the last 6 months of the study and were censored at their last visit date. Olanzapine was dispensed more than once to 17,142 (89.5%) of the patients in the olanzapine group, and risperidone was dispensed more than once to 12,259 (82.9%) of the patients in the risperidone group.

Patients in the olanzapine group tended to be younger and more frequently male (Table 1). More of the olanzapine users were diagnosed with schizophrenia; 62% compared with 39% of the risperidone patients. Olanzapine users were also more likely to be prescribed haloperidol (see Table 1).

Overall, 319 patients developed diabetes after being prescribed olanzapine, and 217, after being prescribed risperidone; a crude hazard ratio of diabetes was 1.08 (95% CI = 0.89 to 1.31, p = .43) (Table 2). These crude rates may be misleading, because they do not take the imbalances of age, gender, and other characteristics into account.

Table 2. Diabetes Event Rates in Olanzapine Versus Risperidone Users and Crude Relative Risk, According to Gender, Age, and Duration of Treatment

Characteristic	Olanzapine		Risperidone		Relative Risk (95% CI)	p Value
	No. of Diabetes Cases	Rate ^a	No. of Diabetes Cases	Rate ^a		
All patients	319	17	217	16	1.08 (0.89 to 1.31)	.43
Gender						
Male	118	12	85	14	0.86 (0.60 to 1.23)	.41
Female	201	23	132	18	1.28 (1.05 to 1.67)	.02 ^b
Age group						
< 45 years	147	13	70	11	1.14 (0.79 to 1.65)	.49
45-64 years	113	24	56	19	1.26 (0.89 to 1.90)	.22
≥ 65 years	59	24	91	20	1.19 (0.94 to 1.51)	.16
Treatment duration						
< 3 months	60	26	31	21	1.21 (0.84 to 1.75)	.31
3 < 6 months	24	17	16	13	1.23 (0.62 to 2.44)	.56
6 < 12 months	53	17	31	14	1.20 (0.72 to 2.01)	.49
≥ 12 months	182	16	119	15	1.04 (0.76 to 1.42)	.80

^aRates per 1000 person-years.^bSignificant p value.

Table 3. Relative Risk of Developing Diabetes in Olanzapine Versus Risperidone Users (adjusted for age, gender, and haloperidol use)

Model	Adjusted Relative Risk (95% CI)	p Value
All patients	1.20 (1.00 to 1.43)	.03
Women	1.30 (1.05 to 1.65)	.02
Drug exposure time		
< 3 months	1.90 (1.40 to 2.57)	.0004
3 < 6 months	1.16 (0.75 to 1.78)	.50
6 < 12 months	1.11 (0.81 to 1.51)	.51
≥ 12 months	1.06 (0.86 to 1.31)	.58

When age, gender, and haloperidol use were controlled for using proportional hazard analysis, the relative risk of diabetes was increased 20% (95% CI = 0% to 43%, $p = .05$) for olanzapine compared with risperidone (Table 3). This analysis also revealed significant interaction between olanzapine use and gender. Consequently, the proportional hazard analyses were also stratified by gender. Among women, the relative risk of diabetes was increased 30% (95% CI = 5% to 65%, $p = .02$) comparing olanzapine with risperidone, after adjusting for age, schizophrenia diagnosis, and haloperidol use (see Table 3). Adjusting for use of other antipsychotic medications did not change our findings.

Proportional hazard analyses adjusting for the duration of olanzapine exposure indicated that, particularly in the first 3 months of olanzapine treatment, there was a 90% increase (95% CI = 40% to 157%, $p < .0001$) in the risk of developing diabetes when compared with risperidone (see Table 3).

DISCUSSION

In our study of a large population of patients, olanzapine use was associated with an increased risk of devel-

oping diabetes, especially during the first 3 months of treatment, when compared with risperidone. Other researchers have also noted that, in most cases, the onset of diabetes occurred within a year of initiating treatment.^{16,28} In addition, significant increases in glucose levels have recently been observed among patients treated with olanzapine,^{16,33} but not risperidone.¹⁶ This study supports the suggestion that it is appropriate to consider periodic glucose monitoring in olanzapine-treated patients and, if hyperglycemia is observed, to consider withdrawal of olanzapine to see if the condition remits.³⁴

Several features of our study must be considered in interpreting the findings. The study is a retrospective analysis based on RAMQ medication claims data. These data have been validated, however, and have been shown to be an accurate and comprehensive means of determining the medications dispensed.³⁵ The RAMQ data have also been used to study other adverse events.^{36,37} The data are believed to accurately reflect services used, as underreporting is not in the provider's interest and claims are not processed with incomplete mandatory fields.

The RAMQ database includes information only from patients aged 65 years and older, welfare recipients, and those without private insurance. Consequently, the patient demographics and other characteristics, including known risk factors for developing diabetes, may not be representative of the broader population of patients receiving atypical antipsychotics.

This database did not include data on diagnoses recorded at admission to the hospital, so any patients admitted to the hospital for treatment of diabetes may have been missed. Also, any patients with hyperglycemia controlled by diet but without a primary diagnosis of diabetes being recorded at a visit to their physicians would not have been identified in these analyses. The recording of a primary diagnosis of diabetes or dispensing of an antidiabetic

medication was used to determine the occurrence of diabetes. On the basis of oral glucose tolerance testing, it is believed that, for every diagnosed case of diabetes, there may be about 1 undiagnosed case.²⁰ Some diabetic cases may not have been excluded from or counted during this study, as the physician may not have made a diagnosis of diabetes. So, this study design does not yield an accurate estimate of the total number of cases of diabetes.

Diabetes incidence rates are higher among women and increase with age.²¹ Given that there were imbalances between treatment groups in both of these characteristics, this study adjusted the results for age and gender, with resulting increases in the relative risk. Data were not available on race, body mass index, or whether there was a family history of diabetes, which are characteristics also known to affect the risk of diabetes, so these could not be considered as covariates.

Patients who were prescribed olanzapine were also more frequently diagnosed with schizophrenia, and some research has indicated that patients with this disorder may have an increased prevalence of diabetes compared with the general population.^{22,41} In our study, however, schizophrenia diagnosis was not a significant predictor of diabetes and did not change our finding of a higher risk of diabetes among patients prescribed olanzapine.

Clozapine has also been associated with an increased risk of diabetes,⁴²⁻⁴⁵ so patients who received this drug were excluded from the study. Approximately one third of the patients prescribed olanzapine or risperidone also received haloperidol. In our study, haloperidol use was found to be a significant predictor of developing diabetes (relative risk = 1.24, 95% CI = 1.05 to 1.47), adjusting for age and gender. Controlling for haloperidol use, however, did not eliminate the association between olanzapine and a higher risk of developing diabetes. Although conventional antipsychotic agents have been associated with an increased risk of diabetes in some studies,^{24,25} we did not exclude patients who were prescribed other antipsychotic products (except clozapine) concurrently with olanzapine or risperidone. In our study, the inclusion of use of other antipsychotic agents in the models did not eliminate the association between olanzapine and a higher risk of developing diabetes.

Other commonly prescribed medications may also be associated with diabetes. For example, diabetes or impaired glucose metabolism has been associated with oral contraceptives, β -blockers, thiazides, glucocorticoids, lithium, and valproic acid. Some of the diabetes cases observed could be due to these other products, and this could explain the increased relative risk of diabetes among patients receiving olanzapine, but only if these drugs were preferentially coadministered to the patients receiving olanzapine.

There are many limitations to the information currently available to assess the degree to which patients re-

ceiving atypical antipsychotic agents are at risk of developing diabetes. The information comprises case reports and 4 retrospective claims database analyses, but full details of the design are not available for 3 studies, as the main findings have been presented only in abstracts. Despite the limitations of this retrospective study, the design and sample size allowed us to quantify the additional risks associated with olanzapine compared with risperidone.

It is important for prescribers to be aware of the potential risk of developing diabetes with olanzapine treatment, so that they may assess each patient's risk profile and decide whether to monitor glucose levels regularly, as well as react swiftly to manage the diabetes and, should it arise, consider discontinuing olanzapine. Further research is required to confirm whether olanzapine is associated with a higher risk than risperidone of development of diabetes and to better understand the precise biological basis of this association in order to identify patients at higher risk.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others).

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Article

Association of Diabetes Mellitus With Use of Atypical Neuroleptics in the Treatment of Schizophrenia

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Objective: The development of both type I and type II diabetes after initiation of some atypical neuroleptics has been reported, primarily in studies involving small series of patients. This study used administrative data from a large national sample of patients with a diagnosis of schizophrenia to compare the prevalence of diabetes mellitus in patients receiving prescriptions for atypical and typical neuroleptics.

Method: All outpatients with schizophrenia treated with typical and atypical neuroleptics over 4 months in 1999 in the Veterans Health Administration of the Department of Veterans Affairs (VA) were included in this study. Patients treated with atypical neuroleptics were those who received prescriptions for clozapine, olanzapine, risperidone, or quetiapine. Patients with a diagnosis of diabetes were also identified by using ICD-9 codes in VA administrative databases. The prevalence of diabetes mellitus across age groups and among patients receiving prescriptions for different atypical neuroleptics was examined with multiple logistic regression.

Results: A total of 38,632 patients were included in the study: 15,984 (41.4%) received typical neuroleptics and 22,648 (58.6%) received any atypical neuroleptic (1,207 [5.3%] received clozapine; 10,970 [48.4%], olanzapine; 955 [4.2%], quetiapine; and 9,903 [43.7%], risperidone; 387 patients received prescriptions for more than one atypical neuroleptic). When the effects of age were controlled, patients who received atypical neuroleptics were 9% more likely to have diabetes than those who received typical neuroleptics, and the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine, but not risperidone. However, for patients less than 40 years old, all of the atypical neuroleptics were associated with a significantly increased prevalence of diabetes.

Conclusions: In this large group of patients with schizophrenia, receipt of a prescription for atypical neuroleptics was significantly associated with diabetes mellitus.

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Atypical neuroleptics such as clozapine (1), olanzapine (2), quetiapine (3), and risperidone (4) have demonstrated efficacy in the treatment of schizophrenia with fewer extrapyramidal side effects than other neuroleptics (5). However, other side effects have been described. The use of olanzapine, for example, has been associated with weight gain (6), exacerbation of previously well controlled diabetes (7), and onset of type I and type II diabetes mellitus (7-9), although a recent report failed to demonstrate an association between weight gain and development of hyperglycemia (10). Clozapine use has also been associated with weight gain in several reports (11-14). Although an association between clozapine-induced weight gain and the development of either hyperglycemia or diabetes mellitus has not been demonstrated (14), there have been several reports of hyperglycemia and diabetes mellitus (both type I and type II) directly associated with clozapine use (9, 14-21). There is also a single case report of quetiapine-associated new-onset diabetes mellitus (22).

The degree to which patients who receive prescriptions for atypical neuroleptics are at risk for development of di-

abetes mellitus cannot be ascertained definitively from the reports thus far. To our knowledge, nearly all of the studies of this issue to date are case reports. There have been exceptions, including two uncontrolled studies (14, 21) and one study (20) that used an unmatched comparison group of patients treated with typical neuroleptics. A naturalistic study of clozapine treatment reported that 30% of patients received a diagnosis of type II diabetes during the 5-year follow-up (14). This study did not include a comparison group. In addition, a comparison of patients randomly assigned to receive olanzapine or haloperidol and followed over several years failed to demonstrate a difference in the incidence of nonfasting glucose levels equal to 160 mg/dl (10); the rate of high nonfasting glucose level was 4.6% after 2.54 years in the olanzapine-treated patients and 5.0% after 1.15 years the haloperidol-treated patients. However, this analysis failed to stratify the data for age, which might have obscured important differences between the two groups—especially in younger patients, for whom the baseline rate of diabetes is not as high as in older patients. The authors were also si-

lent about family history of diabetes in these patients and about ethnicity. However, the two groups did not differ significantly in baseline body mass index. A well-matched comparison group is particularly important, as patients with schizophrenia, regardless of treatment, have been reported to have a higher rate of diabetes than the general population (23, 24). For example, the rate of diabetes mellitus in the general U.S. male population age 20–39 years is 1.1% (25); in patients with schizophrenia age 18–44 years, rates of 5.6%–6.7% have been reported (23).

Although no pathophysiologic mechanism connecting atypical neuroleptic treatment and the development of diabetes mellitus has been delineated to date, olanzapine prescription has been associated with weight gain, hyperlipidemia, hyperinsulinemia, and insulin resistance (21), suggesting both direct and indirect mechanisms by which the medication may be involved in dysregulation of relevant metabolic pathways. Clozapine has also been found to induce insulin resistance (26). With regard to weight gain, a review has estimated that after 10 weeks of treatment a patient receiving clozapine would gain an average of 3.99 kg; a patient receiving olanzapine, an average of 3.51 kg; and a patient receiving risperidone, an average of 2 kg; and after 6 weeks of treatment, a patient receiving quetiapine would gain an average of 2.18 kg.

Thus, although researchers have reported that some patients treated with the atypical neuroleptics clozapine, olanzapine, and quetiapine develop diabetes mellitus that is sometimes, but not always, reversible, these studies have involved relatively small groups of patients. Studies have also demonstrated that prescription of olanzapine and clozapine can result in the development of metabolic abnormalities associated with diabetes mellitus (21, 26). In these studies, as well, the numbers of patients studied has been small. In summary, although the association between atypical neuroleptic prescription and development of diabetes mellitus has been observed and some potential pathophysiologic mechanisms have been elucidated, the risk of developing diabetes mellitus for patients who receive prescriptions for atypical neuroleptics has not been well studied.

This study used data for a comprehensive national sample of patients treated in the Veterans Health Administration of the Department of Veterans Affairs (VA) who had a diagnosis of schizophrenia and received prescriptions for either typical or atypical neuroleptics to test the hypothesis that prescription of atypical neuroleptics is associated with an increased prevalence of diabetes. Although the study design precluded an assessment of either a causal relationship or a mechanism of action, it provided a means for determining the potential public health risk. The large number of patients with schizophrenia treated within the VA system also allowed for examination of the prevalence of diabetes associated with each of the atypical neuroleptics available at the time of study—clozapine, olanzapine, quetiapine, and risperidone.

Method

Patients

All patients with a diagnosis of schizophrenia during fiscal year 1999 (October 1, 1998, to September 30, 1999) were identified through VA workload databases. A diagnosis of schizophrenia was operationally defined as having at least two outpatient encounters in a specialty mental health outpatient clinic for which either the primary or secondary diagnosis was schizophrenia (corresponding to ICD codes 295.00–295.99).

Data describing patient characteristics such as age, income, gender, ethnicity, receipt of VA compensation or pension, comorbid medical and psychiatric diagnoses, hospital utilization, and zip code of residence were also obtained from the VA workload databases. By using the zip code and data from the American Hospital Association annual survey, the distances from the center of the district designated by the patient's zip code to the nearest VA and non-VA hospitals were calculated (27). We controlled for distance as a proxy measure for access, since the likelihood of receiving a diagnosis of diabetes mellitus might increase with easier access to care.

For all patients identified as having a diagnosis of schizophrenia, records of all medications prescribed between June (when data first became available) and September (the end of the fiscal year) of 1999 were obtained from the VA Drug Benefit Management System. For each patient, the last neuroleptic prescription written between June and September 1999 was identified as the index prescription. All prescriptions written for neuroleptics in the previous week were also identified. If any of the prescriptions written during that 7-day period were for clozapine, olanzapine, quetiapine, or risperidone, then the patient was entered into the atypical neuroleptic group, regardless of whether the patient was also prescribed typical neuroleptics at the same time. If a patient received only typical neuroleptics during that week, the patient was entered into the typical neuroleptic group. If a patient had no neuroleptic prescription written for the entire 4-month period, the patient was not included in this analysis. Within the atypical group, 94% of patients received the same atypical neuroleptic for the entire 4-month period and 8.9% also received a prescription for a typical neuroleptic (28).

For the group of patients identified as having a diagnosis of schizophrenia and receiving neuroleptic medications, computerized administrative data were examined for record of a diagnosis of diabetes mellitus. A patient was operationally defined as having a diagnosis of diabetes mellitus if the patient had at least one outpatient encounter or inpatient stay with either a primary or secondary diagnosis of diabetes mellitus (corresponding to ICD codes 250.00–250.99) during the 4-month period for which the prescribing data were available.

Analysis

Because of the strong relationship between age and development of diabetes (25), the patients in both the atypical and typical neuroleptic groups were stratified into five age groups: under 40, 40–49, 50–59, 60–69, and over 70 years. Within each age division, the percentages of patients with a diagnosis of diabetes in the atypical and typical neuroleptic groups were compared with chi-square tests.

To address potentially confounding factors, we used logistic regression analysis to calculate odds ratios for the association of atypical neuroleptic prescription and the diagnosis of diabetes within each of the age strata, controlling for the effects of the demographic, diagnostic, and treatment factors listed in Table 1.

These analyses were then repeated to examine the prevalence of diabetes mellitus associated with each atypical neuroleptic. A series of four dichotomous variables was included in these analy-

TABLE 1. Characteristics of Patients With Schizophrenia Receiving Prescriptions for Atypical and Typical Neuroleptic Medication Within Department of Veterans Affairs (VA) Health Services in a 4-Month Period in 1999

Characteristic	Patients Receiving Prescriptions for Atypical Neuroleptics (N=22,648)		Patients Receiving Prescriptions for Typical Neuroleptics (N=15,984)		Analysis		
	Mean	SD	Mean	SD	t	df	p
Age (years)	50.7	11.5	54.5	11.7	31.6	33980.3	0.0001
Income (dollars/year)	14,149.49	16,973.88	15,034.72	16,902.82	5.1	38630	<0.0001
Distance to nearest VA hospital (miles)	24.8	91.0	22.0	80.1	3.2	36828.3	<0.002
	N	%	N	%	χ^2	df	p
Female	1,369	6.0	711	4.4	46.9	1	<0.0001
African American	5,689	25.1	3,983	24.9	0.2	1	0.65
Hispanic	945	4.2	696	4.4	0.8	1	0.38
VA service-connected compensation (rating of degree of disability)							
10%-50%	3,049	13.5	2,284	14.3	5.4	1	0.02
>50%	9,703	42.8	7,672	48.0	100.6	1	<0.0001
Comorbid diagnosis							
Organic brain syndrome or Alzheimer's disease	1,805	8.0	993	6.2	43.1	1	0.0001
Substance abuse	5,407	23.9	2,489	15.6	397.0	1	<0.0001
Alcohol abuse/dependence	4,202	18.6	1,877	11.7	327.8	1	<0.0001
Nonalcohol abuse/dependence	3,655	16.1	1,565	9.8	323.0	1	<0.0001
Major depression or bipolar disorder	9,619	42.5	4,539	28.4	799.5	1	<0.0001
Posttraumatic stress disorder	3,200	14.1	1,452	9.1	225.2	1	<0.0001
Neurosis or adjustment disorder	4,591	20.3	2,159	13.5	297.3	1	<0.0001
Personality disorder	1,724	7.6	683	4.3	178.8	1	<0.0001
Other psychiatric diagnosis	2,274	10.0	1,026	6.4	157.3	1	<0.0001
Days hospitalized in psychiatric facility in the previous year							
1-18	3,182	14.0	1,284	8.0	331.8	1	<0.0001
>18	3,389	15.0	1,061	6.6	637.3	1	<0.0001
Atypical neuroleptic prescribed ^a							
Clozapine	1,207	5.3					
Olanzapine	10,970	48.4					
Quetiapine	955	4.2					
Risperidone	9,903	43.7					

^a Number of patients receiving prescriptions for any atypical neuroleptic is less than the total for the individual atypical neuroleptics because some patients received prescriptions for more than one atypical neuroleptic.

ses to represent each of the atypical medications available at the time of the study.

In a final analysis the five age groups were combined in a single analysis with age as a covariate to determine the population-wide prevalence of diabetes in association with atypical neuroleptic prescription and in association with each particular atypical medication.

Results

In the 4-month study period, 38,632 patients identified with schizophrenia received a prescription for a neuroleptic. Of those patients, 22,648 (58.6%) received an index prescription for an atypical neuroleptic and 15,984 (41.4%) received an index prescription for typical neuroleptics alone. A comparison of the two groups is presented in Table 1. Significant differences were examined by using t tests for continuous variables and chi-square tests for dichotomous variables.

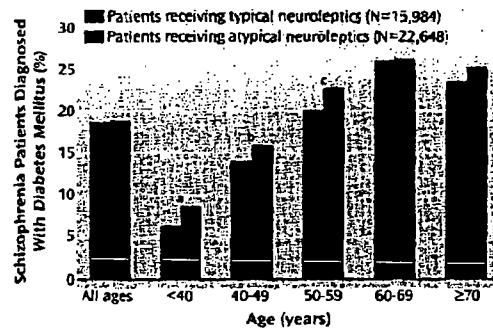
Compared to the patients who received prescriptions for typical neuroleptics, the patients who received prescriptions for atypical neuroleptics were significantly younger and had less income. They were significantly more likely to be female and have another psychiatric diagnosis, includ-

ing organic brain syndrome or Alzheimer's dementia, substance abuse, major depression or bipolar disorder, post-traumatic stress disorder, neurosis or adjustment disorder, personality disorder, or other, unspecified, psychiatric disorder. Patients in the atypical group lived significantly further from the nearest VA hospital and were significantly more likely to have been hospitalized. Patients in the typical neuroleptic group were more likely to be receiving service-connected compensation from the VA.

Patients who received atypical neuroleptic medications demonstrated a statistically significant higher rate of diagnosis of diabetes in the three youngest age strata (Figure 1). Among patients less than 40 years old, for example, 8.75% of those receiving an atypical neuroleptic had a diagnosis of diabetes mellitus, compared to 6.43% of those receiving typical neuroleptics ($\chi^2=7.24$, $df=1$, $p=0.007$). This relationship was also observed in the 40-49-year age group (15.89% versus 13.93%) ($\chi^2=9.81$, $df=1$, $p=0.002$) and in the 50-59-year age group (22.73% versus 20.56%) ($\chi^2=8.53$, $df=1$, $p=0.003$). No significant association was observed in either the 60-69-year group or the group age 70 and older. Comparing across all ages, 18.84% of the patients who received a prescription for an atypical neuro-

DIABETES AND ATYPICAL NEUROLEPTICS

FIGURE 1. Percentage of Patients With Schizophrenia Receiving Prescriptions for Atypical and Typical Neuroleptic Medication Who Also Had a Diagnosis of Diabetes Mellitus



^a $\chi^2=7.24$, $df=1$, $p<0.07$.

^b $\chi^2=9.81$, $df=1$, $p=0.002$.

^c $\chi^2=8.53$, $df=1$, $p=0.003$.

leptic and 18.64% of those who received a prescription for a typical neuroleptic also had a diagnosis of diabetes, a nonsignificant difference.

The adjusted odds ratios for the entire group and each of the age groups are presented in Table 2. For the entire group (all ages), the odds of having a diagnosis of diabetes mellitus were significantly greater for patients receiving any atypical neuroleptic and, specifically, for patients receiving clozapine, olanzapine, and quetiapine, but not risperidone. In the under-40-year age group, the odds were significantly greater for all of the atypical neuroleptics. In the 40–49-year-old age group, a prescription for clozapine, olanzapine, or quetiapine was associated with significantly increased odds for having a diagnosis of diabetes mellitus, but a risperidone prescription was not. In the 50–59-year age group, only olanzapine and risperidone were associated with a significantly increased prevalence of a diagnosis of diabetes. In the 60–69-year age group, clozapine was associated with a significantly decreased prevalence.

Discussion

This study demonstrated, overall, a significant association between prescription of clozapine, olanzapine, and quetiapine, but not risperidone, and diagnosis of diabetes mellitus, compared with prescription of typical neuroleptics. In analyses that controlled for age, the strongest effect was observed in patients less than 40 years old (odds ratio=1.63, 95% CI=1.23–2.16), and each of the atypical neuroleptics was associated with an increased prevalence of diabetes mellitus in at least two of the age groups. These results are consistent with recent reports of significantly higher serum glucose levels in patients randomly assigned to olanzapine, compared to those receiving haloperidol (10), even without adjustments for age.

TABLE 2. Logistic Regression Analysis of Association Between Prescription of Atypical and Typical Neuroleptic Medication and Presence of a Diagnosis of Comorbid Diabetes Mellitus in Patients With Schizophrenia, by Age Group

Age Group and Medication Prescribed	Odds Ratio	95% Confidence Interval	p
All ages			
Any typical (N=15,984)			
Any atypical (N=22,648) ^a	1.09	1.03–1.15	0.002
Clozapine (N=1,207)	1.25	1.07–1.46	<0.005
Olanzapine (N=10,970)	1.11	1.04–1.18	<0.002
Quetiapine (N=955)	1.31	1.11–1.55	<0.002
Risperidone (N=9,903)	1.05	0.98–1.12	0.15
<40 years			
Any typical (N=1,105)			
Any atypical (N=3,076) ^a	1.63	1.23–2.16	0.001
Clozapine (N=232)	2.73	1.36–3.35	<0.002
Olanzapine (N=1,474)	1.64	1.23–2.21	0.0009
Quetiapine (N=165)	1.82	1.05–3.15	<0.04
Risperidone (N=1,267)	1.51	1.12–2.04	<0.008
40–49 years			
Any typical (N=4,980)			
Any atypical (N=8,479) ^a	1.16	1.04–1.28	<0.006
Clozapine (N=566)	1.43	1.13–1.81	<0.003
Olanzapine (N=4,203)	1.19	1.06–1.34	<0.003
Quetiapine (N=368)	1.86	1.43–2.41	0.0001
Risperidone (N=3,518)	1.04	0.92–1.17	0.55
50–59 years			
Any typical (N=5,065)			
Any atypical (N=6,648) ^a	1.16	1.06–1.27	<0.002
Clozapine (N=322)	1.17	0.88–1.54	0.28
Olanzapine (N=3,256)	1.16	1.04–1.29	<0.008
Quetiapine (N=281)	1.19	0.89–1.59	0.24
Risperidone (N=2,891)	1.13	1.01–1.26	<0.05
60–69 years			
Any typical (N=2,547)			
Any atypical (N=2,453) ^a	0.90	0.79–1.03	0.14
Clozapine (N=69)	0.50	0.26–0.96	<0.04
Olanzapine (N=1,172)	0.90	0.77–1.07	0.23
Quetiapine (N=92)	0.90	0.55–1.46	0.66
Risperidone (N=1,156)	0.94	0.80–1.10	0.44
≥70 years			
Any typical (N=2,287)			
Any atypical (N=1,992) ^a	1.01	0.87–1.17	0.91
Clozapine (N=18)	1.61	0.59–4.37	0.35
Olanzapine (N=865)	0.99	0.82–1.19	0.91
Quetiapine (N=49)	0.62	0.30–1.28	0.19
Risperidone (N=1,071)	1.02	0.86–1.21	0.82

^a Number of patients receiving prescriptions for any atypical neuroleptic is less than the total for the individual atypical neuroleptics because some patients received prescriptions for more than one atypical neuroleptic.

The observation that there are no overall differences in the rates of diabetes mellitus in the older age groups suggests that those with the predilection to develop diabetes in these age groups have already done so, and those left, lacking the diathesis for its development, will not develop diabetes despite being exposed to atypical neuroleptics. Thus the increased prevalence associated with atypical antipsychotics may be thought of hastening the onset of diabetes rather than precipitating it *de novo*. The observation of no difference at older ages may also suggest that, in those groups, age may be a more important risk factor for comorbid diabetes than the neuroleptic prescribed.

Both the typical and atypical treated groups demonstrated very high rates of diabetes mellitus. The rate of di-

abetes mellitus in the general U.S. male population age 20–39 years is 1.1% (25), whereas we observed rates of 6.2%–8.7%. These findings are consistent with previous reports of rates of 5.6%–6.7% in U.S. patients with schizophrenia age 18–44 years (23).

Several methodological limitations deserve mention. First, although this study examined data from more than 38,000 patients with a diagnosis of schizophrenia who received prescriptions for neuroleptics, the narrow time frame of 4 months yielded a virtual cross-sectional sample, precluding determination of the temporal relationship between the prescription of neuroleptics and the development of diabetes mellitus. It is possible, therefore, that patients may have been switched from an atypical to either a typical neuroleptic or another atypical secondary to development of diabetes before the 4-month prescription window. Such a switch would have the practical consequence of underestimating the risk for those medications more likely to cause diabetes and overestimating the risk for those medications less likely to cause the disease.

Second, data on changes in weight in patients who received prescriptions for atypical neuroleptics were also unavailable. These data might have clarified one potential mechanism of action for the development of diabetes.

Third, the patients who received prescriptions for typical neuroleptics may have been less likely to take the medications because of their side effect profiles than were those with prescriptions for the atypical neuroleptics. Thus, even if both groups of neuroleptics were equally likely to cause diabetes, more cases of diabetes might be seen in the atypical group if patients were taking more of their prescribed medication. We think, however, that this explanation is unlikely because empirical data show that, although patients taking atypical neuroleptics are more likely to continue on those medications for an extended period of time, they are no more likely to take the prescribed dosage than patients who take typical neuroleptics (29).

Fourth, this study relied on screening an administrative database for appropriate ICD-9 codes to identify cases of diabetes mellitus. Although the validity of this method has not been established empirically, there is no reason to believe that this method would result in any bias in the assignment of cases of diabetes to either the typical or atypical neuroleptic groups.

Finally, several possible alternative explanations for our observation deserve comment. First, it is possible that patients with preexisting diabetes mellitus were selectively switched to atypical neuroleptics. This explanation is unlikely, since the literature has implicated atypical neuroleptics in potentially inducing or exacerbating diabetes mellitus. It is more likely that clinicians, aware of case reports asserting a connection between some atypical neuroleptics and diabetes mellitus, might have avoided these medications in patients with diabetes, artificially decreasing our ability to detect an association. It is also possible, however, that clinicians who were aware of the potential

risks could have chosen to monitor blood sugars more carefully in patients taking atypical neuroleptics, thereby identifying additional cases of diabetes and inflating the effect size.

A second alternative interpretation is that both atypical neuroleptic prescription and receipt of a diagnosis of diabetes could be associated with more severe forms of schizophrenia. If more severe cases of schizophrenia have a higher risk of diabetes mellitus, then more symptomatic patients may be both more likely to receive atypical antipsychotics and to be at greater risk for diabetes, although the atypical neuroleptics are not the causal agent. Although we cannot rule out these potentially confounding associations, we have attempted to adjust for them by covarying the effect of several measures of severity in our analyses.

Third, it is possible that receipt of atypical neuroleptics and having a diagnosis of diabetes both reflect a higher overall quality of medical care, including careful medical monitoring and state-of-the-art psychopharmacology.

Thus, although this study in a large national sample has demonstrated a substantial and statistically significant association between atypical neuroleptic prescription and diabetes mellitus, it did not definitively establish a causal relationship. The results are, however, strongly suggestive of such a relationship and demonstrate both the potential magnitude and public health importance of this association, as well as the potential utility of monitoring patients who receive atypical neuroleptics for signs and symptoms of diabetes mellitus.

In a recent comprehensive review of the effectiveness of atypical neuroleptics, Geddes et al. (30) concluded that the primary benefit of atypical antipsychotics was in reducing side effects. If it is established that these medications reduce the risk of extrapyramidal symptoms but increase the risk of diabetes, the risk/benefit ratio of these medications might be significantly altered.

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PRACTICE INSIGHTS

Comparative Study of the Development of Diabetes Mellitus in Patients Taking Risperidone and Olanzapine

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Objectives. A growing body of literature suggests that certain atypical antipsychotics, especially olanzapine and clozapine, may induce glucoregulatory dysfunction. We assessed the differences in risk of developing diabetes mellitus during treatment with olanzapine and risperidone by using patients treated with haloperidol and fluphenazine as control subjects in whom we would not expect to see an increased risk.

Methods. We conducted a retrospective analysis of the Veteran's Integrated Service Network 10 Veterans Affairs (VA) database. Data for patients receiving olanzapine, risperidone, haloperidol, or fluphenazine from January 1, 1997–December 31, 2000, were included. Diabetes was defined as any health system encounter associated with the *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis for diabetes (250.xx) or prescription for a hypoglycemic agent. Data of patients with markers for diabetes within 1 year before their index date, female patients, racial groups other than Caucasian or African-American, and patients receiving clozapine were not analyzed. We performed a Cox regression, with antipsychotic therapy as a time-dependent covariate. Other covariates considered for inclusion in the final model were number of days supply of antipsychotic drug, age, race, psychiatric diagnoses, substance abuse, lithium, valproic acid, and other typical or atypical antipsychotic agents.

Results. Data for 5837 patients were analyzed. Overall rate of developing diabetes in the study population was 6.3% (368 of 5837 patients). Olanzapine therapy was associated with a significantly higher risk of development of diabetes compared with risperidone (hazard ratio [HR] 1.37, 95% confidence interval 1.06–1.76, $p=0.016$) while controlling for race, age, diagnosis, substance abuse, lithium, valproic acid, and other atypical antipsychotic agents. No differences in the rate of developing diabetes were detected between fluphenazine and risperidone (HR 1.11, $p=0.69$), or haloperidol and risperidone (HR 0.89, $p=0.41$).

Conclusions. Olanzapine was associated with a 37% (HR 1.37) increased risk of development of diabetes compared with risperidone in a VA population, even after adjusting for other factors associated with the development of diabetes and temporal exposure to study drug. Because of limitations associated with database research, prospective studies should be conducted to corroborate these findings.

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Hyperglycemia and diabetes mellitus are major public health problems. Type 2 diabetes mellitus is 2 times more prevalent in individuals with schizophrenia compared with the general population¹⁻³ and is associated with both acute and chronic complications related to macrovascular and microvascular disease. Evidence is mounting to indicate that this increased risk of diabetes is amplified by treatment with certain atypical antipsychotics.⁴⁻³⁶ Although to our knowledge no long-term prospective longitudinal study has been conducted, data suggest that clozapine, olanzapine, and quetiapine are more likely to be associated with diabetes than is risperidone.³⁷ Ziprasidone became commercially available in 2001. In a recent head-to-head study of ziprasidone and olanzapine, olanzapine significantly increased fasting insulin and insulin resistance from baseline compared with nonsignificant increases for ziprasidone.³⁸ Currently, no cases of diabetes requiring emergency treatment have been reported with ziprasidone.³⁹ However, a case of hyperglycemia was reported.⁴⁰ To our knowledge, no reports have been published on aripiprazole, the newest addition to the antipsychotic drug class, and an association with diabetes. Data suggesting an association between older typical antipsychotics and diabetes are limited, although the low-potency agents (e.g., chlorpromazine) may have a greater risk compared with that of high-potency agents (e.g., haloperidol).²

Potential mechanisms for antipsychotic-induced diabetes are numerous. Weight gain is an important risk factor for the development of type 2 diabetes mellitus.²⁴ Ninety percent of patients with diabetes have type 2 diabetes, and up to 90% of type 2 diabetics are overweight.⁴¹ Antipsychotic drugs induce weight gain to varying degrees.⁴² An increase in weight may explain some or all of the treatment-related

changes in glucose metabolism; however, case reports and controlled studies suggest that this may also be a direct adverse effect of dibenzodiazepine-derived compounds, clozapine and olanzapine, on glucose tolerance independent of the contribution of weight gain.^{2,43} Antipsychotics may cause insulin resistance. When pancreatic β cells cannot produce adequate insulin to compensate for insulin resistance, hyperglycemia results. Blockade of serotonin (5-HT) receptors 5-HT_{1A} on pancreatic β cells also has been postulated as a mechanism for hyperglycemia,⁴⁴ and the 5-HT₂ receptors may be involved in glucose metabolism as well. However, the precise role that these receptors may play in regulating glucose metabolism remains unknown.

Several large comparative database studies that evaluated the prevalence and risk of diabetes among various atypical and typical antipsychotic agents have been published.^{37, 45, 46} However, these studies were limited by a short study duration and analyses that failed to consider therapeutic switching among antipsychotic agents. We assessed the differences in risk of developing diabetes between patients who were prescribed risperidone and those who received olanzapine; patients treated with haloperidol and fluphenazine were the control subjects.

Methods

This was a retrospective analysis of data in the Veteran's Integrated Service Network 10 database, which includes health care records for all Veterans Affairs (VA) hospitals in Ohio. All pharmacy, inpatient, and outpatient encounters within the VA system are captured in this database. The local investigational review board approved this study.

Patients were included in the analysis if they received one of the following four antipsychotic agents for at least 30 days: risperidone, olanzapine, haloperidol, or fluphenazine during the study period of January 1, 1997–December 31, 2000. The date of first prescription for one of these four agents during the study period was assigned as the index date. All formulations of haloperidol or fluphenazine were treated as one drug. The primary focus of our analysis was to compare the rates of development of diabetes between risperidone and olanzapine. Patients who were prescribed haloperidol and fluphenazine served as comparison groups in which we did not expect to see a significant increased risk of the development of diabetes.^{37, 45, 46}

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Because patients prescribed haloperidol and fluphenazine functioned as control subjects for the olanzapine and risperidone groups, it was important at the outset of the study to ensure they had no recent exposure to olanzapine or risperidone. Therefore, patients whose index drug was haloperidol or fluphenazine were excluded if they received olanzapine or risperidone within 30 days of the index date. Women were excluded, as were patients of races other than Caucasian and African-American (because of very small samples in these sex and racial groups). Additional exclusion criteria were the presence of a marker of diabetes (an *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] diagnosis 250.xx or prescription with insulin, sulfonylureas, metformin, etc.) within 365 days of the index date or a prescription for clozapine within 365 days of the index date or during the study period.

During the study, patients with diabetes were identified by any prescription for insulin, sulfonylureas, metformin, troglitazone, pioglitazone, rosiglitazone, acarbose, miglitol, repaglinide, or precore; or by the presence of an inpatient or outpatient encounter associated with an ICD-9-CM code of 250.xx.

Our statistical analysis sought to address serious methodologic challenges associated with studies in this population. Specifically, the prevalence of switching between drugs and treatment with concomitant antipsychotic drugs pose potential threats to internal validity. Two common approaches to addressing the problem of drug switching and concomitant therapy are to use an intent-to-treat approach or to analyze each treatment episode independently. The intent-to-treat approach does not account for subsequent changes of antipsychotic drug therapy, which is important to account for when assessing associations between drug and disease. Alternatively, treating drug episodes independently has the potential to discount the effects of therapy other than the current therapy (e.g., effects of previous drugs). Therefore, to statistically account for switching to, or concomitant treatment with, different antipsychotic drugs and to preserve the effect of a patient's drug history over time, we employed a Cox regression model with use of treatment group as a time-dependent covariate.⁴⁷ This enabled each patient's antipsychotic therapy to be tracked over time, giving more weight to therapy that occurred closer in time to the development of diabetes.

Because of this approach, the common way of thinking of independent drug groups does not apply. Assignment to an index group does not prohibit a patient from receiving any (or all) of the other therapies. Therefore, for instance, it is not meaningful to report the frequency of diabetes for each index drug group; the index drug group loses meaning as patients switch to different therapies. Our analysis sought to explain the relationship between the occurrence of diabetes and prescription with antipsychotic drugs, weighting highest those drugs that occurred temporally closer to the occurrence of diabetes.

In addition to capturing therapy as a time-dependent covariate in the Cox regression model, the following covariates were considered:

- Number of days supply for each prescription of the main therapies treated as a time-dependent covariate.
- Race (African-American or Caucasian).
- Age (at index date).
- Substance abuse (any time from 1 year before the index date through the end of study period or development of diabetes, yes or no; includes both drug and alcohol abuse) defined by ICD-9-CM codes 303.x-305.x.
- Bipolar diagnosis (marker for bipolar diagnosis during study period, defined by primary ICD-9-CM codes 296.4-296.8).
- Depression diagnosis (marker for depression diagnosis during study period, defined by primary ICD-9-CM codes 296.20-296.30, 298.0, 300.4, or 311).
- Dementia diagnosis (marker for dementia diagnosis during study period, defined by primary ICD-9-CM codes 290.00-290.90).
- Schizophrenia and schizoaffective diagnosis (marker for schizophrenia diagnosis during study period, defined by primary ICD-9-CM codes 295.00-295.90).
- Other diagnosis (marker for other diagnosis during study period, defined by any ICD-9-CM code between 290 and 299 that did not meet the definition for bipolar, depression, dementia, or schizophrenia).
- Valproic acid during 1 year before the index date.
- Valproic acid during the study period.
- Lithium during 1 year before the index date.
- Lithium during the study period.
- Low-potency antipsychotic prescriptions (chlorpromazine, thioridazine, or mesoridazine) during 1 year before the index date.

Table 1. Characteristics by Therapy

Characteristic	Risperidone (n=2493)	Olanzapine (n=3056)	Fluphenazine (n=428)	Haloperidol (n=1790)	All (n=5837)
Age, yrs					
Mean	53	51	48	55	53
Median	50	49	47	51	50
SD	14	12	10	15	14
Race, no. (%)					
African-American	678 (27)	704 (23)	160 (37)	610 (34)	1572 (27)
Caucasian	1812 (73)	2352 (77)	268 (63)	1180 (66)	4265 (73)
Average daily dose, mg					
Mean	2.8	10.0	12.2	8.4	
Median	2.0	10.0	10.0	5.0	
SD	2.0	5.5	9.7	8.7	

Some patients are summarized in more than one therapy column because prescription changes occurred during the course of therapy. The "n" represents total number of patients who received the drug during the study, either at the index date or subsequently.

- Low-potency antipsychotic prescriptions (chlorpromazine, thioridazine, or mesoridazine) during the study period.
- Other atypical antipsychotic prescriptions (quetiapine) during 1 year before start of main therapy.
- Other atypical antipsychotic prescriptions (quetiapine) during the study period.

These covariates were considered in the final Cox regression model to determine the hazard ratio (HR) of developing diabetes, using risperidone as the reference group. The HR is equal to the amount of increased risk of developing diabetes for an individual patient, relative to that of a patient taking risperidone. A p value less than 0.05 was considered to indicate a statistically significant difference.

Results

A total of 5837 patients met inclusion criteria, and their data were considered for the analysis. Demographic data are listed in Table 1. The total study population included 73% Caucasian patients and 27% African-American patients. Patients had a range of psychiatric diagnoses, including schizophrenia (61%), depression (47%), bipolar disorder (26%), and dementia (8%). Fifty-eight percent of patients were treated for drug or alcohol abuse during the study period. Olanzapine was the index drug for 37% of patients, followed by risperidone (32%), haloperidol (26%), and fluphenazine (5%). As expected, there was a high degree of switching from the index drug to another antipsychotic agent after the index date (Table 2).

Three hundred sixty-eight patients (6.3% of

the total study population) developed a marker for diabetes after their index date. The average time from the index date to development of diabetes was 15 months, with a median time of 11 months (range 1 day–52 mo). In univariate analysis, using risperidone as the reference group, only olanzapine-treated patients had a significantly increased risk of developing diabetes (HR 1.29, 95% confidence interval [CI] 1.00–1.67, $p=0.046$). In the multivariate Cox regression model, controlling for the covariates listed above and using risperidone as the reference group, only olanzapine was associated with an increased risk of developing diabetes (HR 1.37, 95% CI 1.06–1.76, $p=0.016$). The risk of developing diabetes, using risperidone as the reference group, was 1.11 (95% CI 0.68–1.79, $p=0.69$) for fluphenazine, and 0.89 (95% CI 0.67–1.17, $p=0.41$) for haloperidol.

Discussion

The most significant finding of this analysis was that olanzapine was associated with a 37% increased risk of the development of diabetes compared with risperidone. None of the other primary treatment groups was found to have such an association. The increased risk of diabetes with olanzapine was consistent across both univariate and multivariate analyses, the latter of which controlled for factors such as race, age, substance abuse, psychiatric diagnoses, days supply of treatment, and administration of lithium, valproic acid, and both low-potency and other atypical antipsychotic agents.

Handling treatment group as a time-dependent covariate in this analysis allowed for tracking of

Table 2. Index Drug and Drug Switched to After the Index Date in the 5837 Patients

Index Drug, No. (%)	Postindex Drug, No (%)
Risperidone, 1837 (31.5)	Olanzapine, 370 (20.1)
	Fluphenazine, 34 (1.8)
	Haloperidol, 101 (5.5)
	Low-potency antipsychotic, 108 (5.9)
	Quetiapine, 196 (10.7)
	Lithium, 193 (10.5)
	Valproic acid, 81 (4.4)
Olanzapine, 2149 (36.8)	Risperidone, 265 (12.3)
	Fluphenazine, 50 (2.3)
	Haloperidol, 95 (4.4)
	Low-potency antipsychotic, 122 (5.7)
	Quetiapine, 189 (8.8)
	Lithium, 291 (13.5)
	Valproic acid, 99 (4.6)
Fluphenazine, 308 (5.3)	Risperidone, 108 (35.1)
	Olanzapine, 189 (61.5)
	Haloperidol, 51 (16.6)
	Low-potency antipsychotic, 33 (10.7)
	Quetiapine, 62 (20.1)
	Lithium, 47 (15.3)
	Valproic acid, 16 (5.2)
Haloperidol, 1543 (26.4)	Risperidone, 283 (18.3)
	Olanzapine, 348 (22.5)
	Fluphenazine, 36 (2.3)
	Low-potency antipsychotic, 81 (5.2)
	Quetiapine, 119 (7.7)
	Lithium, 145 (9.4)
	Valproic acid, 98 (6.4)

These represent distinct groups at the index date. The total number of patients receiving any of the above drugs can be calculated by adding the number who received the drug in each index group. For example, the total number of patients who received risperidone at any time during the study is calculated as follows: 1837 + 265 + 108 + 283 = 2493. In this way, Table 2 corresponds with Table 1.

treatment changes over time for each patient. Consequently, treatment episodes with different drugs in the same patient were not treated as independent episodes, but rather were analyzed as part of a continuum of care. In this way, a strong statistical association was formed between drugs with a close temporal relationship to the development of diabetes without ignoring the effect of drugs with a more distant temporal relationship to the development of diabetes. This method represents an improvement over methods such as logistic regression, in which treatment episodes are considered to be independent. Analyzing treatment episodes independently ignores the patient's drug history and the potential impact of drugs either forward or backward in time. Our analysis is also an improvement over an intent-to-treat analysis, in which switches subsequent to the assignment of a treatment group are not accounted for, or are

simply accounted for with a yes or no variable that does not capture the relationship between time of switch and the development of diabetes. These considerations are particularly important in a population for whom drug switching is prevalent, such as those with mental illness. The methodology of time dependency allows for the capture of switches in therapy and accounts for the time of the switch during the study period. Thus, accounting for time in the model captures a more realistic picture of the patients' courses of therapy. The patients in this study, as in many studies of psychiatric patients, experienced a high degree of antipsychotic switching (Table 2).

Our results are consistent with, and yet improve on, the methods and study time frame of previous studies that assessed the risk of diabetes with antipsychotic drugs. A previous study in a VA population found an increased risk of diabetes mellitus with olanzapine, but interpretation is limited by suboptimal methods of analysis.³⁷ Our study also was conducted in the VA system, but differed from their analysis in several important ways. In that study,³⁷ the authors analyzed a national data set; however, the study period was only 4 months. Furthermore, the analysis used a logistic regression model, which does not account for time. Finally, the analysis did not exclude patients with preexistent diabetes. Nevertheless, olanzapine-treated patients were associated with an increased risk of the development of diabetes (odds ratio 1.11, 95% CI 1.04–1.18, $p < 0.002$). A recent epidemiologic survey of United States Food and Drug Association MedWatch reports⁴⁹ and a recent population-based case-control study⁴⁵ also support the relationship between olanzapine and the precipitation of diabetes. Another group of authors³⁰ also presented data on the association of diabetes with risperidone. In addition, many published case reports,^{3, 3–7, 14, 17, 20, 33, 34} and abstracts and articles^{51–53} associate the onset of diabetes with olanzapine. Although some published study abstracts did not find a difference in the risk of diabetes between olanzapine- and risperidone-treated patients, there is insufficient detail regarding study methodology, sample size, and analysis plan to make firm conclusions. We are not aware of any published studies that have shown an increased risk for risperidone compared with olanzapine.

Several limitations of this study should be mentioned. Although significant effort was expended to control for important potential confounders, these efforts are not foolproof.

Factors other than antipsychotic drug, controlled for or not, may have influenced the results of this analysis, such as a patient's weight, family history of diabetes, or the dosage of antipsychotic. Unfortunately, weight and family history were not captured in the retrospective database used for this study. Drug dosage is particularly difficult to use as a covariate in a study of this nature because dose commonly changes over time. The focus of our analysis was to determine the relationship between exposure to drug and the development of diabetes. Future studies may want to include design elements that allow a focus on drug dosage as an explanatory factor. This study relied on ICD-9-CM diagnosis codes and drug prescriptions as markers for the development of diabetes. These markers are fairly specific clinically and have been used similarly by previous investigators. Nevertheless, our results are subject to scrutiny to the extent that these markers are unreliable. Also, the diagnosis of diabetes possibly may have been underestimated since these markers tend to underestimate new-onset diabetes. Despite these limitations, our results agree with similar retrospective published reports that show an increased risk of development of diabetes for olanzapine.

Conclusion

Olanzapine was associated with a 37% (HR 1.37) increased risk of development of diabetes compared with risperidone in a VA population, even after adjusting for other factors associated with the development of diabetes and temporal exposure to study drug. Because of limitations associated with database research, prospective studies should be conducted to corroborate these findings.

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Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study

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Abstract

Objective To quantify the association between olanzapine and diabetes.

Design Population based nested case-control study.

Setting United Kingdom based General Practice Research Database comprising 3.5 million patients followed between 1987 and 2000.

Participants 19 637 patients who had been diagnosed as having and treated for schizophrenia. 451 incident cases of diabetes were matched with 2696 controls.

Main outcome measures Diagnosis and treatment of diabetes.

Results Patients taking olanzapine had a significantly increased risk of developing diabetes than non-users of antipsychotics (odds ratio 5.8, 95% confidence interval 2.0 to 16.7) and those taking conventional antipsychotics (4.2, 1.5 to 12.2). Patients taking risperidone had a non-significant increased risk of developing diabetes than non-users of antipsychotics (2.2, 0.9 to 5.2) and those taking conventional antipsychotics (1.6, 0.7 to 3.8).

Conclusion Olanzapine is associated with a clinically important and significant increased risk of diabetes.

Introduction

Since the late 1980s new antipsychotic agents with different mechanisms of action from conventional antipsychotics have been developed and widely adopted in the treatment of schizophrenia. The main advantage of these newer antipsychotics is a reduction of extrapyramidal side effects¹; however, they are associated with a different spectrum of side effects, including weight gain, alterations in glucose metabolism, increased concentrations of blood cholesterol and lipids, myocarditis, and cardiomyopathy.²⁻⁵ These metabolic effects may pose a burden as serious as the extrapyramidal effects.⁶

We used data from the United Kingdom based General Practice Research Database to quantify the risk of diabetes associated with conventional and newer generation antipsychotics, specifically olanzapine and risperidone in patients with schizophrenia.

Methods

Study population

Our study population comprised patients with a recorded doctor diagnosis of and drug treatment for schizophrenia registered with medical practices in the General Practice Research Database between June 1987 and September 2000. This database contains data from around 400 general practices dealing with 3.5 million patients in England and Wales, providing more than 30 million patient years of observation.^{7,8}

Cohort

Eligibility criteria for our study included a diagnosis of and treatment for schizophrenia recorded at any time and at least three months of up to standard data. We calculated the incidence rates from the number of patients who developed diabetes within three months of using the drug of interest divided by the person time use for the drug of interest.

Selection of participants

Cases

Incident cases of diabetes were defined as the earliest date of a diagnosis of or treatment for diabetes (index date), occurring at least three months after the beginning of the study period. To ensure that the patients with diabetes were incident cases, we checked the medical and prescription records for any diagnosis of or treatment for diabetes before the study began. Patients identified as cases should not have had a prescription for insulin or oral antidiabetic agents within three months of the index date.

Controls

For each case we matched six controls with study periods at least as long as that of the case by age at index date (SD 5 years), sex, and index date. Controls that met the matching criteria were selected at random from patients who had been diagnosed as having or treated for schizophrenia but not diagnosed as having or treated for diabetes at any time.

Drug use

We classified antipsychotics as conventionals (depot or non-depot; see bmj.com), olanzapine, risperidone, and other newer drugs, including amisulpride, remoxipride, and sertindole.

We abstracted all prescriptions written by the doctor for the treatment of schizophrenia and diabetes between the start of the study period and the index date. We defined drug use as the receipt of at least one prescription for an antipsychotic within three months of the index date. The selection of a three month window was based on a review of the case reports suggesting a mean time to onset of glucose dysregulation of three months after starting olanzapine. Patients not taking the drugs of interest were those who did not have a prescription for an antipsychotic within three months of the index date.

Statistical analysis

Our main study comprised a nested case-control analysis. We modelled the effect of drug use on the risk of diabetes development using conditional logistic regression.⁹ In addition to the matching variables, we adjusted the analysis for use of other drugs known to affect the risk of diabetes, such as α blockers, β blockers,

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Table 1 Characteristics of cases and controls. Values are numbers (percentages)

Characteristic	Cases (n=451)	Controls (n=2696)
Age (years):		
<20	2 (0.4)	14 (0.5)
20-44	74 (16.4)	440 (16.3)
45-64	191 (42.4)	1158 (43.0)
>65	184 (40.8)	1084 (40.2)
Sex:		
Female	282 (62.5)	1697 (62.6)
Male	169 (37.5)	1009 (37.4)
Use of antipsychotic within 3 months of index date*:		
Conventional antipsychotics	268 (59.4)	1428 (53.0)
Olanzapine	9 (2.0)	15 (0.6)
Risperidone	11 (2.4)	42 (1.6)
Other newer agents	1 (0.2)	7 (0.3)

*Categories not mutually exclusive.

thiazide diuretics, corticosteroids, phenytoin, oral contraceptives containing norgestrel, and valproate.

Results

Cohort analysis

Between 1 June 1987 and 24 September 2000, 21 145 patients were diagnosed as having and treated for schizophrenia. We excluded 916 of these with less than three months' follow up, 582 diagnosed as having or treated for diabetes before the start of their follow up period, and 10 with no information on diabetes diagnosis or treatment dates. This left 19 637 patients for study.

Males and females were equally represented in the study population, with a mean age of 51 (SD 20) years (see [bmj.com](#)). Overall, 17 320 (88.2%) had at least one prescription for non-depot conventional antipsychotics, 4421 (22.5%) for depot conventional antipsychotics, 970 (4.9%) for olanzapine, 1683 (8.6%) for risperidone, and 578 (2.9%) for other newer antipsychotics.

In total, 451 patients developed diabetes during a mean follow up of 5.2 (SD 3) years. The incidence rate of diabetes among all patients with schizophrenia treated with antipsychotics was 4.4/1000 person years. Women exhibited a higher incidence rate than men (5.3 v 3.5/1000 person years). The incidence rate within three months of a prescription was 10.0/1000 person years for olanzapine (95% confidence interval 5.2 to 19.2), 5.4/1000 person years for risperidone (3.0 to 9.8), and 5.1/1000 person years for conventional antipsychotics (4.5 to 5.8).

Case-control analyses

We matched 451 cases of diabetes with 2696 controls. Three patients had fewer than six controls per case, totalling 10 missing controls. The prevalence of conventional antipsychotic use differed among the cases and controls and among olanzapine users but not among risperidone users (table 1).

Compared with no antipsychotic use olanzapine significantly increased the risk of diabetes (adjusted odds ratio 5.8, 2.0 to 16.7; table 2), followed by risperidone (2.2, 0.9 to 5.2) and conventional antipsychotics (1.4, 1.1 to 1.7). Olanzapine was associated with a significantly increased risk of diabetes (4.2, 1.5 to 12.2) compared with conventional antipsychotics, unlike risperidone (1.6, 0.7 to 3.8; table 2).

Discussion

Several mechanisms are proposed for the observed association between diabetes and antipsychotic use, including weight gain and disruption of glucose metabolism. A meta-analysis showed a mean increase in weight of 4 kg for patients taking olanzapine and 2 kg for those taking risperidone.⁸ Type 2 diabetes seems to be strongly and consistently associated with obesity and weight gain.^{10 11} Antagonism of histamine is also known to cause weight gain.¹² It is possible that serotonin antagonism plays a part in the weight gain associated with the newer drugs.^{13 14} Weight gain can also be due to increased leptin secretion, which in turn leads to a disturbance of insulin secretion and diabetes mellitus.¹⁵ Lastly, dopamine has been shown to stimulate insulin secretion by a β adrenergic mediated mechanism.^{16 17}

Limitations of study

Our study has several limitations. Drug use was inferred from automated prescribing data. Also, patient specific data were limited to that recorded in the database. However, one study showed that 95% of prescriptions and 74% of consultations in the General Practice Research Database were recorded on computer compared with 42% and 75% in written records.¹⁸ In addition, there was no direct information on the severity of schizophrenia, race, social class, or weight gain. We were thus unable to adjust for these variables. Confounding by indication remains a concern in observational pharmacoepidemiological studies. Clinicians may have prescribed one drug over the other based on the severity of the schizophrenia. We

Table 2 Comparison of patients using olanzapine and risperidone within three months of index date with patients not using antipsychotics or those using conventional antipsychotics

Antipsychotic*	Cases (n=451)	Controls (n=2696)	Adjusted odds ratio (95% CI)†	P value
No antipsychotics (reference)	158	1228		
Conventional antipsychotics	268	1404	1.4 (1.1 to 1.7)	0.004
Olanzapine	9	11	5.8 (2.0 to 16.7)	0.001
Risperidone	11	26	2.2 (0.9 to 5.2)	0.079
Other newer agents	1	3	1.6 (0.2 to 17.1)	0.699
Conventional antipsychotics (reference)	233	1404		
Olanzapine	7	11	4.2 (1.5 to 12.2)	0.008
Risperidone	7	26	1.6 (0.7 to 3.8)	0.290
Other newer agents	1	3	1.2 (0.1 to 12.4)	0.900

*Categories mutually exclusive. Results not shown for patients using more than one antipsychotic, included in model.

†Adjusted for age, sex, index year, duration of follow up, and use of either α blocker, β blocker, β blocker and thiazide diuretic, corticosteroid, thiazide diuretic, lithium, oral contraceptives containing norgestrel, or valproate.

attempted to reduce this confounding by adjusting for known risk factors for diabetes. However, since confounders must be associated with both the use of the drug and the disease, we believe it is unlikely that the severity of schizophrenia would be linked to the incidence of diabetes. It was not possible to study the association between an important newer antipsychotic, clozapine, and diabetes as clozapine therapy must be started when patients are in hospital, and these patients are not included in the General Practice Research Database. Another limitation of our analysis was that we ignored the use of antipsychotics before the three month exposure period, therefore patients may have used different antipsychotics during the study period. Lastly, our analysis lacked power to compare the odds ratios between olanzapine and risperidone users.

Olanzapine use is consistently associated with a clinically important increased risk of diabetes, and this association, after adjustment for relevant risk factors, is significant. The metabolic consequences of antipsychotic therapy should be considered by treating doctors.

The General Practice Research Database is compliant with the Data Protection Act, 1998.

Contributors: See bmj.com

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What is already known on this topic

Recent evidence has suggested an association between the newer class of antipsychotics and diabetes.

Most of these studies were case reports.

The association has not been confirmed in epidemiological studies, with the relation adjusted for comorbid factors.

What this study adds

Olanzapine is associated with a clinically important increased risk of diabetes.

After adjustment for relevant risk factors this association is significant.

The metabolic consequences of olanzapine should be considered by treating doctors.

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When I use a word

When I use a mocking bird

Of all types of slang, perhaps the best known is Cockney rhyming slang. It developed in London during the first half of the 19th century, at about the same time as Robert Peel was inaugurating his police force, perhaps to be used by criminals as a secret language that the slops (back slang, from ecilop) would not understand. Later, it spread with the convicts who were deported to Australia, and then to America, where it became known as Australian slang.

Several now familiar words in the English language had their origins in rhyming slang. For example, a dicky is a shirt because it is the shortened form of "dicky dirt", and perhaps there is an association with the German Decke, a cover. "Dickey" on the other hand means unwell, from "Uncle Dick," sick. To rabbit (rabbit and pork) is to talk. The brass tacks that people get down to are facts. The rude noise known as a raspberry is actually a raspberry tart. And who among us would call someone a silly berk if they knew that the word originates from rhyming slang "Berkshire I hunt"?

The best rhyming slang uses expressions that themselves reflect the meaning of the original word. For example, of the several

expressions for syphilis, the best is bang and buff, which not only rhymes with "syph" but also carries a suggestion of how you might catch it. Then there is a "snake's hiss," meaning an act of urination (oh, all right, a piss), which conveys its meaning through the sound that it suggests, not to mention the suggestive shape of the snake. Occasionally the meaning is subverted, as in "do me good", a Wood (Woodbine cigarette). Humour is important too. For instance, the Jim-bris or Jimmy Brits, shortened to "the jimmies", is Australian rhyming slang for diarrhoea; "Jimmy" (or "Jimmy Grant") is an immigrant, so not only is this a deft expression, it is also a neat insult of the Australians' traditional enemy.

So the next time you're feeling a bit Tom, Harry, and Dick or get fruck and frill with a bout of threepenny bits or a dose of the horse and trap, and you think you're going to crack-a-cry, go to see the King's Proctor and ask him for some Jenny Hills to make you feel all harbour light. Under-cum-stumble!

Jeff Aronson clinical pharmacologist, Oxford

Differential Effects of Risperidone, Olanzapine, Clozapine, and Conventional Antipsychotics on Type 2 Diabetes: Findings From a Large Health Plan Database

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Background: Case series suggest that some antipsychotics may induce or exacerbate type 2 diabetes. This study measured the association of antipsychotic treatments with diabetes at a population level.

Method: Claims data for psychosis patients (ICD-CM-9 290.xx-299.xx) within health plans encompassing 2.5 million individuals were analyzed. Patients reporting preexisting type 2 diabetes up to 8 months prior to observation were excluded. The frequency of newly reported type 2 diabetes in untreated patients and among patients treated with antipsychotics from 5 categories (risperidone, olanzapine, clozapine, and high-potency and low-potency conventionals) was compared. Logistic regression models compared the odds of diabetes based on exposure to each of the antipsychotic categories.

Results: Based on 12 months of exposure, the odds of type 2 diabetes for risperidone-treated patients (odds ratio = 0.88, 95% CI = 0.372 to 2.070) was not significantly different from that for untreated patients, whereas patients receiving other antipsychotics had a significantly greater risk of diabetes than untreated patients ($p < .05$): olanzapine, 3.10 (95% CI = 1.620 to 5.934); clozapine, 7.44 (95% CI = 0.603 to 34.751); high-potency conventionals, 2.13 (95% CI = 1.097 to 4.134); and low-potency conventionals, 3.46 (95% CI = 1.522 to 7.785). Older age and greater use of non-antipsychotic psychotropic medications also contributed to risk of type 2 diabetes. Olanzapine also showed significantly higher ($p < .01$) odds of diabetes associated with increasing dose.

Conclusion: Consistent with previously published literature, these data suggest that olanzapine, clozapine, and some conventional antipsychotics appear to increase the risk of acquiring or exacerbating type 2 diabetes and that the effect may vary by drug. In contrast to these agents, risperidone was not associated with an increased risk of type 2 diabetes.

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On the basis of several reported cases, it is suspected that some atypical antipsychotics may induce or exacerbate type 2 diabetes (also known as non-insulin-dependent and adult-onset diabetes mellitus).¹⁻²³ Other studies have retrospectively reviewed patients for changes in insulin and glucose levels as well as new-onset diabetes associated with atypical antipsychotics.²⁴⁻²⁸ These studies found significant elevations in glucose levels and diabetes onset after treatment with some atypical antipsychotics was initiated. A number of potential mechanisms by which the atypicals may induce type 2 diabetes have been postulated. Two recent review articles discuss the potential mechanisms of glucose dysregulation associated with antipsychotics.^{29,30} Central regulation of blood glucose is controlled by the hypothalamus. Hypothalamic dopamine antagonism by conventional antipsychotics and some atypical antipsychotics may therefore lead to dysregulated blood glucose control. Several other receptors have also been postulated to be associated with antipsychotic-induced diabetes, including serotonin 5-HT_{1A} and 5-HT₂, and histamine-1.⁶ Actions on these receptors may result in inhibition of insulin release, insulin resistance, or impairment of glucose utilization. A significant relationship between some atypicals and excessive weight gain has been observed in clinical trials and clinical experience.³¹⁻³⁷ Obesity, particularly abdominal, is a risk factor for type 2 diabetes and was reported in many of the cited cases. Weight gain caused by some

atypical antipsychotics may also be related to altered glucose-insulin homeostasis. As yet, no clear mechanism of action for antipsychotic-induced diabetes has been determined. It is likely that diabetes may be attributed to multiple factors. There have also been reports associating conventional antipsychotics with type 2 diabetes.^{38,39}

Despite the several case reports and logical mechanisms linking some atypical antipsychotics to type 2 diabetes, the evidence is inconclusive. Reported cases were identified as new-onset cases only because none of the afflicted individuals had a prior medical history of glucose intolerance. It is possible that glucose intolerance prior to treatment was subclinical and that treatment with atypical antipsychotics exacerbated preexisting conditions. Given the relatively high incidence of type 2 diabetes, it would be expected to observe a few cases in which the onset or worsening of this condition occurred following initiation of an antipsychotic therapy. Thus, case findings are inconclusive. A study based on sufficiently large numbers of psychosis patients is required to examine the association between antipsychotics and type 2 diabetes. A recent study by Sernyak et al.⁴⁰ compared presence of type 2 diabetes among schizophrenia patients within the Veterans Health Administration hospital system who were treated with atypical antipsychotics (clozapine, risperidone, olanzapine, and quetiapine) versus those treated with conventional antipsychotics. All of the atypicals except risperidone were found to have higher odds of being associated with type 2 diabetes. While based on large numbers, the study did not control for preexisting type 2 diabetes or the level of patient exposure (e.g., treatment duration) to each of the antipsychotics.

The present study further investigated the relationship between antipsychotic therapy and type 2 diabetes using claims records of several thousand psychosis patients drawn from 2 health plans. The large numbers enabled more conclusive determination of antipsychotic contributions to the onset or exacerbation (i.e., movement from subclinical to clinical) of type 2 diabetes. The study design also controlled for preexisting (clinical) type 2 diabetes and the level of antipsychotic exposure. The study did not include type 1 (insulin-dependent) diabetes.

The onset or exacerbation of type 2 diabetes was measured among individuals treated with the various antipsychotics. As a control, the onset or exacerbation of this condition was also measured among individuals with reported psychoses but without antipsychotic treatment for the period encompassed by the data. To ensure measurement of the onset or exacerbation of type 2 diabetes rather than continuation of already existing states of health, only psychosis patients who had complete data and no documented evidence of type 2 diabetes during a specified period prior to observation were included. The period was extended to assess the sensitivity of results to preexisting type 2 diabetes.

METHOD

The analysis was based on the combined data from 2 mixed indemnity and managed care health plans encompassing 2.5 million individuals, one located in the northeast region of the United States and the other in the southeast. The data available from each of these plans extended from January 1996 through December 1997. A total of 7933 individuals within these 2 plans were identified as having some form of psychosis (ICD-CM-9 290.xx-299.xx) and either not receiving any antipsychotic medication or having antipsychotic prescriptions of at least 60 contiguous days' supply. ICD-CM-9 diagnostic criteria are related to medical claims and were used in lieu of DSM-IV criteria. Psychosis patients with antipsychotic prescriptions of fewer than 60 days' supply were excluded because it was judged that they qualified neither as treated individuals nor as controls. These almost without exception involved a single 30-day prescription, and there was no guarantee that individuals with a single antipsychotic prescription used the product (noncompliance). The presence of a second prescription provided reasonable assurance of compliance. A total of 4308 psychosis patients received at least 60 contiguous days of an antipsychotic therapy during the study period, whereas 3625 received no treatment.

Five categories of antipsychotic therapy were defined: risperidone, olanzapine, clozapine, high-potency conventionals (e.g., haloperidol, fluphenazine), and low-potency conventionals (e.g., chlorpromazine, thioridazine). For treated psychosis patients, sampling units consisted of antipsychotic treatment episodes rather than patients per se. Treatment episodes best fit the data, in that treated patients were characterized by varying degrees of antipsychotic use and by some patients being treated with the same or a different antipsychotic at different times. For each of the above antipsychotic therapies, treatment episodes were generally measured from the date of the first prescription for an antipsychotic to the final date of treatment calculated from the date of the last prescription plus its days' supply. Identification of a prescription as the first prescription in a treatment episode required that it not be preceded by another prescription for that antipsychotic for at least 90 days. Therefore, no treatment episode began before April 1, 1996. For treatment episodes truncated by disenrollment or the end of the study period, the disenrollment date or December 31, 1997, was used as the final date of treatment. Using this procedure, we determined 1591 treatment episodes with risperidone, 1178 with olanzapine, 1681 with high-potency conventionals, 556 with low-potency conventionals, and 81 with clozapine. About 16% of treated psychosis patients had more than 1 treatment episode during the April 1996 through December 1997 period with either the same antipsychotic or a different one. We considered the possibility of interdependence of sampling units and determined that it

was not a problem in this case (see Discussion). Treatment episodes with different antipsychotics overlapped in about 15% of the observations. This overlap was expected since temporary concurrent use of the prior antipsychotic is recommended when making a transition to a new antipsychotic therapy.⁴¹

The boundaries of a treatment episode were not strictly appropriate for associating new or resurgent cases of type 2 diabetes. Specifically, some individuals may have discontinued an antipsychotic therapy before they were diagnosed and treated for type 2 diabetes that may have been induced or exacerbated by that therapy. To adjust for this potential problem, the observation period was lagged by 30 days. For example, if a treatment episode with a particular antipsychotic extended from June 15, 1996, through March 10, 1997, the observation period for identifying type 2 diabetes was from July 15, 1996, through April 10, 1997. The 30-day lag is also consistent with the likelihood that any diabetic effects of antipsychotics will take some time to emerge after initiating therapy. Nearly all of the case literature reported diabetic effects occurring in excess of 30 days beyond the start of an antipsychotic therapy.¹⁻²³

For untreated psychosis patients, observation periods for identifying new or resurgent cases of type 2 diabetes were constructed using 3 index dates as starting points: June 1, 1996, November 1, 1996, and April 1, 1997. Untreated individuals were randomly assigned these starting dates. The purpose of the staggered observation start dates for psychosis patients untreated with antipsychotics was to create enough variation in observation period length so as not to confound it with the presence or absence of antipsychotic treatment. Observation periods ranged from 1 of the starting dates to the end of the study period (December 31, 1997) or to an individual's disenrollment date.

Individuals with type 2 diabetes were identified using ICD-CM-9 codes specifically for this condition and its manifestations or National Drug Codes for antidiabetic medications:

Type 2 diabetes ICD-CM-9 codes: 250.x0 and 250.x2.

Type 2 diabetes medications: first and second-generation sulfonylureas, metformin, rezulin, and acarbose.

Insulin, without an accompanying ICD-CM-9 code for type 2 diabetes, was not used as an indicator, because it is also the treatment for type 1 diabetes. Among the 8712 observations, a total of 647 cases of type 2 diabetes were identified using the above criteria. Many of these, however, were preexisting cases (i.e., existing prior to the observation period) and were excluded depending on the length of the screening period.

In screening for psychosis patients with preexisting type 2 diabetes, prior periods of 4 months and 8 months

were applied. Patients reporting type 2 diabetes within the specified prescreening period were excluded. Patients were also excluded if their claims records did not extend back to or beyond the beginning of the specified prescreening period. The 8-month prescreening period reduced the number of observations. While this affected tests for statistical significance, it was important to assess the sensitivity of results to the preexistence of type 2 diabetes.

Because the data for this study are claims data and were not generated in a controlled trial, relative odds of type 2 diabetes could not be accurately calculated from frequency tables. Untreated psychosis patients and the 5 categories of treated patients differed in other respects that could have affected the frequency of reported type 2 diabetes within each group. For example, the likelihood of observing type 2 diabetes within a population increases with the period of observation. Also, type 2 diabetes is age related, and age differences among the groups could have caused dissimilarities in reporting. Race may also affect incidence of diabetes; however, race was not included in this analysis as it was not available from the database. Logistic regression was used to control for these and other differences among the groups. The models measured the odds of type 2 diabetes for each of the 5 antipsychotic categories versus no treatment. Two sets of logistic regressions were estimated excluding observations with preexisting type 2 diabetes at 4 and at 8 months prior to observation.

The dependent variable in a logistic model is binary (taking a value of "1" if the event (type 2 diabetes) occurs for a given observation and "0" otherwise). Two sets of variables were specified in the models to capture the diabetic effects of each of the 5 antipsychotic categories:

1. Antipsychotic treatment duration. If an antipsychotic has a diabetic effect, it seems likely that this effect increases with the duration of treatment. Five variables measured treatment duration for each of the 5 antipsychotic categories as well as the absence of treatment. Each variable equaled the length of treatment in months if the observed patient used that therapy and "0" otherwise. Zeros for all 5 of the antipsychotic categories implied the sixth category—no treatment.
2. Antipsychotic dosage. The likelihood of a diabetic effect could also increase with the dosage level. Five variables measured dosage for each of the 5 antipsychotic categories as well as the absence of treatment. Each variable equaled the amount of antipsychotic used in milligrams per day of treatment. Zeros for all 5 of the antipsychotic categories implied the sixth category—no treatment. Dosages for all of the antipsychotics were expressed in risperidone-equivalent milligrams.

This was done to allow comparisons among the antipsychotic categories. High- and low-potency conventional groups each combined multiple antipsychotics, which necessitated standardization. Reported milligrams were converted to risperidone equivalents by applying weights to the doses on prescription records based on the observed range in daily dose for each antipsychotic. The range (difference between the maximum and minimum daily dose) rather than the mean daily dose was used to avoid case mix effects. Weights were calculated by dividing risperidone's daily dose range by each antipsychotic's range. For example, observed milligram ranges for risperidone and olanzapine were 6.8 mg and 17.9 mg, respectively, for a weight of 0.38 applied to olanzapine doses.

Preliminary tests indicated that antipsychotic treatment duration and dosage were highly correlated. Simultaneous inclusion of these variables would have resulted in distorted parameter estimates and unreliable tests for statistical significance. To deal with this problem, the frequently used approach of dropping 1 of the correlated variables was chosen.⁴² The model was estimated twice, first with the 5 treatment duration variables only and then with the 5 dosage variables only. While this approach avoids extreme distortions in parameter estimates and allows for more reliable statistical tests, it has the limitation of omitted variable bias,⁴³ which in this context means that a diabetic effect attributed to the specified measure of antipsychotic exposure may in part be due to the omitted measure.

The following control variables were also specified in the models:

1. Concurrent use of antipsychotics. Concurrent use of antipsychotics, which occurred in about 21% of observations with treated patients and was normally limited to the first month or so of a new treatment, was largely taken into account by the fact that treatment episodes overlapped in such cases. A diabetic event encompassed by 2 different overlapping therapies would be assigned to both therapies. However, an antipsychotic treatment episode in which another antipsychotic is also used is not the same as one involving monotherapy. To account for this difference and its potential confounding effects, a variable was added that measured the ratio of other antipsychotics' days' supply to treatment antipsychotic's days' supply (always "0" for untreated patients with psychosis).
2. Age. The likelihood of observing type 2 diabetes was assumed to increase with age. Age was expressed as a continuous variable.
3. Gender. The case studies cited showed a much

higher proportion of males than females acquiring type 2 diabetes after initiating antipsychotic treatment. Gender was expressed as a binary variable taking a value of "1" if male and "0" if female.

4. Observation period length. The likelihood of observing type 2 diabetes increases with the period of observation, particularly in claims data, which are affected by reporting. Unlike in clinical trials, in real life antipsychotic treatment durations vary, which causes observation periods to vary. Observation period length was expressed in months.
5. Use of other psychotropic drugs. Antidepressants, anxiolytics, anticholinergics, hypnotics, and mood stabilizers are often used in conjunction with antipsychotics. A limited number of studies suggest associations between these medications and type 2 diabetes.^{44,45} Individuals' use of non-antipsychotic psychotropic medications was expressed in dollars per month.
6. Type of health care coverage. Individuals in both health plans had either an indemnity or managed care form of coverage. While type of health care coverage does not affect type 2 diabetes, it may affect the likelihood that the condition is diagnosed and treated. Type of coverage was expressed as a binary variable where managed care was set equal to "1" and indemnity to "0."
7. Type of psychosis. Type 2 diabetes may be related to a specific mental health condition,⁴⁶⁻⁴⁸ and, to the extent that the groups differed with respect to type of psychosis, this could have contributed to differences in reporting. Psychosis patients were grouped into 5 categories: schizophrenia, bipolar and manic major depressive, dementia, and other psychoses. These were represented by binary variables for the first 4, with zeros for all 4 indicating the fifth category.

Logistic regression generates an odds ratio, expressed below, for each of the variables specified in the model:

$$[P_i/(1-P_i)]/[P_0/(1-P_0)]$$

Using treatment duration for one of the antipsychotics as an example and starting from zero treatment, this ratio is interpreted as follows:

- P_i is the probability of the event (type 2 diabetes) occurring given 1 month of treatment with the antipsychotic.
 $(1-P_i)$ is the probability of the event not occurring given 1 month of treatment with the antipsychotic.
 P_0 is the probability of the event occurring given no treatment with the antipsychotic.
 $(1-P_0)$ is the probability of the event not occurring given no treatment with the antipsychotic.

The odds ratio for antipsychotic treatment duration measures the degree by which the base probability of type 2 diabetes is greater due to 1 additional month of treatment with that antipsychotic. The base probability depends on the base dose of the antipsychotic (assumed to be "0" in the above example) and other characteristics of the population to which the antipsychotic is applied. Odds ratios for increments of antipsychotic treatment greater than 1 month are obtained simply by raising the 1-month odds ratio to a power equal to the desired number of months of additional treatment. Using the above example, the odds ratio for 12 months of treatment with the antipsychotic versus no treatment is

$$([P_1/(1-P_1)]/[P_0/(1-P_0)])^{12}$$

This same odds ratio would also apply to 13 months of treatment with the antipsychotic versus 1 month, 14 months versus 2 months, and so forth. A similar interpretation is given to antipsychotic dosage or any other continuous variable specified in the logistic model. (For more detailed discussion of continuous variables in logistic regression, the reader is referred to Schlotzhauser²⁹ and Hosmer and Lemeshow.³⁰)

The logistic model as specified measures for each antipsychotic the odds of type 2 diabetes relative to no treatment. Odds ratios estimated as such can be manipulated to calculate the odds of type 2 diabetes of one antipsychotic relative to another. Consider, for example, antipsychotics 1 and 2:

$$\{[P_1/(1-P_1)]/[P_0/(1-P_0)]\}/\{[P_2/(1-P_2)]/[P_0/(1-P_0)]\} = [P_1/(1-P_1)]/[P_2/(1-P_2)]$$

The odds ratio for antipsychotic 1 versus untreated divided by the odds ratio for antipsychotic 2 versus untreated—the left-hand expression—yields the odds ratio for antipsychotic 1 versus antipsychotic 2—the right-hand expression.

RESULTS

Descriptive Results

Psychosis patients with type 2 diabetes were identified by the first medical claim reporting this condition or, if it appeared first, by the first prescription claim for an antidiabetic medication. (As noted, because of its use in type 1 diabetes, insulin was not used as a primary indicator.) Over 70% of diabetes cases were identified with medical claims, and 90% of these were for type 2 diabetes without complication. There were no appreciable differences between patients treated with antipsychotics and those who were untreated in how they were identified.

Table 1 reports the frequency of diabetes associated with all psychosis patients treated with antipsychotics and psychosis patients not treated with antipsychotics, as well as the frequency associated with 5 categories of antipsy-

Table 1. Frequency of Reported Type 2 Diabetes Among Psychosis Patients by Length of Observation Period

Antipsychotic Treatment Group ^a	4-Month Prescreening			8-Month Prescreening		
	All Patients, N	With Diabetes N	%	All Patients, N	With Diabetes N	%
Untreated patients						
< 4 mo	111	0	0.0	74	0	0.0
≥ 4 to < 8 mo	166	3	1.8	94	2	2.1
≥ 8 to < 12 mo	754	12	1.6	631	8	1.3
≥ 12 mo	2030	68	3.3	939	24	2.6
All treated patients						
< 4 mo	1779	21	1.2	1447	13	0.9
≥ 4 to < 8 mo	1301	34	2.6	992	17	1.7
≥ 8 to < 12 mo	702	30	4.3	563	23	4.1
≥ 12 mo	552	38	6.9	239	14	5.9
Risperidone						
< 4 mo	556	3	0.5	440	1	0.2
≥ 4 to < 8 mo	432	6	1.4	324	4	1.2
≥ 8 to < 12 mo	188	5	2.7	140	3	2.1
≥ 12 mo	192	11	5.7	90	2	2.2
Olanzapine						
< 4 mo	462	8	1.7	440	6	1.4
≥ 4 to < 8 mo	325	11	3.4	301	7	2.3
≥ 8 to < 12 mo	200	9	4.5	189	8	4.2
≥ 12 mo	60	4	6.7	56	4	7.1
High-potency conventionals						
< 4 mo	544	6	1.1	410	4	1.0
≥ 4 to < 8 mo	395	12	3.0	271	4	1.5
≥ 8 to < 12 mo	233	13	5.6	170	9	5.3
≥ 12 mo	204	13	6.4	64	3	4.7
Low-potency conventionals						
< 4 mo	203	3	1.5	144	1	0.7
≥ 4 to < 8 mo	130	4	3.1	86	1	1.2
≥ 8 to < 12 mo	66	3	4.5	52	3	5.8
≥ 12 mo	81	8	9.9	25	4	16.0
Clozapine						
< 4 mo	15	1	6.7	13	1	7.7
≥ 4 to < 8 mo	19	1	5.3	10	1	10.0
≥ 8 to < 12 mo	15	0	0.0	12	0	0.0
≥ 12 mo	15	2	13.3	4	1	25.0

^aTime ranges refer to length of observation period.

chotic medication. Patients were screened for preexisting diabetes at 4 and 8 months prior to observation and were eliminated when the condition was reported or there were insufficient data to make a determination. Patients were also divided according to observation period length to enable better comparisons among the groups. As would be expected, across all groups diabetes cases were relatively more frequent among patients observed over longer periods. The 4 categories of observation period length are exclusive. Also across all groups, the relative frequency of diabetes cases tended to decline as the prescreening period increased. Screening at 4 months may not exclude relatively mild, preexisting cases since for these diet and exercise alone may suffice to keep symptoms under control for long periods. Screening at 8 months is more likely to reflect new-onset type 2 diabetes or exacerbation of conditions that were previously subclinical. Regardless of the degree of prescreening, a higher percentage of treated

Table 2. Profile of Psychosis Population Without Type 2 Diabetes at 4 Months Prior to Observation*

Variable	All Untreated Patients	All Treated Patients	Risperidone	Olanzapine	High-Potency Conventionals	Low-Potency Conventionals	Clozapine
Age							
Mean (SD)	41.9 (14.8)	45.3 (19.3)	43.0 (20.7)	43.1 (16.9)	48.4 (18.7)	48.3 (20.5)	39.4 (14.1)
Median	43	44	43	43	47	46	40
Gender							
Male	1236	1588	550	396	465	151	26
Female	1825	2746	818	651	911	329	37
Type of health care coverage							
Managed care	1248	1295	426	308	417	115	29
Indemnity	1813	3039	942	739	959	365	34
Observation period, mo							
Mean (SD)	13.8 (4.8)	6.4 (4.6)	6.4 (4.7)	5.6 (3.5)	6.7 (4.9)	6.8 (5.0)	8.8 (5.4)
Median	14.2	4.9	4.8	4.6	5.0	4.9	7.2
Antipsychotic treatment duration, mo							
Mean (SD)	NA	5.8 (4.7)	6.8 (4.8)	6.1 (3.6)	7 (5.1)	7.1 (5.2)	9.4 (5.5)
Median	NA	5.2	5.2	5.0	5.3	5.0	7.7
Antipsychotic dosage, mg/d risperidone equivalents							
Mean (SD)	NA	2.4 (2.1)	2.3 (1.8)	3.6 (2.0)	1.7 (1.9)	1.7 (2.7)	2.5 (1.9)
Median	NA	1.8	1.7	3.3	1.1	1.0	2.2
Basis of psychosis diagnosis							
Schizophrenia (ICD-9 295.xx)	32	744	191	235	228	54	36
Bipolar and manic (ICD-9 296.0, 296.1, 296.4-296.9)	1595	932	270	260	277	113	12
Major depressive (ICD-9 296.2, 296.3)	1049	1683	579	396	508	189	9
Dementia (ICD-9 290.xx)	208	276	86	22	119	49	0
Other psychoses (ICD-9 291.xx-294.xx, 297.xx, 298.xx, 299.xx)	177	701	242	134	244	75	6
Use of other psychotropic drugs, US \$/mo							
Mean (SD)	46.29 (72.91)	66.42 (90.51)	69.77 (81.09)	77.26 (107.34)	56.61 (79.97)	60.11 (76.19)	76.16 (175.52)
Median	20.21	41.38	50.40	50.72	32.85	31.23	24.35
Concurrent use of other antipsychotics, % of patients	NA	20.6	18.6	24.6	17.9	22.1	34.9

*Values shown as Ns unless otherwise noted.
Abbreviation: NA = not applicable.

psychosis patients reported type 2 diabetes than untreated patients. Among the 5 antipsychotic categories, risperidone consistently had the lowest percentage of patients reporting type 2 diabetes, similar to untreated patients, while clozapine had the highest. Percentages reporting type 2 diabetes for olanzapine and high- and low-potency conventionals were greater than for risperidone but less than for clozapine. Comparisons based on frequency tables, however, can be misleading if the groups being compared are dissimilar in other relevant respects.

Treated psychosis patients differed with respect to antipsychotic treatment duration and dosage, while differences in age, gender, and other patient characteristics affected all groups. These characteristics have already been identified as explanatory variables in the logistic models and are reported in Table 2. The group means and other statistics are based on the largest population used in the analysis, i.e., that screened for preexisting type 2 diabetes at 4 months prior to observation. Treated patients were older than untreated patients and had a higher proportion of females. Treated patients also had a much higher pro-

portion of individuals with indemnity coverage versus managed care. This characteristic may affect the onset or exacerbation of type 2 diabetes because of a different emphasis on prevention as well as the likelihood of seeking professional care. Observation periods among untreated patients were more than double the length of those of treated patients, increasing the likelihood of observing type 2 diabetes in that group. Treated and untreated patients also differed considerably with respect to type of psychosis, with schizophrenia patients being virtually absent among untreated patients. The largest numbers using antipsychotics were among patients with bipolar, major depressive, and manic forms of psychosis. This is expected, as the membership of the 2 health plans comprised mostly employed individuals and their dependents, among whom schizophrenia is less likely to be found. Untreated patients had lower per capita use of other psychotropic medications than patients treated with antipsychotics.

Considerable differences also existed among the 5 antipsychotic categories. Patients treated with risperidone

Table 3. Logistic Regression Results: Type 2 Diabetes Among Psychosis Patients Excluding Preexisting Type 2 Diabetes at 4 Months Prior to Observation^a

Variable ^b	Model I (treatment duration)		Model II (dose)	
	Odds Ratio	Probability > Chi-Square	Odds Ratio	χ^2
Treatment duration (yes = months; no = 0)				
Risperidone	1.021	0.2629	NA	NA
Olanzapine	1.082	0.0008*	NA	NA
High-potency conventionals	1.047	0.0031*	NA	NA
Low-potency conventionals	1.058	0.0090*	NA	NA
Clozapine	1.079	0.0708*	NA	NA
Dosage (yes = mg/d; no = 0)				
Risperidone	NA	NA	0.909	0.3155
Olanzapine	NA	NA	1.161	0.0012*
High-potency conventionals	NA	NA	1.090	0.1738
Low-potency conventionals	NA	NA	1.072	0.3322
Clozapine	NA	NA	1.095	0.6179
Age	1.028	0.0001*	1.030	0.0001*
Gender (male = 1)	1.079	0.6172	1.041	0.7920
Observation period (mo)	1.081	0.0001*	1.097	0.0001*
Other psychotropic drugs (\$ units/mo)	1.002	0.0003*	1.002	0.0003*
Concurrent antipsychotic (ratio of days' supply)	1.060	0.8565	1.175	0.6167
Coverage (managed care = 1; indemnity = 0)	1.085	0.6144	1.071	0.6709
Schizophrenia (yes = 1; no = 0)	1.534	0.1657	1.613	0.1238
Bipolar/manic (yes = 1; no = 0)	1.157	0.5892	0.984	0.9528
Major depressive (yes = 1; no = 0)	1.192	0.5012	1.113	0.6809
Dementia (yes = 1; no = 0)	1.243	0.5080	1.166	0.6378

^aNumber reporting type 2 diabetes (1) = 206; number not reporting type 2 diabetes (0) = 7189; total observations = 7395.

^bPatients untreated with antipsychotics are represented by zeros for each of the 5 specified antipsychotic categories.

*Significant difference at $p < .01$; [†]different approaches significance at $p < .10$.

Abbreviation: NA = not applicable.

and olanzapine were similar in age, while those treated with high- and low-potency conventionals were somewhat older. Patients treated with clozapine were younger. All of the antipsychotic categories had higher proportions of females. Indemnity was the principal form of coverage across all categories. Observation periods were longest for clozapine and shortest for olanzapine, which is largely explained by the newness of olanzapine to the market at the time of the data. If not controlled for, shorter observation periods might find less diabetes in a medication group, thereby giving that medication an inappropriate advantage. Antipsychotic treatment durations, which on average were longer than observation periods, were also longest for clozapine and shortest for olanzapine. Antipsychotic dosage (risperidone-equivalent milligrams per day of treatment) differed substantially among the antipsychotics, with olanzapine having the highest dosage and low-potency conventionals the lowest. The breakdown of patients by type of psychosis shows significant differences among the antipsychotics. Clozapine had the largest proportion with schizophrenia, while low-potency conventionals had the smallest. All antipsychotic categories except clozapine had major depressive psychosis as the dominant type. Olanzapine users had the highest per capita use of other psychotropic medications, while those treated with high-potency conventionals had the lowest. Clozapine users had the highest percentage that concurrently used other antipsychotics, while users of high-potency conventionals had the lowest.

Logistic Regression Results

Logistic regression was used to estimate effects on odds of type 2 diabetes of exposure to each of the 5 antipsychotics versus no treatment. Exposure was captured by variables measuring antipsychotic treatment duration and dosage. Additional variables were specified to control for other differences among the groups that could also affect the odds of type 2 diabetes. Two versions of the logistic regression model described in the Methods section were estimated: one with treatment duration (Model I), and the other with average daily dose (Model II), as the measure of antipsychotic exposure. These 2 versions were estimated 2 times: excluding psychosis patients reporting type 2 diabetes at 4 months and at 8 months prior to observation. Model I includes the 5 variables measuring treatment duration in months with each of the antipsychotics, while Model II includes the 5 variables measuring dose in risperidone-equivalent milligrams per day. No antipsychotic treatment, the base for comparison, was represented by "zero" values for all of these variables. The odds ratio for each antipsychotic reflects the odds of type 2 diabetes associated with a 1-unit (month or milligram) increment in antipsychotic exposure.

Results based on 4 months' prescreening. Odds ratios with levels of significance are listed for the antipsychotic exposure and control variables in Table 3. The models were estimated on the basis of 7395 observations, 206 of whom reported type 2 diabetes while 7189 did not. As the odds ratios for antipsychotic treatment duration

Table 4. Logistic Regression Results: Type 2 Diabetes Among Psychosis Patients Excluding Preexisting Type 2 Diabetes at 8 Months Prior to Observation^a

Variable ^b	Model I (treatment duration)		Model II (dose)	
	Odds Ratio	Probability > Chi-Square	Odds Ratio	χ^2
Treatment duration (yes = months; no = 0)				
Risperidone	0.989	0.7650	NA	NA
Olanzapine	1.099	0.0006*	NA	NA
High-potency conventionals	1.065	0.0252**	NA	NA
Low-potency conventionals	1.109	0.0030*	NA	NA
Clozapine	1.182	0.0104*	NA	NA
Dosage (yes = mg/d; no = 0)				
Risperidone	NA	NA	0.811	0.2367
Olanzapine	NA	NA	1.222	0.0002*
High-potency conventionals	NA	NA	1.111	0.3086
Low-potency conventionals	NA	NA	1.089	0.3062
Clozapine	NA	NA	1.304	0.1844
Age	1.025	0.0004*	1.029	0.0001*
Gender (male = 1; female = 0)	0.822	0.3824	0.771	0.2432
Observation period (mo)	1.125	0.0001*	1.161	0.0001*
Other psychotropic drugs (\$units/mo)	1.002	0.0083*	1.002	0.0131**
Concurrent antipsychotic (ratio of days' supply)	1.425	0.4011	1.454	0.3950
Coverage (managed care = 1; indemnity = 0)	0.990	0.9677	0.966	0.8831
Schizophrenia (yes = 1; no = 0)	0.994	0.9897	0.939	0.8920
Bipolar/manic (yes = 1; no = 0)	1.159	0.6989	0.944	0.8786
Major depressive (yes = 1; no = 0)	1.151	0.7014	1.079	0.8350
Dementia (yes = 1; no = 0)	1.449	0.4017	1.362	0.4818

^aNumber reporting type 2 diabetes (1) = 101; number not reporting type 2 diabetes (0) = 4878; total observations = 4979.

^bPatients untreated with antipsychotics are represented by zeros for each of the 5 specified antipsychotic categories.

*Significant difference at $p < .01$; **significant difference at $p < .05$.

Abbreviation: NA = not applicable.

indicate (Model I), risperidone had no statistically significant effect on diabetes. The diabetic effects of olanzapine, high-potency conventionals, and low-potency conventionals were all statistically significant at $p < .01$. Clozapine's diabetic effect was significant only at $p < .10$; however, this is likely due to its relatively small sample. Clozapine and olanzapine had the highest odds ratios (largest diabetic effects), which is consistent with the case literature. Each 1-month increment of treatment with olanzapine increased the odds of type 2 diabetes by 8.2%. When treatment duration was replaced with dosage (Model II), only olanzapine was statistically significant ($p < .01$). Olanzapine's odds ratio of 1.161 implies that each increment of 1 risperidone-equivalent milligram of this antipsychotic (2.6 actual milligrams of olanzapine) increased the odds of type 2 diabetes by 16.1%.

Among the control variables, age was highly significant ($p < .01$), as would be expected for type 2 diabetes. Since "age" is a continuous variable expressed in years, its odds ratio indicates the percent increment in the odds of type 2 diabetes as an individual ages by 1 year. Logically, the length of the observation period also affected the likelihood of observing type 2 diabetes ($p < .01$). The use of non-antipsychotic psychotropic medications (measured in \$10 units) was highly correlated with the likelihood of type 2 diabetes ($p < .01$). Since mechanisms through which antipsychotics and other medications may affect type 2 diabetes have not been fully investigated, it is possible that antidepressants, anxiolytics, mood stabilizers, etc., also induce or exacerbate this condition. None

of the other control variables were statistically significant. The variables reflecting psychosis type did not approach statistical significance, and, as Table 2 indicates, there was considerable variation among the groups in this regard.

Results based on 8 months' prescreening. Results based on 8 months' prescreening are reported in Table 4. Prescreening at 8 months further reduced observations to 4979, with 101 reporting type 2 diabetes. Results with this "cleaner" population were essentially the same as with the population prescreened at 4 months: all of the antipsychotics except risperidone showed diabetic effects. Results based on antipsychotic treatment duration (Model I) strengthened with prescreening at 8 months. Odds ratios for olanzapine, clozapine, and high- and low-potency conventionals increased and were all significant at $p < .05$ or better. In contrast, risperidone's odds ratio declined to 0.989 (still not significant). For antipsychotic dosage (Model II), olanzapine was statistically significant ($p < .01$) at 8 months' prescreening. Its odds ratio rose to 1.222, implying that a risperidone-equivalent dose of 1 mm (2.6-mg actual dose of olanzapine) increased the odds of type 2 diabetes by 22.2% over baseline. The same control variables were statistically significant with the populations prescreened at 8 months as with the population prescreened at 4 months.

Table 5 provides some useful calculations based on the odds ratios for antipsychotic treatment duration estimated

Table 5. Extrapolation of Type 2 Diabetes Odds Ratios for Antipsychotic Treatment Duration Excluding Preexisting Type 2 Diabetes at 8 Months Prior to Observation

Antipsychotic Treatment	Odds vs Untreated at 1 Month of Treatment		Odds vs Untreated at 12 Months of Treatment		Odds vs Risperidone at 12 Months of Treatment
		95% CI		95% CI	
Risperidone	0.989	0.921 to 1.063	0.88	0.372 to 2.070	NA
Olanzapine	1.099	1.041 to 1.160*	3.10	1.620 to 5.934*	3.53**
High-potency conventionals	1.065	1.008 to 1.126*	2.13	1.097 to 4.134*	2.42
Low-potency conventionals	1.109	1.036 to 1.187*	3.46	1.522 to 7.785*	3.93**
Clozapine	1.182	1.040 to 1.344*	7.44	1.603 to 34.751*	8.45**

*Odds ratio of 1.00, meaning effect is no different from untreated, falls outside of 95% CI.

**p < .05.

Abbreviation: NA = not applicable.

with the population prescreened for type 2 diabetes at 8 months prior to observation. There is a higher certainty that this population does not have preexisting diabetes; therefore, these odds ratios are more accurate indicators of antipsychotic diabetic effects. Estimated odds ratios, which reflect diabetic effects associated with 1 month of treatment, are listed in column 1. Ninety-five percent CIs are shown in column 2. These ratios were converted to reflect 12 months of treatment (column 3) with corresponding CIs (column 4). Risperidone's ratio of 0.88 implies that patients treated for 12 months with this antipsychotic face odds of type 2 diabetes that are 12% below baseline, but this is not statistically significant. In contrast, the 12-month ratios for the other antipsychotics are greater than 2.0 and are statistically significant. Olanzapine's ratio is 3.10, meaning that 12 months of treatment with this antipsychotic increases the odds of diabetes by 210% above baseline. Similar interpretations apply to clozapine and high- and low-potency conventionals. The last column shows the odds of type 2 diabetes for each of the other antipsychotics versus risperidone assuming 12 months of treatment. Olanzapine's ratio of 3.53 implies that its diabetic effect is 2.5 times greater than that of risperidone, which is statistically significant at $p < .05$ based on a chi-square test for homogeneity of odds ratios (using the Woolf method designed to compare results from separate trials⁵¹). Odds ratios for low-potency conventionals (3.93) and clozapine (8.45) versus risperidone are also high and statistically significant ($p < .05$). The odds ratio for high-potency conventionals versus risperidone is not statistically significant.

DISCUSSION

Recent data collected by the Schizophrenia Patient Outcomes Research Team (SPOR1) suggest that people with schizophrenia may be at increased risk for type 2 diabetes because of the side effects of antipsychotic medication, poor overall physical health, less healthy lifestyles, and inadequate health care.⁵² A possible relationship between the atypical antipsychotics olanzapine and clozapine and type 2 diabetes has been suggested in a number

of case reports.^{1-15,19-23} Three recent reports¹⁶⁻¹⁸ suggested a possible association with risperidone, and earlier case reports^{38,39} linked conventional antipsychotics with an increased risk of diabetes. Because of the small numbers involved and the relatively high incidence of type 2 diabetes, case findings are inconclusive.

To overcome this limitation and to provide an alternative source of evidence, this study used administrative data from 2 large health plans to investigate the medical histories of several thousand psychosis patients both treated and untreated with antipsychotics. While frequency tables were constructed to contrast treated and untreated patients and the various antipsychotic categories, in light of other important differences among the groups, logistic regression was used to more accurately estimate antipsychotic effects on the odds of type 2 diabetes.

Both frequency tables and logistic regression showed risperidone to have little or no diabetic effect. Based on logistic regression results with treatment duration as the measure of antipsychotic exposure, psychosis patients treated with risperidone were no more likely to acquire or exacerbate type 2 diabetes than untreated patients. This was true regardless of the degree of prescreening for type 2 diabetes. In contrast, the other antipsychotics, including olanzapine, clozapine, and high- and low-potency conventionals, had statistically significant effects on diabetes that were relatively large. These effects were strongest with 8 months' prescreening.

Positive and statistically significant effects of antipsychotic dosage on diabetes were observed for olanzapine only. These, too, were strongest with 8 months' prescreening. The absence of a significant dose effect for clozapine and high- and low-potency conventionals may have been due to the relative weakness of average daily dose as a measure of antipsychotic exposure. Antipsychotic dose is likely to vary over the course of treatment, and average dose, the most practical measure, may be weakly related to the dose that caused the diabetes. Also, antipsychotic dose is dependent on patient body weight, so that different doses may imply the same degree of antipsychotic exposure for patients with different body weights (patient weight is not reported in claims data).

Among the control variables, older age and greater use of non-antipsychotic psychotropic medications increased the odds of type 2 diabetes. Type of psychosis was not a statistically significant predictor of diabetes, which casts doubt on the view that diabetic effects are diagnosis related rather than antipsychotic related.

Because some patients had more than 1 treatment episode, interdependence of sampling units was considered as a potential statistical problem. Multiple antipsychotic treatment episodes for the same patient may violate the independence of sampling units if the type 2 diabetes is linked to inherent patient characteristics, e.g., genes. However, the mechanism(s) through which antipsychotics may cause type 2 diabetes are still unknown, and there is little reason to assume that inherent patient characteristics play a key role. Also, we reestimated the logistic equations keeping only the first treatment episode for each patient. With the exception of clozapine, which was already compromised by a small sample, results were virtually unchanged. In any case, dropping the first or second antipsychotic episode can create bias where episodes overlap or if being first or second is not random.

A number of potential mechanisms for antipsychotic-induced diabetes have been proposed, and it is likely that no one mechanism fully describes the relationship. This study showed differential effects of antipsychotics on diabetes. This finding may indicate that different medications have different mechanisms for causing diabetes. Olanzapine and clozapine may have an increased risk of diabetes due to induction of insulin resistance, nonspecific serotonin antagonism, and/or excessive weight gain. Conventional antipsychotics are typically potent dopamine-2 receptor antagonists, which may lead to increased risk of diabetes. Risperidone has not been associated with increased insulin resistance or significant weight gain and may interact with fewer receptors implicated in changes in glucose.

Given efforts made to identify individuals with pre-existing type 2 diabetes and to accurately associate new-onset cases with the antipsychotics through the use of treatment episodes, we believe that our findings are reliable. Limitations to this study include the inability to control for potential confounders to the results and the limited ability to determine previous history of and risk factors for diabetes. Both race and changes in weight can affect the incidence of diabetes. Neither of these variables was available in the database studied. The study was able only to establish that individuals did not require medical attention for type 2 diabetes for determined periods prior to initiation of specific antipsychotic therapies. Therefore, the need for diabetes medical attention after initiation of antipsychotic treatment could be interpreted as reflecting either the onset of diabetes or the exacerbation of a pre-existing condition. It is suggested that future studies should include an analysis of the association of antipsychotics

with diabetes controlling for changes in weight as well as ethnicity.

The present study demonstrates an increased risk of diabetes with some antipsychotics, primarily low-potency conventionals, olanzapine, and clozapine. In contrast to these, this study suggests that risperidone has no increased diabetic effect.

Drug names: acarbose (Precose), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), fluphenazine (Prolozin, Permitil, and others), haloperidol (Haldol and others), metformin (Glucophage and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others).

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Differential Effects of Antipsychotic Agents on the Risk of Development of Type 2 Diabetes Mellitus in Patients with Mood Disorders

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ABSTRACT

Background: Atypical antipsychotics are being used increasingly in the management of mood disorders.

Objective: The objective of this study was to investigate the association between exposure to antipsychotic therapy and newly reported type 2 diabetes mellitus in patients with mood disorders.

Methods: Claims data for the period January 1996 through December 1997 were analyzed for patients with mood disorders in 2 large US health plans. Logistic regression models were used to determine the odds of reporting diabetes in patients exposed to risperidone, olanzapine, or high- or low-potency conventional antipsychotics compared with untreated patients, taking into account duration of treatment and dosage. Some of the covariates used in the models were concurrent use of antipsychotics, use of other psychotropic drugs, age, sex, and length of observation.

Results: Based on the claims data, 849 patients were exposed to risperidone, 656 to olanzapine, 785 to high-potency conventional antipsychotics, and 302 to low-potency conventional antipsychotics; 2644 patients were untreated. The odds of newly reported type 2 diabetes in patients who received risperidone were not significantly different from those in untreated patients (12-month odds ratio [OR] = 1.024; 95% CI, 0.351–3.015). The odds in patients treated with high-potency conventional antipsychotics also did not differ significantly from those of

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untreated patients (12-month OR = 1.945; 95% CI, 0.794–4.786). Unlike patients who received risperidone or high-potency conventional antipsychotics, patients who received olanzapine (12-month OR = 4.289; 95% CI, 2.102–8.827) and low-potency conventional antipsychotics (12-month OR = 4.972; 95% CI, 1.967–12.612) had significantly higher odds for the development of type 2 diabetes compared with untreated patients.

Conclusions: These findings suggest that some antipsychotics may increase the risk for the development of type 2 diabetes in patients with mood disorders and that the effect may vary by drug. In contrast to olanzapine and low-potency conventional antipsychotics, risperidone and high-potency conventional antipsychotics were not associated with an increased risk for development of type 2 diabetes in this patient population. (*Clin Ther.* 2003;25:1150–1171) Copyright © 2003 Excerpta Medica, Inc.

Key words: atypical antipsychotics, conventional antipsychotics, type 2 diabetes, olanzapine, risperidone, managed care.

INTRODUCTION

Patients with mental illness may be at an increased risk for the development of type 2 diabetes mellitus as a result of poor overall physical health, unhealthy lifestyle, and inadequate access to health care services.¹ Epidemiologic studies suggest that the incidence of type 2 diabetes in manic-depressive and depressed patients is double that in the general population.^{2,3} Conversely, it has been reported that the odds of depression increase 2- to 3-fold in patients with type 2 diabetes, suggesting a pathophysiologic relationship between these 2 conditions.^{4,5} Results of a number of studies support a link between type 2 diabetes and mood disorders.^{6–12} Some of the biochemical abnormalities that have been proposed as common to both conditions include abnormal cerebral glucose metabolism, impaired phospholipid metabolism, and abnormal fatty acid-related signal transduction.^{13,14} None of the theories have been able to completely explain the connection between type 2 diabetes and mood disorders, and the exact mechanism by which these conditions affect each other remains to be elucidated.

In addition to theories based on the pathophysiologic similarities between diabetes and mood disorders, there is an emerging body of literature suggesting an iatrogenic explanation for this relationship. Specifically, use of antipsychotics has been associated with the development of diabetes. A comprehensive search of MEDLINE and Current Contents/Clinical Medicine for reports published in English between 1966 and 2002 found that in most reported cases of antipsychotic-induced type 2 diabetes, patients were taking the atypical antipsychotics clozapine or olanzapine,^{15–31} whereas there was a suspected association with risperi-

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done and type 2 diabetes in only 5 cases.³²⁻³⁵ Conventional antipsychotics have also been linked with type 2 diabetes.³⁶⁻³⁸

Although most of the published cases of newly reported type 2 diabetes in patients with mood disorders occurred in those with schizophrenia, there have been a number of published cases of antipsychotic-induced diabetes in this patient population.^{15,24,30,31,39} With the growing body of evidence supporting the use of atypical antipsychotics in the management of mood disorders, the off-label use of these agents has become increasingly common. In the management of bipolar mania, for instance, national practice guidelines recommend the use of atypical antipsychotics as first-line therapy in combination with a mood stabilizer.⁴⁰ A recent study by Rosenheck et al⁴¹ conducted in a national sample of the Veterans Affairs population reported that 42.8% of patients receiving atypical antipsychotics did not have schizophrenia. Estimates from other national databases suggest that up to 36% of prescriptions for atypical antipsychotics are for the treatment of mood disorders.⁴²

Two recent review articles discussed the possible mechanisms by which antipsychotics may cause glucose dysregulation.^{43,44} Some antipsychotics antagonize dopamine in the hypothalamus, which controls the central regulation of blood glucose, potentially disrupting blood glucose control mechanisms. Atypical antipsychotics are thought to exert their pharmacologic effect in part through antagonism of 5-hydroxytryptamine (HT)_{1A} receptors.⁴⁵ It is believed that antagonism of the 5-HT_{1A} receptors causes a decrease in insulin, leading to hyperglycemia.²² Weight gain caused by some atypical antipsychotics may also be related to impaired glucose-insulin homeostasis. A strong relationship between atypical antipsychotics and weight gain has been observed in clinical trials as well as in the practice setting.⁴⁶⁻⁵³ Obesity, particularly abdominal obesity, is a risk factor for type 2 diabetes and has been reported in many of the cited cases of antipsychotic-induced diabetes.^{15,17-22,30,33} Other psychotropic medications such as antidepressants, mood stabilizers, and anxiolytics are commonly used in conjunction with antipsychotics to manage mood disorders and have also been linked to type 2 diabetes.⁵⁴⁻⁵⁷

A recent study by Sernyak et al⁵⁸ compared the prevalence of type 2 diabetes in schizophrenia patients in the Veterans Affairs system who received atypical antipsychotics (clozapine, risperidone, olanzapine, and quetiapine) with those who received conventional antipsychotics. All of the atypicals except risperidone were found to have higher odds of association with type 2 diabetes. Although based on large numbers, this study did not control for preexisting type 2 diabetes or for the level of exposure (eg, treatment duration) to each of the antipsychotics.

The purpose of the present study was to investigate the association of antipsychotic treatment with type 2 diabetes and to determine whether the risk of diabetes differs by exposure to particular antipsychotics. As the number of reported

cases in which antipsychotic use was associated with type 2 diabetes is low relative to the total number of patients who receive these drugs, this assessment was conducted in a large population of patients to obtain a more conclusive determination of the contribution of antipsychotics to the development of type 2 diabetes.

METHODS

Data Source

The study was based on data from 2 mixed indemnity and managed care health plans located in the northeastern and southeastern United States. Approximately 2.5 million lives are covered under these health plans. The claims data used in this study were de-identified (encrypted) for both member and provider information, and the data were used solely for the approved research purpose to ensure full compliance and member protection. The data from each plan extended from January 1996 through December 1997. Because there was less awareness of the diabetic effects of atypical antipsychotics during this period, use of these data reduced the possibility of selection bias. Patients with mood disorder were identified through medical claims with *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnostic codes 296.xx. These ICD-9-CM codes correspond to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*⁵⁹ diagnoses of major depressive disorders, bipolar I and II disorders, and bipolar disorders not otherwise specified.

Antipsychotic Categories

Patients with mood disorder were classified as either untreated or treated with an antipsychotic agent. Treated patients had to be receiving an antipsychotic for ≥60 contiguous days. Patients who were receiving antipsychotic therapy for <60 days were excluded because they were judged to qualify neither as treated patients nor as controls. The cohort of treated patients was divided into 4 categories: (1) risperidone, (2) olanzapine, (3) high-potency conventional antipsychotics (perphenazine, fluphenazine, trifluoperazine, thiothixene, haloperidol, molindone, loxapine, prochlorperazine, and acetophenazine), and (4) low-potency conventional antipsychotics (chlorpromazine, promazine, triflupromazine, thioridazine, mesoridazine, and chlorprothixene). Patients with mood disorder who received clozapine were excluded because the sample size was too small to enable reliable analysis. The database did not include the more recent antipsychotics quetiapine and ziprasidone.

Treatment Episodes

For treated patients, sampling units consisted of antipsychotic treatment episodes rather than patients per se. Treatment episodes best fit the data, which reflected varying periods of antipsychotic use and included some patients who re-

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ceived the same or a different antipsychotic at different times. For each of the 4 antipsychotic categories, treatment episodes were measured from the date of the first prescription for an antipsychotic to the final date of treatment. The final date of treatment was calculated from the date of the last prescription plus its days' supply. In cases in which the treatment episode was terminated by disenrollment or the end of the study period, the disenrollment date or December 31, 1997, was used as the final date of treatment. Identification of a prescription as the first prescription in a treatment episode required that it not be preceded by another prescription for that antipsychotic for ≥ 90 days. Therefore, no treatment episode began before April 1, 1996.

Because 1 treated patient could have >1 treatment episode, there were $\sim 15\%$ more episodes than patients. As temporary concurrent use of the previous antipsychotic is recommended when making the transition to a new antipsychotic,⁶⁰ treatment episodes with different antipsychotics overlapped in $\sim 20\%$ of observations. We considered the possibility of interdependence of sampling units and determined that it was not a problem in this case.

For patients with mood disorder who received antipsychotics, the boundaries of a treatment episode were not strictly appropriate for evaluating the association of antipsychotic use with new or resurgent cases of type 2 diabetes. Some individuals may have discontinued an antipsychotic agent before receiving a diagnosis and treatment for the type 2 diabetes that may have been caused by that therapy. To adjust for this potential, the observation period was lagged by 30 days. For example, if a treatment episode with a particular antipsychotic extended from June 15, 1996, through March 10, 1997, the observation period for identifying type 2 diabetes was from July 15, 1996, through April 10, 1997. The 30-day lag is also consistent with the likelihood that any diabetic effect of antipsychotics may take some time from the initiation of therapy to emerge. Many of the cases of antipsychotic-induced diabetes reported in the literature occurred >30 days after the start of therapy with the antipsychotic.¹⁵⁻³³ To avoid uniformity for untreated patients with mood disorder, observation periods were constructed using 3 randomly assigned dates as starting points. Patients were randomly assigned to the starting dates of June 1, 1996, November 1, 1996, and April 1, 1997, with observation periods extending from these dates to the end of the study period (December 31, 1997) or to the disenrollment date, if this came first. The purpose of the staggered observation start dates for untreated patients was to create enough variation in the length of observation periods to avoid confounding this with the presence or absence of antipsychotic treatment.

Individuals with type 2 diabetes were identified by the first medical claim for this condition (ICD-9-CM 250.x0 and 250.x2) or, if appearing first, the first prescription claim for an antidiabetic medication (first- and second-generation sulfonylureas, metformin, troglitazone, or acarbose). Insulin was not included be-

cause of its primary association with type 1 diabetes. In many patients identified as having type 2 diabetes, the condition was preexisting (ie, existing before the observation period). Patients were screened for preexisting diabetes at 4 and 8 months before observation and were eliminated from the study if the condition was reported or there were insufficient data to make a determination. Although the longer prescreening period affected tests of statistical significance by reducing the number of observations, it was important to assess the sensitivity of results to the preexistence of type 2 diabetes.

The groups of patients analyzed in this study differed in ways other than type of antipsychotic treatment that could also have affected the frequency of type 2 diabetes in each group. Observation periods varied in length, primarily because treatment episodes varied, affecting the likelihood of observing type 2 diabetes. Furthermore, type 2 diabetes is age related, and age differences between groups may have contributed to differences in reporting. Race and changes in body weight may also affect the incidence of type 2 diabetes; however, none of these variables were included in the analysis, as they were not available in the database.

Logistic Regression Models

Logistic regression was used to estimate the odds of occurrence of type 2 diabetes for each of the 4 antipsychotic categories compared with no treatment, controlling for differences between groups. Occurrence of type 2 diabetes was the dependent variable in the logistic models. This binary variable was given a value of 1 if the event (type 2 diabetes) occurred for a given observation; it was otherwise given a value of 0. Exposure to each antipsychotic was measured by treatment duration (in months) and daily dose (in risperidone-equivalent milligrams). Preliminary tests indicated that antipsychotic treatment duration and dosage were highly correlated. Simultaneous inclusion of these variables would have resulted in distorted parameter estimates (possibly extreme) and unreliable tests of statistical significance. This problem was addressed by dropping 1 of the correlated variables.⁶¹ Two logistic models were estimated, first with the 4 treatment-duration variables only (model I) and then with the 4 dosage variables only (model II). Both models were estimated 2 times, once excluding patients with preexisting type 2 diabetes at 4 months before observation and the other excluding patients with preexisting type 2 diabetes at 8 months.

Model I: Antipsychotic Treatment Duration

If an antipsychotic has a diabetic effect, then it is logical to assume that the likelihood of this effect increases with the length of treatment. Four variables measured treatment duration for each of the 4 antipsychotic categories, as well as measuring the absence of treatment. Each variable equaled the length of treatment in months if the observed patient used that therapy and equaled 0 other-

wise. Zeros for all 4 of the antipsychotic categories implied the fifth category—no treatment.

Model II: Antipsychotic Dosage

The likelihood of a diabetic effect could also increase with antipsychotic dosage. Four variables measured dosage for each of the 4 antipsychotic categories, as well as measuring the absence of treatment. Each variable equaled the amount of antipsychotic in milligrams per day if the observed patient used that therapy and equaled zero otherwise. Zeros for all 4 of the antipsychotic categories implied the fifth category—no antipsychotic treatment. Dosages for all antipsychotics were expressed in risperidone-equivalent milligrams to allow comparisons between antipsychotic categories. In addition, each of the categories for high- and low-potency conventional antipsychotics combined multiple antipsychotics, which necessitated standardization of their different milligram scales. Reported milligrams were converted to risperidone equivalents by applying weights to the doses in prescription records based on the observed daily dose range for each antipsychotic. The range (difference between maximum and minimum daily doses) rather than the mean daily dose was used to avoid case-mix effects. Weights were calculated by dividing risperidone's daily dose range by the range for each antipsychotic. For example, observed daily milligram ranges for risperidone and olanzapine were 6.8 and 17.9 mg, respectively, resulting in a weight of 0.38 applied to olanzapine doses. Therefore, 4 mg of risperidone was approximately equivalent to 11 mg of olanzapine.

Other Independent Variables Specified in the Models

Seven additional independent variables were specified in both models: (1) concurrent use of antipsychotics, (2) age, (3) sex, (4) length of observation period, (5) use of other psychotropic drugs, (6) type of health care coverage, and (7) type of mood disorder. Descriptions of these variables and the rationale for their inclusion in the models are detailed in Table I.

RESULTS

A total of 5723 patients were identified as having some form of mood disorder and had sufficient data for study inclusion. A total of 2608 patients with mood disorder received ≥60 contiguous days of an antipsychotic during the study period, and 3115 received no treatment with an antipsychotic. There were a total of 6119 observations (3004 receiving treatment with antipsychotics and 3115 untreated). Of these, 339 cases were identified as having type 2 diabetes. After screening patients at 4 and 8 months for preexisting type 2 diabetes, there were a respective 5236 and 3496 observations left for analysis.

Table II summarizes the demographic and baseline disease characteristics of untreated patients and those in the various antipsychotic-treatment groups. As

Table 1. Independent variables included in the logistic models.

Variable	Rationale	Description
Concurrent use of antipsychotics	Concurrent use of antipsychotics, which occurred in ~20% of observations and was normally limited to the first month or so of a new treatment, was largely taken into account by the fact that treatment episodes overlapped in such cases. A diabetic event encompassed by 2 overlapping therapies was assigned to both therapies. However, an antipsychotic treatment episode in which another antipsychotic is also used is different from one involving monotherapy.	To account for this difference and its potentially confounding effects, a variable was added that equaled the ratio of the days' supply of other antipsychotics to the days' supply of the treatment antipsychotic (always 0 for untreated patients).
Age	The likelihood of observing type 2 diabetes mellitus was assumed to increase with age.	Age was expressed as a continuous variable.
Sex	The case studies cited showed a much higher proportion of men than women developing type 2 diabetes after initiation of treatment with an antipsychotic.	Sex was expressed as a binary variable given a value of 1 if male and 0 if female.
Length of observation period	The likelihood of observing type 2 diabetes increases with the period of observation, particularly when using claims data, which are affected by reporting.	The length of the observation period was expressed in months.
Use of other psychotropic drugs	Antidepressants, anxiolytics, anticholinergics, hypnotics, and mood stabilizers are often used in conjunction with antipsychotics.	Individual use of nonantipsychotic psychotropic medications was expressed in multiples of \$10 per month.
Type of health care coverage	Individuals in both health plans had either an indemnity or managed care form of coverage. Although type of health care coverage does not affect type 2 diabetes, it may affect the likelihood of the condition being diagnosed and treated.	Type of coverage was expressed as a binary variable with managed care equal to 1 and indemnity to 0.
Type of mood disorder	As <i>International Classification of Diseases, Ninth Revision</i> codes allow the clinician to specify whether the patient is in a manic state, it was possible to classify patients according to 3 distinct groups.	Mood disorders were represented by binary variables for bipolar and major depressive disorders, with 0 for both indicating a manic state.

Table II. Characteristics of patients with a diagnosis of mood disorder* and no type 2 diabetes mellitus 4 months before observation.

	All Patients Not Taking Antipsychotics (n 2644)	All Patients Taking Antipsychotics (n 2592)	Risperidone (n 849)	Olanzapine (n 656)	High-Potency Conventional Antipsychotics (n 785)	Low-Potency Conventional Antipsychotics (n 302)
Age, y						
Mean (SD)	41.8 (14.3)	42.2 (15.8)	40 (17.0)	42.7 (15.5)	43.9 (14.4)	42.7 (15.5)
Median	43	43	41	44	44	44
Sex, no. (%)						
Female	1616 (61.1)	1767 (68.2)	546 (64.3)	443 (67.5)	557 (71.0)	221 (73.2)
Male	1028 (38.9)	825 (31.8)	303 (35.7)	213 (32.5)	228 (29.0)	81 (26.8)
Type of health care coverage, no. (%)						
Indemnity	1587 (60.0)	1715 (66.2)	541 (63.7)	448 (68.3)	508 (64.7)	218 (72.2)
Managed care	1057 (40.0)	877 (33.8)	308 (36.3)	208 (31.7)	277 (35.3)	84 (27.8)
Length of observation period, mo						
Mean (SD)	13.7 (4.9)	6.1 (4.4)	6.1 (4.5)	5.4 (3.4)	6.5 (4.7)	6.5 (4.7)
Median	14.2	4.6	4.5	4.4	4.9	4.7

(continued)

Table II. (Continued)

	All Patients Not Taking Antipsychotics (n = 2644)	All Patients Taking Antipsychotics (n = 2592)	Risperidone (n = 849)	Olanzapine (n = 656)	High-Potency Conventional Antipsychotics (n = 785)	Low-Potency Conventional Antipsychotics (n = 302)
Duration of antipsychotic treatment, mo						
Mean (SD)	NA	6.5 (4.6)	6.5 (4.7)	5.9 (3.6)	6.8 (4.9)	6.8 (4.9)
Median	NA	4.9	4.8	4.9	5.1	4.9
Antipsychotic dosage, risperidone-equivalent mg/d						
Mean (SD)	NA	2.2 (1.9)	2.1 (1.7)	3.4 (1.8)	1.6 (1.6)	1.6 (2.3)
Median	NA	1.7	1.6	3.1	1.1	1.1
Type of mood disorder, no. (%)						
Bipolar	1272 (48.1)	794 (30.6)	230 (27.1)	229 (34.9)	237 (30.2)	98 (32.5)
Major depressive	1049 (39.7)	1672 (64.5)	579 (68.2)	396 (60.4)	508 (64.7)	189 (62.6)
Manic	323 (12.2)	126 (4.9)	40 (4.7)	31 (4.7)	40 (5.1)	15 (4.9)
Use of other psychotropic drugs						
Mean (SD), \$/mo	49.40 (74.73)	81.76 (91.83)	86.38 (92.29)	88.90 (104.86)	72.99 (81.37)	76.06 (83.79)
Median, \$/mo	23.71	59.22	66.21	62.97	54.38	49.15
Concurrent use of other antipsychotics, %	NA	17.2	17.1	18.9	15.0	19.5

NA = not applicable.

*Based on patient episodes as the unit of measurement.

demographic characteristics were included in the multivariate analysis, univariate comparisons were not performed. The group means and other statistics are based on the population of patients screened for preexisting type 2 diabetes at 4 months before observation. The mean age of treated and untreated patients was 42.2 and 41.8 years, respectively. More than 60% of patients in both groups were female and had indemnity coverage. Whereas the type of coverage is not assumed to have clinical implications, it may affect the likelihood that a patient will seek professional care for type 2 diabetes. Observation periods were a mean of 13.7 months in untreated patients and only 6.1 months in treated patients. Major depression was the most common diagnosis among treated patients, and bipolar disorder was the most common diagnosis in untreated patients.

Patients who received risperidone treatment were ~3 to 4 years younger than those who received other antipsychotics. All of the antipsychotic categories had higher proportions of women, and indemnity was the principal form of coverage across all categories. Observation periods were longest for the high- and low-potency conventional antipsychotics and shortest for olanzapine. Antipsychotic treatment durations, which on average were longer than observation periods, were longest for high- and low-potency conventional antipsychotics and shortest for olanzapine. When patients were stratified by type of mood disorder, major depression was the largest diagnostic category in all treatment groups. The mean antipsychotic dosage (measured in risperidone-equivalent milligrams per day) was 3.4 mg for olanzapine, 2.1 mg for risperidone, and 1.6 mg for both high- and low-potency conventional antipsychotics. Concurrent use of different antipsychotics was most prevalent in the low-potency conventional antipsychotic group and least prevalent in the group receiving high-potency conventional antipsychotics.

Logistic Regression Results

Results from the logistic regression models are reported in Tables III and IV. Odds ratios (ORs) and levels of significance are given for the antipsychotic-exposure and control variables. Model I includes the 4 variables measuring duration of treatment in months for each of the antipsychotics, and model II includes the 4 variables measuring dosage in risperidone-equivalent milligrams per day. For all these variables, no antipsychotic treatment, the basis for comparison, was represented by 0. The OR for each antipsychotic reflects the odds of type 2 diabetes associated with a 1-unit increment (in months or milligrams) in antipsychotic exposure.

Table III reports results for the models based on prescreening for type 2 diabetes at 4 months before observation. The models were estimated on the basis of 5236 observations, 135 of which involved type 2 diabetes. As indicated by the ORs for duration of antipsychotic treatment (model I), patients who received ris-

Table III. Results of the logistic regression analysis of the occurrence of type 2 diabetes mellitus among patients with mood disorder, excluding those with preexisting type 2 diabetes at 4 months before observation.*

Variable	Model I (Treatment Duration)		Model II (Dosage)	
	OR	P > Chi Square	OR	P > Chi Square
Duration of treatment (yes = mo; no = 0) [†]				
Risperidone	1.025	0.3037	NA	NA
Olanzapine	1.115	0.0001 [‡]	NA	NA
High-potency conventional antipsychotics	1.058	0.0036 [‡]	NA	NA
Low-potency conventional antipsychotics	1.064	0.032 [§]	NA	NA
Dosage (yes = mg/d; no = 0) [†]				
Risperidone	NA	NA	1.026	0.8127
Olanzapine	NA	NA	1.291	0.0001 [‡]
High-potency conventional antipsychotics	NA	NA	1.203	0.017 [§]
Low-potency conventional antipsychotics	NA	NA	1.101	0.2522
Age	1.033	0.0001 [‡]	1.036	0.0001 [‡]
Sex (male = 1)	1.02	0.9162	0.995	0.9783
Observation period, mo	1.087	0.0001 [‡]	1.111	0.0001 [‡]
Other psychotropic drugs, \$/mo	1.002	0.0318 [§]	1.002	0.0427 [§]
Concurrent antipsychotics: ratio of days' supply	1.783	0.1617	1.901	0.1253
Coverage (managed care 1; indemnity 0)	1.073	0.7159	1.065	0.7437
Type of mood disorder (yes 1; no 0) ^{‡‡}				
Major depressive	1.775	0.1886	1.981	0.1141
Bipolar	1.961	0.1234	1.981	0.117

OR = odds ratio; NA = not applicable.

*Number reporting type 2 diabetes = 135; number not reporting type 2 diabetes = 5101; total observations = 5236.

[†]Untreated patients are represented by 0 for all variables for duration of antipsychotic treatment and dosage.

[‡]P < 0.01.

[§]P < 0.05.

^{‡‡}Patients with manic disorder are represented by 0 for major depressive and bipolar disorders.

peridone were not significantly more likely to develop type 2 diabetes than were untreated patients. Patients who received olanzapine and high- and low-potency conventional antipsychotics had significantly higher odds of developing type 2 diabetes than did untreated patients ($P < 0.05$). With an OR of 1.115 ($P < 0.001$), olanzapine's diabetic effect was by far the largest, suggesting that 1 month of treat-

Table IV. Results of logistic regression analysis of the occurrence of type 2 diabetes mellitus among patients with mood disorder, excluding those with preexisting type 2 diabetes at 8 months before observation.*

Variable	Model I (Treatment Duration)		Model II (Dosage)	
	OR	P > Chi Square	OR	P > Chi Square
Duration of treatment (yes = mo; no = 0)†				
Risperidone	1.002	0.9582	NA	NA
Olanzapine	1.129	0.0001‡	NA	NA
High-potency conventional antipsychotics	1.057	0.146	NA	NA
Low-potency conventional antipsychotics	1.143	0.0007‡	NA	NA
Dosage (yes = mg/d; no = 0)‡				
Risperidone	NA	NA	0.854	0.4958
Olanzapine	NA	NA	1.337	0.0001‡
High-potency conventional antipsychotics	NA	NA	1.178	0.1903
Low-potency conventional antipsychotics	NA	NA	1.13	0.1394
Age	1.032	0.0007‡	1.035	0.0003‡
Sex (male = 1)	0.69	0.2031	0.643	0.1285
Observation period, mo	1.128	0.0002‡	1.18	0.0001‡
Other psychotropic drugs, \$/mo	1.002	0.0243§	1.002	0.0613
Concurrent antipsychotics, ratio of days' supply	2.01	0.1489	2.299	0.1029
Coverage (managed care = 1; indemnity = 0)	0.927	0.7928	0.869	0.6268
type of mood disorder (yes = 1; no = 0)‡				
Major depressive	1.375	0.6089	1.69	0.395
Bipolar	1.63	0.4287	1.7	0.5898

OR = odds ratio; NA = not applicable.

*Number reporting type 2 diabetes = 66; number not reporting type 2 diabetes = 3430; total observations = 3496.

†Untreated patients are represented by 0 for all variables for duration of antipsychotic treatment and dosage.

‡p < 0.01.

§p < 0.05.

¶Patients with manic disorder are represented by 0 for major depressive and bipolar disorders.

ment with this antipsychotic increases the odds of newly reported type 2 diabetes by 11.5% compared with no treatment. Each 1-month increment of treatment with high- and low-potency conventional antipsychotics was associated with respective 5.8% and 6.4% increases in the odds of newly reported type 2 diabetes.

When duration of treatment was replaced by dosage (model II), the ORs for risperidone continued to be statistically nonsignificant. The odds of the occur-

rence of type 2 diabetes also did not differ significantly with low-potency conventional antipsychotics compared with no treatment. Olanzapine ($P < 0.01$) and high-potency conventional antipsychotics ($P < 0.05$), however, continued to be associated with significantly higher odds of type 2 diabetes. In the model, each increment of 1 risperidone-equivalent milligram of olanzapine or high-potency conventional antipsychotic increased the odds of the occurrence of diabetes by 29.1% or 20.3%, respectively. In other words, the OR for olanzapine, 1.291 ($P < 0.001$), suggests that 1 risperidone-equivalent milligram of this antipsychotic daily (2.6 actual milligrams) increased the odds of type 2 diabetes by 29.1%.

Among the control variables, age was highly significant ($P < 0.01$), as would be expected with type 2 diabetes. As age is a continuous variable expressed in years, its OR indicates the percent increment in the odds of occurrence of type 2 diabetes as an individual ages by 1 year. Logically, the length of the observation period also affected the likelihood of observation of type 2 diabetes ($P < 0.01$). The use of nonantipsychotic psychotropic medications was highly correlated with the likelihood of occurrence of type 2 diabetes ($P < 0.05$). This finding is supported by limited literature suggesting an association between these medications and glucose intolerance.⁵⁴⁻⁵⁷ None of the other control variables were statistically significant.

Table IV reports the logistic regression results based on prescreening for type 2 diabetes at 8 months before observation; the remaining observations numbered 3496, with 66 reporting type 2 diabetes. The results were somewhat changed from prescreening at 4 months in this population. The main difference was that high-potency conventional antipsychotics no longer appeared to have a significant effect on the occurrence of type 2 diabetes. Risperidone did not have a significant effect on the risk of diabetes with either measure of antipsychotic exposure. When treatment duration was used in the model, low-potency conventional antipsychotics continued to have a significant effect on the occurrence of type 2 diabetes ($P < 0.01$), with the risk more than doubled. At the more rigorous level of prescreening, the evidence for a diabetic effect was strongest with olanzapine. ORs for both treatment duration and dosage continued to be significant ($P < 0.001$). At 8-month prescreening, the OR for olanzapine based on treatment duration was 1.129, implying that each month of treatment with this antipsychotic increased the odds of occurrence of type 2 diabetes by 12.9%. The OR for olanzapine based on dosage was 1.337, suggesting that each increment of 1 risperidone-equivalent milligram of olanzapine raised the odds of occurrence of type 2 diabetes by 33.7%. The same control variables were statistically significant for the population prescreened at 8 months as for the population prescreened at 4 months.

Table V provides calculations based on the estimated ORs for treatment duration in the population prescreened for type 2 diabetes at 8 months before observation. Because this is the population least likely to have preexisting diabetes,

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Table V. Conversion to 12-month odds ratios (ORs) for duration of antipsychotic treatment, excluding patients with preexisting type 2 diabetes mellitus at 8 months before observation.

	Treatment Duration 1 Month		Treatment Duration 12 Months			
	OR Relative to Untreated	95% CI	OR Relative to Untreated	95% CI	OR Relative to Risperidone	P > Chi Square*
Risperidone	1.002	.917-1.096	1.024	.351-3.015	NA	NA
Olanzapine	1.129	1.064-1.199†	4.289	2.102-8.827†	4.189	0.02958
High-potency conventional antipsychotics	1.057	.981-1.139	1.945	.794-4.786	1.899	0.37312
Low-potency conventional antipsychotics	1.143	1.058-1.235†	4.972	1.967-12.612†	4.854	0.02993

NA = not applicable.

*Calculated using the chi-square test for homogeneity of ORs over different strata (Woolf method⁵²).

†OR of 1.00, meaning effect is no different from untreated, falls outside 95% CI.

these ORs are more accurate indicators of the diabetic effects of antipsychotics. The table shows ORs (95% CIs) reflecting 1 month of treatment estimated with logistic regression. The 1-month ratio for risperidone (1.002) was close to 1, implying virtual equivalence to no treatment, whereas the ratios for olanzapine and low-potency conventional antipsychotics exceeded 1 and were statistically significant. Also reported in the table are estimated ORs (95% CIs) converted to reflect 12 months of treatment. The figure depicts these results graphically. The 12-month OR for risperidone (1.024) is small, again suggesting equivalence to no treatment. In contrast, the 12-month ORs for olanzapine (4.289) and low-potency conventional antipsychotics (4.972) are quite large, implying that these antipsychotics increase the odds of occurrence of type 2 diabetes by 300% to 400% above those of untreated patients. The 12-month OR for high-potency conventional antipsychotics (1.945) is also large and implies odds nearly 100% greater than those with no treatment. Finally, the table shows the odds of type 2 diabetes for each of the other antipsychotics compared with risperidone, assuming 12 months of treatment. Because risperidone was nearly the same as no treatment, these ratios also show 300% to 400% greater odds of the occurrence of

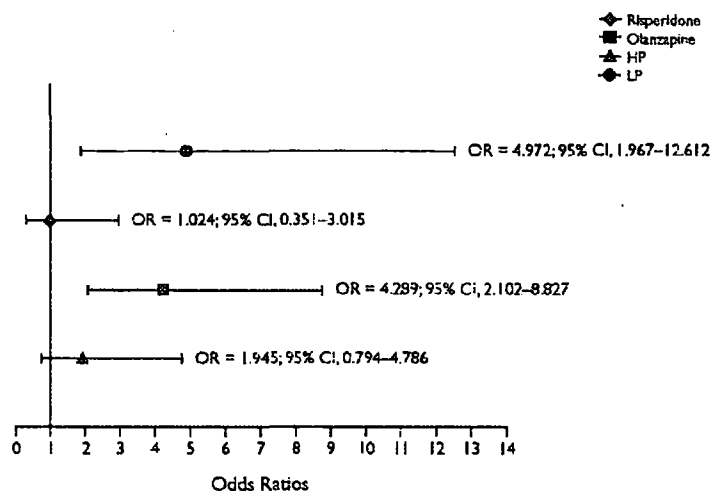


Figure. Odds of newly reported type 2 diabetes mellitus during 12 months of antipsychotic exposure relative to no treatment. HP = high-potency conventional antipsychotics; LP = low-potency conventional antipsychotics; OR = odds ratio.

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type 2 diabetes in patients treated with olanzapine or low-potency conventional antipsychotics and 100% greater odds in those treated with high-potency conventional antipsychotics. The ORs for olanzapine versus risperidone (4.189) and low-potency conventionals versus risperidone (4.854) were statistically significant at $P < 0.05$ based on a chi-square test for homogeneity of ORs over different strata (using the Woolf method for comparing results from separate trials).⁶²

DISCUSSION

The main goal of this study was to assess the association between the use of antipsychotics and the development of diabetes in patients with mood disorders. Based on the regression models, patients with mood disorders who received risperidone were no more likely to develop type 2 diabetes than were untreated patients. This was true regardless of the level of prescreening for type 2 diabetes and of whether antipsychotic exposure was measured by duration of treatment or dosage. In fact, the strongest results showing no diabetic effect for risperidone were obtained with the more stringent level of prescreening at 8 months before observation. In contrast, olanzapine showed positive and statistically significant diabetic effects based on both duration of treatment and dosage at both 4- and 8-month prescreening, with the larger effect occurring at 8 months.

Low-potency conventional antipsychotics were associated with a significantly higher risk for type 2 diabetes at each level of prescreening based on treatment duration, with the larger effect also occurring at 8 months. This group displayed no dose-related risk of type 2 diabetes in either model. A dose-related diabetic effect may not have been observed for 2 reasons. First, the antipsychotic dose is likely to vary over the course of treatment, and dose may be weakly related to a higher incidence of type 2 diabetes. Second, different doses may imply the same degree of antipsychotic exposure in patients with different body weights (body weight was not reported in the claims data). High-potency conventional antipsychotics showed diabetic effects only at 4-month prescreening for both treatment duration and dosage. Among the control variables, older age and greater use of nonantipsychotic psychotropic medications increased the odds of type 2 diabetes. As the prevalence of type 2 diabetes increases with age, one would expect older age to have a significant effect on the risk of diabetes. An association between the use of other psychotropic agents and a higher risk for type 2 diabetes has also been reported in the literature.⁵⁴⁻⁵⁷ The type of mood disorder was not statistically significant, a result that conflicts with the findings of at least 1 other study.¹³

Because some patients had >1 treatment episode, interdependence of sampling units was considered a potential statistical problem. Multiple antipsychotic treatment episodes for the same patient may violate the independence of sampling units if the diabetes is linked to inherent patient characteristics, such as genetic predisposition. However, the exact mechanisms by which antipsychotics may

cause type 2 diabetes are still unknown, and there is little reason to assume that inherent patient characteristics play a key role. Also, when we re-estimated the logistic equations, keeping only the first treatment episode for each patient, there was little difference in the results. In any case, dropping the first or second antipsychotic episode can create bias when episodes overlap or when being first or second is not random.

Our findings suggest that the various antipsychotics may have differing risks of inducing type 2 diabetes. Although there is no accepted mechanism that would explain these differences, it can be postulated that the differential effects of antipsychotics on insulin resistance, serotonin antagonism, and weight gain may translate into different diabetic effects.^{22,46-53} For instance, conventional antipsychotics are typically potent dopamine-2 receptor antagonists, which may explain the increased risk of diabetes observed in our study. Risperidone, in contrast, has not been associated with increased insulin resistance, does not produce significant weight gain, and may interact with fewer receptors implicated in changes in glucose regulation.

The data source for this study did not contain information on patients' race or family history of type 2 diabetes; thus, we were unable to include these variables in the analysis. Changes in body weight over time can also affect the incidence of diabetes and were not captured in the database. The effects of nonpsychotropic medications with diabetogenic potential, such as beta-blockers or corticosteroids, were not included in the analysis. Despite these limitations, the findings of this study are believed to be reliable based on the large numbers of patients involved and the efforts made to accurately assign cases of type 2 diabetes, identify pre-existing cases, and control for important confounding factors. The patient population with mood disorders numbered several thousand, with a high proportion not using antipsychotics. These factors enabled a more robust determination of antipsychotic contributions to the onset or exacerbation of type 2 diabetes.

CONCLUSIONS

The specific mechanism by which patients with mood disorders appear to have an increased risk for development of type 2 diabetes remains unknown, but an increasing body of literature suggests that some of the drugs used in the treatment of mood disorders may have a diabetogenic effect. The results of this study suggest that in patients with mood disorders, treatment with risperidone or high-potency conventional antipsychotics is not associated with a significant risk for the occurrence of type 2 diabetes, whereas treatment with olanzapine and low-potency conventional antipsychotics is associated with a significantly increased risk. In addition to considerations of the diabetogenic potential of each agent, the presence of risk factors such as obesity, sedentary lifestyle, and family history of type 2 diabetes should be taken into account in the selection of a suitable pharmacotherapeutic regimen.

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Antipsychotic-Induced Type 2 Diabetes: Evidence From a Large Health Plan Database

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Abstract: Case evidence suggests that some of the atypical antipsychotics may induce type 2 diabetes. The objective of this study was to evaluate the association of antipsychotic treatment with type 2 diabetes in a large health plan database. Claims data for patients with psychosis within a health plan of nearly 2 million members were analyzed using logistic regression. Frequencies of newly treated type 2 diabetes in patients untreated with antipsychotics and among patients treated with quetiapine, risperidone, olanzapine, and conventional antipsychotics were compared. Based on exposure measured in months of antipsychotic treatment, quetiapine and risperidone patients had estimated odds of receiving treatment for type 2 diabetes that were lower than those of patients untreated with antipsychotics (not statistically significant); patients treated with conventional antipsychotics had estimated odds that were virtually equivalent to those of patients untreated with antipsychotics; olanzapine alone had odds that were significantly greater than those of patients untreated with antipsychotics ($P = 0.0247$). Odds ratios based on 8 months of screening for pre-existing type 2 diabetes and assuming 12 months of antipsychotic treatment were: risperidone = 0.660 (95% CI 0.311–1.408); olanzapine = 1.426 (95% CI 1.046–1.955); quetiapine = 0.976 (95% CI 0.422–2.271); and conventional antipsychotics = 1.049 (95% CI 0.688–1.613). Case reports, prospective trials, and other retrospective studies have increasingly implicated olanzapine and clozapine as causing or exacerbating type 2 diabetes. Few have implicated risperidone while evidence on quetiapine has been limited. This study supports earlier findings on risperidone versus olanzapine and builds evidence on quetiapine. Additional studies are needed to evaluate the association of antipsychotic treatment with type 2 diabetes.

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Atypical antipsychotics approved by the Food and Drug Administration for sale in the United States include clozapine, risperidone, olanzapine, quetiapine, and recently, ziprasidone. These agents have a major advantage over conventional antipsychotics such as haloperidol and perphenazine in that they are less likely to produce extrapyramidal side effects or elevate prolactin levels while being at least as effective in treating the symptoms of schizophrenia and related psychoses.^{1–12} However, atypical and conventional antipsychotics have other side effects that need to be considered when assessing overall safety and efficacy. For example, risk of agranulocytosis, a very serious and potentially fatal blood disorder, has limited the use of clozapine.¹³ This study further investigates the association between antipsychotics and type 2 diabetes.

In a number of reported cases, patients became glucose intolerant after initiating antipsychotic treatment. Most of these cases involved the atypical antipsychotics clozapine^{14–27} and olanzapine,^{19,27–35} with quetiapine suspected in 2 cases^{36,37} and risperidone in 3 cases.^{38–40} The earlier case literature has also associated some conventional antipsychotics with type 2 diabetes.^{41–43} Prospective trials involving relatively small numbers of schizophrenia patients have also examined the association between antipsychotics and diabetes. Lindenmayer et al⁴⁴ found clozapine, olanzapine, and haloperidol, but not risperidone, to be associated with an increase of plasma glucose level. Newcomer et al⁴⁵ found olanzapine-treated and clozapine-treated patients to have significant glucose elevations in comparison to both patients treated with conventional antipsychotics and to healthy controls, while risperidone-treated patients had significantly higher elevations with respect to healthy controls only.

The propensity of antipsychotics to cause weight gain has been postulated as a frequent but not sole mechanism by which they may induce type 2 diabetes,¹⁹ and many antipsychotics have been associated with excessive weight gain in clinical trials and clinical experience.^{46,47} Potential mechanisms of glucose dysregulation associated with antipsychotics have also been discussed in the literature.^{48,49} Central regulation of blood glucose is controlled by the hypothalamus, and hypothalamic dopamine antagonism by

some antipsychotics may lead to dysregulated blood glucose control. Other receptors have also been postulated to be associated with antipsychotic-induced diabetes, including serotonin 5-HT_{1A} and 5-HT_{2c} and histamine-1.¹⁹

Retrospective studies based on large populations have also examined the association between antipsychotics and type 2 diabetes. Hedenmalm et al⁵⁰, using a WHO database, found treatment with clozapine, olanzapine, and risperidone, but not with haloperidol and chlorpromazine, to be significantly associated with glucose intolerance. Sernyak et al⁵¹ compared schizophrenia patients within the U.S. Veterans Administration system who were treated with the atypicals, such as clozapine, risperidone, olanzapine, and quetiapine, versus those treated with conventional antipsychotics and found all of the atypicals except risperidone to have higher risk of diabetes. A study by Koro et al⁵² using data from the United Kingdom compared schizophrenia patients treated with risperidone or olanzapine and found olanzapine, but not risperidone, to be associated with higher risk of diabetes. Caro et al,⁵³ using a Quebec database of patients treated with olanzapine or risperidone and with no prior diabetes, found olanzapine-treated patients to be associated with a higher risk of developing diabetes. Gianfrancesco et al,⁵⁴ using data for psychosis patients within two U.S. health plans, found olanzapine, clozapine, and conventional antipsychotics, but not risperidone, to be associated with a significantly higher risk of diabetes. The study controlled for pre-existing diabetes and the level of patient exposure to each of the antipsychotics.

The present study applied methods similar to Gianfrancesco et al⁵⁴ to more recent data, but used more restrictive criteria to identify type 2 diabetes. Actual treatment for the disease was required as evidenced by prescription claims for antidiabetes medications or insulin. The appearance of a type 2 diabetes diagnosis (ie, ICD-CM-9 code) on a medical claim may simply mean that the patient was examined for this condition and does not necessarily mean that the patient tested positively. The examination itself may have been prompted by the patient's history, including excessive weight gain caused by a prior medication. It may also have been prompted by a perceived risk of diabetes associated with the newly prescribed antipsychotic.

MATERIALS AND METHODS

Design

This was a retrospective analysis of a Blue Cross/Blue Shield claims database with nearly 2 million members who had both medical and drug coverage. The available data extended from April 1997 through October 2000. Antipsychotic effects on type 2 diabetes were estimated by comparing patients with psychosis who received antipsychotic treatment to patients with psychosis who were not treated with antipsychotics (controls). This control group was used

because psychoses may be linked to diabetes independently of the use of antipsychotics.⁵⁵⁻⁵⁸

Patients were identified as having a psychotic disorder (ICD-CM-9 290.xx-299.xx) and who were either not using any antipsychotics or on antipsychotic therapy for 60 consecutive days or more. Continuous use of antipsychotics and at least 1 medical claim for psychosis were deemed sufficient to establish that a patient had psychosis. For individuals not treated with antipsychotics during the study period, at least 4 medical claims for psychosis were required to establish that they were psychotic. Patients with psychosis on antipsychotic therapy for less than 60 days were excluded. Because of the possibility of noncompliance, one 30-day prescription (the typical size) was judged insufficient to indicate that the antipsychotic was actually used.

Four categories of antipsychotic therapy were defined: risperidone, olanzapine, quetiapine, and conventional antipsychotics (perphenazine, fluphenazine, trifluoperazine, thiothixene, haloperidol, molindone, loxapine, prochlorperazine, acetophenazine, chlorpromazine, promazine, triflupromazine, thioridazine, mesoridazine, chlorprothixene). Patients treated with clozapine were ultimately excluded from the treated group because the number was too small. Ziprasidone, which was approved in early 2001, was also not included.

Treatment episodes were used to identify periods of antipsychotic use. Treatment episodes were defined as the time from the date of the first prescription for an antipsychotic to the final date of treatment calculated from the date of the last prescription plus its days' supply. Identification of a prescription as the first prescription in a treatment episode required that it not be preceded by another prescription for that antipsychotic for at least 90 days. Patients could have more than 1 treatment episode. In addition, treatment overlaps were possible due to temporary concurrent use of a prior antipsychotic when transitioning to a new antipsychotic therapy.⁵⁹

Diabetes observation periods for treated patients were constructed to lag antipsychotic treatment episodes by 30 days to account for individuals diagnosed and treated for type 2 diabetes after discontinuation of therapy. A 30-day lag period is also consistent with the likelihood that any diabetogenic effects of antipsychotics would take some time to emerge after initiating therapy. Nearly all of the case literature reported diabetic effects occurring in excess of 30 days beyond the start of an antipsychotic therapy.

The main goal of the research design was to avoid arbitrary assignment of diabetes to the antipsychotics being compared. The use of antipsychotic treatment episodes rather than index dates to assign diabetes cases insured that the onset of diabetes was linked to the actual time that an antipsychotic was used. If treatment episodes with different antipsychotics overlapped and diabetes occurred within the overlap (ie, beyond the 30-day lag), the diabetes case was

assigned to both antipsychotics. While multiple and potentially overlapping antipsychotic treatment episodes for the same patient raised the possibility of interdependence among observations, this was judged to be a lesser problem than that of arbitrary assignment of diabetes. Dropping the 1st or 2nd antipsychotic treatment episode to avoid interdependence can result in arbitrary assignment and create other bias if being 1st or 2nd is not random (eg, quetiapine was far more likely than risperidone and olanzapine to have been a 2nd-line therapy).

For untreated patients, observation periods for type 2 diabetes were constructed using 18 index dates separated by 2-month intervals and starting on December 1, 1997. Untreated individuals were randomly assigned with these starting dates. This procedure was necessary to create sufficient variation in length of observation period for the untreated group to avoid confounding period length with the presence or the absence of antipsychotic treatment. Observation periods lasted from the selected index date to the end of the study period (October 31, 2000); only untreated individuals enrolled for the entire study period were included.

Type 2 diabetes was assumed only if a patient received treatment for this condition. Those treated for type 2 diabetes were identified with prescription claims containing National Drug Codes for antidiabetic medications (1st-generation and 2nd-generation sulfonylureas, biguanides, glucosidase inhibitors, meglitinides, and thiazolidinediones) and National Drug Codes for insulin if individuals also had medical claims with ICD-CM-9 codes for this condition. Insulin is used primarily for type 1 diabetes and acute onset diabetic acidosis secondary to some antipsychotics, whereas antidiabetic medications are used exclusively for type 2 diabetes. The ICD-CM-9 codes for type 2 diabetes are 250.x0 and 250.x2.

An interval of 8 months before each diabetes observation period was used to screen for subjects with prior evidence of type 2 diabetes. Subjects with medical or prescription claims for type 2 diabetes during this period were excluded. The 8-month interval was selected because a shorter interval would have been less sensitive (greater likelihood of including patients with pre-existing type 2 diabetes) and a longer interval would have substantially reduced the sample size.

Analysis

Logistic regression was used to estimate the effects on odds of acquiring type 2 diabetes treatment for patients within each of the 4 antipsychotic categories versus controls. Each of the categories was represented by a continuous variable, which measured months of antipsychotic treatment, with zero values for all 4 categories indicating no antipsychotic treatment. Because antipsychotic treatment duration varied among treated psychosis patients, categorical (1, 0) variables were judged inappropriate for measuring

patient exposure to each antipsychotic. Several other variables were specified in the model to control for other patient characteristics potentially affecting risk of type 2 diabetes or the likelihood of treatment. These included: patient age, sex, length of observation period (which corresponded to length of antipsychotic treatment episode for treated psychosis patients), use of other psychotropic drugs measured in dollars per month (eg, lithium and SSRIs have been associated with glucose intolerance),^{60,61} use of β -blockers measured as a categorical variable (these antihypertensives have been associated with higher risk of type 2 diabetes),⁶² type of healthcare coverage, type of psychosis, and prior treatment for weight gain measured as a categorical variable. A diabetic event, encompassed by 2 overlapping antipsychotic therapies, was assigned to both. However, an antipsychotic treatment episode in which another antipsychotic is also used is not the same as one involving monotherapy. To account for this difference and its potential effects, a variable was added that measured the ratio of other antipsychotic days' supply to treatment antipsychotic days' supply.

Logistic regression generated an odds ratio for each of the variables specified in the model. The odds ratio for each of the 4 variables measuring antipsychotic exposure measured the degree (%) by which some base probability of type 2 diabetes was greater due to 1 month of treatment with that antipsychotic. The base probability depended on other characteristics of the population to which the antipsychotic was applied. Odds ratios for months of antipsychotic treatment >1 were obtained by increasing the 1-month odds ratio to a power equal to the desired months of treatment. The same interpretation applies to other continuous variables specified in the logistic model. This is standard procedure for continuous variables in logistic regression.⁶³

RESULTS

A total of 6582 patients with psychosis received at least 60 consecutive days of antipsychotic therapy during the study period, whereas 10,296 received no antipsychotic treatment. For the treated patients, there were 2860 treatment episodes identified for risperidone, 2703 for olanzapine, 922 for quetiapine, and 2756 for conventional antipsychotics. About 30% of the treated patients had more than 1 treatment episode with either the same or a different antipsychotic. Also, treatment episodes with different antipsychotics overlapped in 27% of the observations.

Patients treated with antipsychotics were somewhat younger than untreated patients and had a larger proportion of males (Table 1). Observation periods among untreated patients were almost twice as long as those of treated patients, increasing the likelihood of observing type 2 diabetes in that group. Although treated and untreated patients differed considerably with respect to type of psychosis, major depression was the most common diagnosis in

both groups (38% and 76%, respectively) and schizophrenia occurred at low rates (14% and 1%, respectively). Untreated patients had a lower per-capita use of other psychotropic medications and of β -blockers, and a lower percentage indicating a prior problem with weight gain.

Differences in patient characteristics also existed among the 4 antipsychotic categories. Observation period and duration of treatment were longest for conventional antipsychotics and shortest for quetiapine, which may be explained by its relative newness to the market at the time of the data collection [April 1997-October 2000]. Patients treated with quetiapine had the highest per-capita use of other psychotropic medications and the highest percentage of patients indicating a prior problem with weight gain; both of these conditions may be partly explained by the fact that patients treated with quetiapine were 2 to 3 times more likely

to have been switched from another antipsychotic. Patients treated with conventionals had the highest percent using β -blockers while those treated with risperidone had the lowest, consistent with the average ages of these 2 groups. The breakdown of patients by type of psychosis was roughly similar among the antipsychotic categories.

Table 2 shows frequencies of treated type 2 diabetes among the antipsychotic categories. Across all groups, type 2 diabetes treatment tended to be relatively more frequent among patients with longer observation periods. Overall, patients treated with antipsychotics had higher rates of type 2 diabetes treatment than patients untreated with antipsychotics. While this suggests that antipsychotics as a class have diabetic effects, the differences were not large. Among the 4 antipsychotic categories, risperidone and quetiapine had the lowest percentages of patients treated for type 2

TABLE 1. Profile of Psychosis Patients

	Without Antipsychotic Treatment	With Antipsychotic Treatment	Risperidone	Olanzapine	Quetiapine	Conventionals
Age						
Mean (SD)	39.5 (14.3)	37.5 (15.1)	33.4 (16.3)	37.1 (14.5)	35.6 (14.5)	43 (12.6)
Median	42	40	36	39	38	44
Sex						
Female	0.64	0.59	0.55	0.57	0.65	0.64
Male	0.36	0.41	0.45	0.43	0.35	0.36
Type of health care coverage						
Managed care	0.66	0.62	0.65	0.62	0.59	0.61
Indemnity	0.34	0.38	0.35	0.38	0.41	0.39
Observation period						
Mean (SD) length in months	18.2 (10.6)	9.7 (9.7)	9.1 (8.9)	8.7 (8.7)	7.1 (6.2)	12.1 (11.8)
Median length in months	17.3	5.9	5.7	5.5	5	7.3
Antipsychotic treatment duration						
Mean (SD) length in months	NA	9.9 (9.8)	9.4 (9.1)	9 (8.9)	7.5 (6.3)	12.3 (12)
Median length in months	NA	6.1	6	5.6	5.3	7.4
Diagnosis						
Schizophrenia	0.01	0.14	0.1	0.11	0.1	0.18
Bipolar and manic	0.16	0.35	0.36	0.37	0.37	0.32
Major depressive	0.76	0.38	0.39	0.39	0.43	0.36
Other psychoses	0.07	0.13	0.15	0.13	0.1	0.14
Use of other psychotropic drugs						
Mean (SD) dollars per month	57 (77)	96 (120)	98 (120)	99 (108)	112 (151)	86 (118)
Median dollars per month	30	67	68	71	81	54
β -Blocker use (percent of patients)	8.03	10.04	7.34	11.17	10.41	12.01
Concurrent use of other antipsychotics						
Percent of patients	NA	27	22	27	33	31
Prior weight gain problem						
Percent of patients	1.4	2.3	2.2	2.3	4	2

NA, not applicable.

TABLE 2. Frequency of Type 2 Diabetes Treatment Among Antipsychotic Categories

	Total	Treated for Diabetes	Percent
Without antipsychotic treatment			
<4 months observation	1090	0	0.0
4–8 months observation	1083	0	0.0
8–12 months observation	1077	3	0.3
>12 months observation	6439	84	1.3
With antipsychotic treatment			
<4 months observation	1995	3	0.2
4–8 months observation	1479	3	0.2
8–12 months observation	721	7	1.0
>12 months observation	1055	17	1.6
Risperidone			
<4 months observation	619	2	0.3
4–8 months observation	483	1	0.2
8–12 months observation	244	0	0.0
>12 months observation	329	2	0.6
Olanzapine			
<4 months observation	687	1	0.1
4–8 months observation	467	1	0.2
8–12 months observation	234	3	1.3
>12 months observation	331	10	3.0
Quetiapine			
<4 months observation	266	0	0.0
4–8 months observation	219	1	0.5
8–12 months observation	83	1	1.2
>12 months observation	114	1	0.9
Conventional			
<4 months observation	423	0	0.0
4–8 months observation	310	0	0.0
8–12 months observation	160	3	1.9
>12 months observation	281	4	1.4

diabetes, while olanzapine and conventional antipsychotics had the highest.

Table 3 presents odds ratios for type 2 diabetes treatment for the 4 antipsychotic categories versus no antipsychotic treatment, as estimated using logistic regression. Antipsychotic exposure was captured by variables measuring duration of treatment. Additional variables were specified to control for other differences among the groups that could also affect the odds of type 2 diabetes treatment. The number of observations was 14,914, with 117 treated for type 2 diabetes. Olanzapine alone had odds of type 2 diabetes treatment that were significantly greater ($P = 0.0247$) than those of patients untreated with antipsychotics (OR = 1.03 for 1 month of olanzapine treatment). This suggests that 1 month of treatment with olanzapine increased the likelihood of type 2 diabetes treatment by 3% above that of untreated

psychosis patients. Risperidone and quetiapine had estimated odds that were lower than for untreated patients (not significant), whereas conventional antipsychotics had odds that were virtually equivalent to untreated patients.

Among the control variables, age was highly significant ($P < 0.0001$), as would be expected for type 2 diabetes. Because age was a continuous variable expressed in years, its odds ratio indicates the percent increment in the odds of type 2 diabetes treatment as an individual aged by 1 year. Logically, the length of the observation period also affected the likelihood of observing type 2 diabetes ($P < 0.0001$). Use of β -blockers was associated with higher odds of diabetes treatment ($P = 0.0002$). Significantly lower odds were associated with bipolar disorder ($P = 0.01$) and major depression ($P = 0.0015$) in comparison to other psychoses, which included alcohol-related and drug-related disorders. While schizophrenia also had lower estimated odds, this was not statistically significant. Other factors, such as patient use of other psychotropic drugs and prior weight gain problems, were not statistically significant.

In Table 4, the odds ratios estimated for 1 month of antipsychotic treatment were converted to 12 months of treatment by increasing the 1-month odds ratios to a power of 12.⁶³ Ninety-five percent confidence intervals for these are also shown. The 12-month odds ratio of olanzapine was highest (1.426), implying a 42.6% greater likelihood of type 2 diabetes than among untreated patients.

DISCUSSION

A possible relationship between antipsychotics, particularly the atypical antipsychotics olanzapine and clozapine, and type 2 diabetes has been suggested in a number of case reports^{14–35} and at least 2 prospective trials.^{44,45} A recent study by Glick et al⁶⁴ comparing olanzapine and ziprasidone showed that after only 6 weeks of treatment with olanzapine, weight, fasting insulin, total cholesterol, and triglycerides rose significantly compared with ziprasidone. Evidence that antipsychotics have differential effects on weight gain also suggests that they may have differential effects in causing or exacerbating type 2 diabetes, with excess body weight as a major risk factor for this disease. According to 2 comprehensive studies,^{46,47} olanzapine and clozapine are more likely to cause excessive weight gain than other antipsychotics.

Because of the small numbers involved, case findings and prospective trials may be limited in their ability to demonstrate statistical associations between specific antipsychotics and type 2 diabetes, particularly over the diverse patient populations using these medications. To overcome this limitation and to provide an alternative source of evidence, this study and earlier studies^{50–54} used health plan data to investigate the medical histories of thousands of patients with psychosis. The current study, which used

TABLE 3. Logistic Regression Results: Treated Type 2 Diabetes Among Psychosis Patients

Variable	Model 1 (Treatment Duration)	
	Odds Ratio	Pr > χ^2
Antipsychotic treatment duration (yes = months; no = 0)		
Risperidone	0.966	0.2848
Olanzapine	1.030	0.0247
Quetiapine	0.998	0.9593
Conventionals	1.004	0.8099
Age	1.055	0.0001
Sex (male = 1)	1.200	0.2947
Observation period (months)	1.067	0.0001
Other psychotropic drugs (dollars per month)	0.999	0.4068
β -Blocker use (yes = 1; no = 0)	2.107	0.0002
Concurrent antipsychotics (ratio of days supply)	0.971	0.9589
Coverage (managed care = 1; indemnity = 0)	0.819	0.2461
Schizophrenia (yes = 1; no = 0)	0.445	0.1076
Bipolar/manic (yes = 1; no = 0)	0.444	0.0100
Major depressive (yes = 1; no = 0)	0.449	0.0015
Prior weight gain problem (yes = 1; no = 0)	0.960	0.9364

Number treated for type 2 diabetes (1) = 117; number not reporting type 2 diabetes (0) = 14,797; total observations = 14,914. Patients with diabetes medical claims during observation but without prescription claims for antidiabetics or insulin are excluded. This group cannot be definitely classified as having or not having type 2 diabetes. Patients untreated with antipsychotics are represented by zeros for each of the four specified antipsychotic categories.

methods similar to Gianfrancesco et al,⁵⁴ is more restrictive than earlier studies in that treatment of type 2 diabetes with oral hypoglycemic medications or insulin was required as evidence of this disease.

The frequency of type 2 diabetes treatment was compared among patients with psychosis who were untreated with antipsychotics and those treated with risperidone, olanzapine, quetiapine, and conventional antipsychotics. Because of important differences among the groups, logistic regression was used to more accurately estimate antipsychotic effects on the odds of type 2 diabetes treatment. Antipsychotic exposure was measured in treatment duration (months). Olanzapine alone had odds of type 2 diabetes treatment that were significantly greater than those of patients with psychosis who were untreated with antipsychotics ($P = 0.0247$). The odds ratio of olanzapine based on 12 months of treatment was 1.426, suggesting a 42.6% greater likelihood of type 2 diabetes than in untreated patients with psychosis.

While not reported, this study did address another measure of antipsychotic exposure, dosage level. As with Gianfrancesco et al,⁵⁴ antipsychotic dose (measured in risperidone-equivalent milligrams) was specified as an alternative measure, but did not achieve statistical significance. Antipsychotic dose is less efficient than duration of treatment. It is dependent on patient body weight, so that different doses may imply the same degree of antipsychotic exposure for

patients with different body weights. While patient weight is not reported in claims data, the relationship between antipsychotic dose and body weight was reflected in the fact that male daily doses averaged 28% higher than female doses. Also, the average dose (the only practical way of capturing this effect) does not reflect the varying dosage levels and their timing during the course of treatment. Consequently, the average dose may be weakly related to diabetes.

The sampling units in this study were antipsychotic treatment episodes rather than patients. Because some patients had more than 1 treatment episode, interdependence of sampling units was considered as a potential statistical problem. Multiple antipsychotic treatment episodes for the same patient may violate the independence of sampling units if the type 2 diabetes is linked to inherent patient characteristics (eg, genes). However, the mechanism(s) through which

TABLE 4. Odds Ratios Converted to 12-Month Treatment Duration

	Odds Ratio	Confidence Interval
Risperidone	0.660	0.311–1.408
Olanzapine	1.426	1.046–1.955
Quetiapine	0.976	0.422–2.271
Conventionals	1.049	0.688–1.613

antipsychotics may cause type 2 diabetes is still unknown, and there is little reason to assume that inherent patient characteristics play a key role. Also, interdependence of sampling units can be caused by other factors (eg, 2 different patients being treated by the same physician). The boundaries set by antipsychotic treatment episodes are crucial for accurate assignment of diabetes cases. When patients use multiple antipsychotics for varying durations, the use of the patient as the sampling unit may result in arbitrary associations. Assignment of diabetes to an antipsychotic should depend not only on whether the patient was treated with that antipsychotic, but on when the diabetes occurred in relation to the treatment.

The approach taken in this study was conservative in that diabetes cases were counted as such only if there was treatment with oral hypoglycemic medications or insulin. This excluded a considerable number of cases in which type 2 diabetes appeared as a diagnosis on medical claims but for which there was no subsequent treatment. While these may have reflected mild cases of glucose intolerance, they may have also reflected patients who tested negative for this condition. A diagnosis of type 2 diabetes may appear on a medical claim if a patient is examined for this condition, but does not necessarily mean that the patient tested positively. Because examination for type 2 diabetes may not be random, but may depend on perceptions of diabetes risk associated with the newly prescribed antipsychotic, dependence on medical claims may create bias.

Under this more conservative approach, patients treated with olanzapine alone were shown to face higher odds of type 2 diabetes than patients with psychosis untreated with antipsychotics. In contrast, risperidone and quetiapine had estimated odds that were less than those of untreated patients, although this difference was not statistically significant. With regard to the risk of type 2 diabetes, these atypical antipsychotics appear to be safer than olanzapine.

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Assessing the Risk of Antipsychotic-Induced Type II Diabetes Among Schizophrenics: A Matched Case-Control Study

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INTRODUCTION

Atypical antipsychotic medications are at least as effective as older medications in the treatment of schizophrenia, and perhaps even more effective in treating negative symptoms. At the same time, they are less likely to cause extra-pyramidal symptoms and tardive dyskinesia, serious side effects common to the typical antipsychotics.

Evidence in the form of case reports and retrospective pharmacoepidemiological studies increasingly suggests a link between certain atypical antipsychotics and the development of type 2 diabetes mellitus.

The purpose of the present study was to quantify the risk of type 2 diabetes mellitus associated with exposure to selected atypical antipsychotic medications, compared to the risk for patients taking conventional antipsychotics.

DEFINING ANTIPSYCHOTIC EXPOSURE

Exposure was defined as receipt of continuous antipsychotic monotherapy for 12 weeks prior to the development of diabetes in the case (or the same 12 weeks in the control).

Atypical drugs included clozapine, olanzapine, quetiapine, and risperidone. Typical drugs included chlorpromazine, fluphenazine, loxapine, pimozide, promazine, trifluoperazine, haloperidol, perphenazine, prochlorperazine, and thioridazine.

The reference group for all comparisons was patients on typical antipsychotic therapy.

METHODS

This case-control study was based on data derived from the California Medicaid (i.e., Medi-Cal) system during 1997-2000. This database included 129,341 patients with schizophrenia. To be a case, patients had to have schizophrenia (ICD-9 295) and diabetes (ICD-9 250, excluding juvenile types, subsequent to schizophrenia), be 18 years or older, and be on only one antipsychotic medication during the 12 weeks prior to their diabetes diagnosis.

Cases and controls had to be continuously eligible for Medicaid benefits during the 12 week period prior to diabetes onset in the case.

Conditional logistic regression assessed the risk of exposure to four atypical agents, controlling for ethnicity and exposure to other diabetes-inducing medications (alpha-blockers, beta-blockers and thiazide diuretics, corticosteroids, phenytoin, oral contraceptives containing norgestrel, and valproate). Analyses were repeated after stratifying by age and sex.

RESULTS

3,102 cases were matched to 8,271 non-diabetic controls (people with schizophrenia matched on gender and age ± 5 years).

Exposure to olanzapine (OR=1.30, 95% CI 1.18-1.43), clozapine (OR=1.43, 95% CI 1.19-1.69) or quetiapine (OR=1.45, 95% CI 1.10-1.90) significantly increased the risk of developing type 2 diabetes compared to conventional antipsychotics.

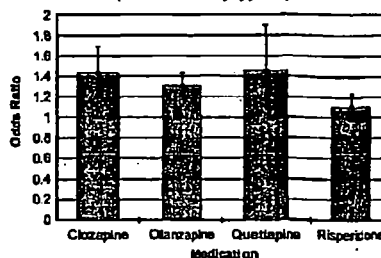
The odds ratio for exposure to risperidone was not reliably greater than 1 (OR=1.10, 95% CI 0.97-1.23).

The risk of exposure to any atypical medication decreased with age but was unaffected by gender.

African-American ethnicity was a significant risk factor for development of type 2 diabetes (OR=1.65, 95% CI 1.47-1.85) as was unknown ethnicity (OR=1.44, 95% CI 1.30-1.58). Exposure to alpha-blockers, beta-blockers and thiazide diuretics (OR=1.52, 95% CI 1.33-1.75), corticosteroids (OR=1.90, 95% CI 1.65-2.18), or phenytoin (OR=1.24, 95% CI 1.02-1.52) also increased risk.

Figure 1

Adjusted Risk of Diabetes for Selected Atypical Antipsychotics (reference is any typical)



*Adjusted for ethnicity, alpha-blockers, beta-blockers and thiazide diuretics, corticosteroids, phenytoin.

Table 1 Characteristics of Cases and Controls

Characteristic	Cases (n=3102)		Controls (n=8271)		Test Statistic	P
	Mean	SD	Mean	SD		
Age						
Mean (SD)	44.34 ^a	13.31	45.32	13.49		
Min	18		18			
Max	96		94			
	N	%	N	%		
Gender						
Male	1473 ^a	47.49%	3909	47.26%		
Female	1629	52.51%	4362	52.74%		
Ethnicity						
White	1501	48.39%	4783	57.83%	81.32 ^b	<.0001
Hispanic	38	1.23%	141	1.70%	3.35	0.07
African-American	640	20.63%	1257	15.20%	47.93	<.0001
Others	21	0.68%	70	0.85%	0.82	0.37
Unknown	902	29.08%	2020	24.42%	25.61	<.0001
Diabetogenic Medications						
Alpha-blockers, beta-blockers, and thiazide diuretics	399	12.86%	713	8.62%	46.02 ^b	<.0001
Corticosteroids	387	12.80%	600	7.25%	88.89	<.0001
Phenytoin	165	5.32%	387	4.68%	2.00	0.16
Oral contraceptives containing norgestrel	11	0.35%	19	0.23%	1.34	0.25
Valproate	0	0%	2	0.02%	0.75	0.39
Exposed to antipsychotics						
Typical	1224	39.46%	3655	44.19%	20.82 ^b	<.0001
Clenzapine	918	29.59%	2151	26.01%	14.73	<.0001
Risperidone	617	19.89%	1708	20.63%	0.75	0.39
Clozapine	249	8.03%	558	6.75%	5.61	0.20
Quetiapine	94	3.03%	201	2.43%	3.22	0.07

Table 2 Parameter Estimates for Conditional Logistic Regression Model Predicting Development of New-Onset Type 2 Diabetes in Patients with Schizophrenia Exposed to One of Four Unifactor Antipsychotics (All Aged)

Variable	Parameter Estimate	S.E.	Chi-Square	P	Odds Ratio	95% Lower	95% Upper
Atypical Antipsychotics							
Clozapine (n=607)	0.35	0.09	16.39	<.0001	1.43	1.19	1.69
Clenzapine (n=3069)	0.26	0.05	23.37	<.0001	1.30	1.18	1.43
Quetiapine (n=295)	0.37	0.14	7.43	0.006	1.45	1.10	1.90
Risperidone (n=2323)	0.09	0.06	2.49	0.114	1.10	0.97	1.23
Ethnicity							
Hispanic	-0.18	0.19	0.90	0.342	0.83	0.58	1.21
African-American	0.50	0.06	68.22	<.0001	1.65	1.47	1.85
Other Ethnicity	-0.19	0.26	0.51	0.474	0.83	0.50	1.38
Unknown Ethnicity	0.36	0.05	49.28	<.0001	1.44	1.30	1.58
Diabetogenic Medications							
Alpha-blockers, beta-blockers, and thiazide diuretics	0.42	0.07	35.55	<.0001	1.52	1.33	1.75
Corticosteroids	0.84	0.07	78.41	<.0001	1.90	1.65	2.18
Phenytoin	0.22	0.10	4.83	0.032	1.24	1.02	1.52

Note. Reference group for clozapine, quetiapine, clenzapine, and risperidone was all other typical antipsychotics.

DISCUSSION/CONCLUSION

Among people with schizophrenia in the California Medicaid system, exposure to clozapine, clenzapine, and quetiapine, but not risperidone, was associated with a significantly increased risk of developing type 2 diabetes when compared to typical antipsychotic medications. These effects were not due to age, gender, ethnicity, or concomitant exposure to other diabetogenic medications. The risk was fairly constant between the ages of 18 and 59 but was not present among those aged 60 and over. African-American ethnicity as well as exposure to concomitant diabetogenic medications were significant,

independent risk factors. More research needs to be done to quantify the personal and societal risk/benefit ratio associated with use of these medications. In the meantime, clinicians should carefully weigh the risk of type 2 diabetes when deciding whether or not to prescribe clozapine, clenzapine, or quetiapine, especially among patients who may be predisposed to develop diabetes (e.g., due to ethnicity, positive family history, age, or body mass). Patients who do receive these medications should be monitored in accordance with recently published guidelines.

The Effects of Olanzapine and Risperidone Use on New-Onset Diabetes and Weight Gain Among Schizophrenic Patients

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INTRODUCTION	METHODS	RESULTS																																																																														
- The newer class of antipsychotic agents exhibit superior safety in terms of extrapyramidal side effects compared to conventional antipsychotics. - Recent evidence from the literature has suggested that use of these agents may lead to weight gain and other metabolic events such as diabetes. - We sought to determine the independent contribution of these agents to the incidence of weight gain and diabetes, adjusted for other risk factors using data from an inner-city hospital's inpatient unit, emergency department, primary care group practice, and city-wide network of mental health providers.	- First year of treatment (n=2,566). Further, we restricted the analyses to those patients aged 18 or more (n=8,578) and those who had been on drug for at least one year (n=3,334). Patients satisfying all of these criteria yielded an effective sample size of 744 of which 112 were olanzapine, 150 were risperidone, and 482 were typical antipsychotic patients. - We used a nested case-control design, matching up to 4 controls to every case on sex, age, and race. Conditional Logistic Regression was used to derive adjusted odds ratios controlling for gender, age, and comorbid conditions that may affect the risk of diabetes. - Exposure to antipsychotic was defined as receipt of at least one prescription for an antipsychotic for a period no less than one year. - The referents for each drug (olanzapine, risperidone), were patients prescribed conventional antipsychotics. - Outcomes: Diagnosis of new-onset diabetes and weight gain of 10 or more lbs. - Comorbid conditions and health care utilization parameters: depression, anxiety, bipolar disorder, personality disorder, dementia, alcohol dependence, drug abuse, liver disease, hypercholesterolemia, hypertension, coronary artery disease, congestive heart failure, restrictive airway disease, stroke, obesity, psychiatric disorders, use of benzodiazepine, use of antiepileptic agents, and smoking, weight, number of primary care visits, mental health visits, and ER visits.	- A total of 36 cases of new-onset diabetes were identified. These were matched to 316 controls. For weight gain >10 lbs, a total of 428 cases were identified and matched to 657 controls. - A significant number of new-onset diabetic cases were seen in olanzapine patients when compared to typical antipsychotic patients (14.3% vs. 7.3%, p=0.015). In contrast, risperidone patients did not differ from typical antipsychotic patients in terms of new-onset diabetic cases (6.7% vs. 7.3%, p=0.805). Weight gain of 10 lbs or more was experienced at a higher rate in both olanzapine (54.5%) and risperidone (50%) patients when compared to typical antipsychotic patients (30.3%, p<0.001). Table 1: Descriptive statistics of study sample by drug group <table> <tr> <th></th><th>Olanzapine n=112</th><th>Risperidone n=150</th><th>Typicals n=482</th></tr> <tr> <td>Diabetes Onset Rate (%)</td><td>14.3</td><td>6.7</td><td>7.3</td></tr> <tr> <td>Weight gain >10 lbs (%)</td><td>54.5</td><td>50.0</td><td>30.3</td></tr> <tr> <td>Females (%)</td><td>67</td><td>65</td><td>65</td></tr> <tr> <td>African-American (%)</td><td>45.5</td><td>48.3</td><td>50</td></tr> <tr> <td>Age (mean [sd])</td><td>44.8 (11.9)</td><td>47.2 (14.9)</td><td>49.9 (14.9)</td></tr> <tr> <td>Duration on agent (mean [sd])</td><td>2.2 (1.2)</td><td>2.3 (1.5)</td><td>5.6 (4.0)</td></tr> </table> Table 2: The odds of weight gain and onset diabetes in subjects exposed to olanzapine and risperidone for at least one year relative to those exposed to conventional antipsychotic medications <table> <tr> <th>Antipsychotic Exposure</th><th>Weight Gain Cases</th><th>Controls</th><th>Unadjusted OR (95% CI)</th><th>Adjusted* OR (95% CI)</th></tr> <tr> <td>Olanzapine</td><td>39 (25.0)</td><td>41 (2.5)</td><td>2.3 (1.3-3.8)</td><td>2.1 (1.0-4.7)</td></tr> <tr> <td>Typicals (Ref)</td><td>111 (75.0)</td><td>263 (85.5)</td><td></td><td></td></tr> <tr> <td>Risperidone</td><td>45 (29.9)</td><td>69 (27.3)</td><td>1.0 (1.1-2.7)</td><td>2.1 (1.1-4.1)</td></tr> <tr> <td>Typical (Ref)</td><td>113 (71.1)</td><td>287 (82.7)</td><td></td><td></td></tr> </table> <table> <tr> <th>Antipsychotic Exposure</th><th>Diabetes Cases</th><th>Controls</th><th>Unadjusted OR (95% CI)</th><th>Adjusted* OR (95% CI)</th></tr> <tr> <td>Olanzapine</td><td>16 (14.3)</td><td>21 (3.8)</td><td>2.1 (1.0-4.6)</td><td>3.02 (1.0-9.0)</td></tr> <tr> <td>Typicals (Ref)</td><td>35 (65.7)</td><td>124 (81.2)</td><td></td><td></td></tr> <tr> <td>Risperidone</td><td>10 (22.2)</td><td>27 (17.4)</td><td>1.3 (0.5-3.2)</td><td>2.22 (0.5-10.0)</td></tr> <tr> <td>Typical (Ref)</td><td>35 (77.8)</td><td>128 (82.6)</td><td></td><td></td></tr> </table> * Adjusted for age, gender, inpatient, depression, anxiety, bipolar disorder, personality disorder, dementia, alcohol dependence, drug abuse, liver disease, hypercholesterolemia, hypertension, coronary artery disease, congestive heart failure, restrictive airway disease, stroke, obesity, psychiatric disorders, use of benzodiazepine, use of antiepileptic agents, smoking, weight, number of primary care visits, mental health visits, and ER visits. Figure 1: Adjusted* odds of diabetes and weight gain >10 lbs in patients exposed to olanzapine and risperidone relative to patients receiving typical antipsychotic medication CONCLUSION Controlling for a wide variety of comorbid chronic medical conditions and intensity of outpatient care, olanzapine use is independently associated both with clinically significant weight gain and with onset diabetes in schizophrenia patients. Risperidone use is also associated with weight gain, but not with onset diabetes.		Olanzapine n=112	Risperidone n=150	Typicals n=482	Diabetes Onset Rate (%)	14.3	6.7	7.3	Weight gain >10 lbs (%)	54.5	50.0	30.3	Females (%)	67	65	65	African-American (%)	45.5	48.3	50	Age (mean [sd])	44.8 (11.9)	47.2 (14.9)	49.9 (14.9)	Duration on agent (mean [sd])	2.2 (1.2)	2.3 (1.5)	5.6 (4.0)	Antipsychotic Exposure	Weight Gain Cases	Controls	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Olanzapine	39 (25.0)	41 (2.5)	2.3 (1.3-3.8)	2.1 (1.0-4.7)	Typicals (Ref)	111 (75.0)	263 (85.5)			Risperidone	45 (29.9)	69 (27.3)	1.0 (1.1-2.7)	2.1 (1.1-4.1)	Typical (Ref)	113 (71.1)	287 (82.7)			Antipsychotic Exposure	Diabetes Cases	Controls	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Olanzapine	16 (14.3)	21 (3.8)	2.1 (1.0-4.6)	3.02 (1.0-9.0)	Typicals (Ref)	35 (65.7)	124 (81.2)			Risperidone	10 (22.2)	27 (17.4)	1.3 (0.5-3.2)	2.22 (0.5-10.0)	Typical (Ref)	35 (77.8)	128 (82.6)		
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A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States

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Abstract

Treatment-emergent diabetes mellitus (DM) has been described for conventional and atypical antipsychotics. In our study, antipsychotic prescription claims from AdvancePCS's database were used to identify patients starting antipsychotic monotherapy. The relative risk of developing DM was determined using prescription claims for antidiabetic agents in the following cohorts: AdvancePCS general patient population, combined conventional antipsychotics, and combined atypical antipsychotics. Cox proportional hazards regression was used to adjust for differences in age, gender, and duration of antipsychotic exposure between cohorts in the estimation of risk of developing diabetes. Hazard ratios for developing DM in the combined conventional, combined atypical, and individual conventional and atypical antipsychotic treatment cohorts were greater than the AdvancePCS general patient population cohort. An increased risk of developing diabetes compared with the AdvancePCS general patient population was observed during treatment with conventional or atypical antipsychotics. © 2003 Elsevier Science Inc. All rights reserved.

Keywords: Antipsychotics; Diabetes; Epidemiologic study

1. Introduction

Studies over several decades have suggested that diabetes mellitus (DM), impaired glucose tolerance, and insulin resistance are more common in patients with psychiatric disorders, including major mood disorders and schizophrenia, than in the general population [1–6]. Literature reports have associated treatment-emergent glucose intolerance with conventional antipsychotics [7–15] and atypical antipsychotics [16–23] in humans. This possibility has been supported also by animal studies, where chlorpromazine was shown to cause hyperglycemia in normal animals [24,25]. However, a role of neuroleptics in the development of DM has not been supported by all investigations [26,27] because higher than expected rates of insulin resistance and impaired glucose tolerance had been reported in patients with schizophrenia before the introduction of neuroleptics [28–32].

A number of recent studies have attempted to clarify whether the rate of diabetes is elevated in patients treated

with antipsychotics. However, reports in the literature have consisted primarily of small case series and prevalence studies in relatively small population samples [33–36]. These studies have been marked by significant methodologic limitations, and the results have been largely inconclusive. Questions regarding the frequency of DM in patients treated with antipsychotics are most effectively answered in epidemiologic studies. Due to their large sample size and less rigorous exclusion criteria compared with prospective clinical trials, epidemiologic studies can accurately assess the frequency of relatively rare events and provide results that are more representative of the general population.

Recently, there has been increasing interest in the pharmacoeconomics of antipsychotics and DM. Mahmoud et al [37] examined prescription claims data from two large mixed indemnity and managed health care plans in the United States and determined the hazard ratios (HR) for developing DM during exposure to antipsychotic medications. They identified treatment-emergent diabetes by prescription claims and ICD-CM-9 diagnostic criteria over a 2-year period, with 4- and 8-month prescreening periods before the initiation of antipsychotic therapy. They reported an increased risk of developing DM in patients exposed to high- and low-potency

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conventional antipsychotics, clozapine, and olanzapine. Another recent epidemiologic study by Caro et al retrospectively examined treatment-emergent diabetes during exposure to risperidone or olanzapine from prescription claims and physician diagnoses from the Régie de l'Assurance Maladie du Québec (RAMQ) [38]. The results of this study showed a greater incidence of DM for the olanzapine cohort (1.7%) as compared with the risperidone (1.5%) cohort. On the basis of a crude relative risk of 1.08 (95% confidence interval [CI] 0.89–1.31) and IIR of 1.2 (95% CI 1.0–1.43), the authors concluded that the risk of developing diabetes was higher for patients treated with olanzapine than for those who had been treated with risperidone. The Mahmoud [37] and RAMQ [38] studies included patients in their cohorts who were taking more than one antipsychotic medication concurrently. To our knowledge, no large-scale, peer-reviewed epidemiologic study evaluating the potential association of diabetes with antipsychotic treatment has been published.

In the present retrospective cohort study, the AdvancePCS (Scottsdale, AZ) prescription claim database was used to identify large cohorts of patients treated with a single antipsychotic during a defined period of observation. The purpose of this study was to estimate the incidence and risk of developing DM among patients in the United States who received a single antipsychotic drug, irrespective of indication. Individual antipsychotic cohorts were compared with each other and with the AdvancePCS general patient population.

2. Methods

This is a retrospective cohort study that determined the risk of developing DM during antipsychotic treatment using prescription claim data from AdvancePCS, Inc. AdvancePCS processes over 300 million prescription claims per year for the over 50 million members covered by the over 2000 nationwide employers and managed care plans represented in this database. Most of these claims are submitted by pharmacies handling the outpatient prescription needs for this membership; however, some prescriptions are filled in long-term care settings. There was no difference among study groups in terms of how patients received their prescriptions. In this study, we followed patients who maintained coverage with AdvancePCS. Once a patient discontinued their coverage, they were censored in the data analyses. Approximately 15% of the AdvancePCS members are over 65, and the >65 group represents over 24% of AdvancePCS's patient population. As of 1997, 42% of the patients starting an antipsychotic prescription were covered by Medicaid. The data cut-off point for this study was August 31, 2000.

2.1. Study cohorts

Only subjects who were prescribed a single antipsychotic were included in the antipsychotic cohorts for this study, regardless of indication for antipsychotic therapy. For the purpose of this study, monotherapy refers only to antipsychotics

and not to any other medications. The cohorts studied (1) a combined conventional antipsychotic cohort (comprised of subjects treated with all agents in this class), (2) a combined atypical antipsychotic cohort, (3) cohorts of individual antipsychotics (comprised of subjects treated with a particular agent [eg, the haloperidol cohort]), and (4) the AdvancePCS general patient population cohort. The general patient population cohort included all subjects who had made a prescription claim for any AdvancePCS-covered benefit during a 2-month enrollment window (1 January 2000 to 29 February 2000). They must not have made a claim for diabetes drug(s) for at least 12 months before enrollment. In addition, they must not have been dispensed an antipsychotic for at least 6 months before and 6 months after enrollment.

Antipsychotic agents included conventional antipsychotics (chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, trifluoperazine, and triflupromazine) and atypical antipsychotics (clozapine, olanzapine, quetiapine, and risperidone).

The enrollment window for subjects in the antipsychotic cohorts was 1 December 1998 through 29 February 2000. Subjects who started therapy during this period and continued to be treated with the same single antipsychotic during this period were included in the antipsychotic cohorts. Only subjects who were eligible for prescription claims through the AdvancePCS system for at least 12 months before enrollment were included in any of the cohorts. There were no significant differences among the number of patients using a diabetes medication when comparing a 12-month pre-enrollment period versus a 24-month pre-enrollment period. Thus, for this study, the 12-month pre-enrollment period was used. The exclusion criteria applicable to all cohorts were (1) a pre-existing history of DM as evidenced by a prescription claim for any anti-diabetic medication during the 12-month period before enrollment, (2) a prescription claim for any antipsychotics within the 6-month period before enrollment date, (3) the absence of information on sex or the year of birth, and (4) being <18 years of age. For all antipsychotic cohorts, patients who received more than one antipsychotic during the evaluation period were excluded. Although the enrollment windows differ between the general patient population and the antipsychotic groups, age at the point of entry into the study was used as the reference age for each study subject for the data analysis. In addition, adjustments for age differences were addressed by including an age variable in the regression analyses.

2.2. Identification of incident cases of DM

New onset of DM during antipsychotic exposure was identified by claim(s) for any medication(s) indicated for the treatment of diabetes, regardless of the route of administration. For subjects in any cohort, the earliest date during the enrollment window that any given subject received an antipsychotic agent (in the case of antipsychotic cohorts) or a nonantipsychotic agent (in the case of the AdvancePCS gen-

eral patient population) was considered the enrollment date for that subject. To identify the timing of onset of new cases of DM, the date of the first antidiabetic agent prescribed after the enrollment date was considered the start of antidiabetic therapy. Each patient in the antipsychotic cohort was tracked for a new onset of DM from the enrollment date (ie, the start of antipsychotic therapy for the antipsychotic cohorts) to the time that the antipsychotic was discontinued for more than 15 days or until 31 August 2000 (the data set cut-off point), whichever came first. Thus, length of therapy was used as the dependent variable in the proportional hazards model.

2.3. Comparison of the risk of developing diabetes among cohorts

To compare the risk of developing DM among cohorts, incidence density and HRs were determined. Because the incidence of DM for antipsychotic cohorts might not be linearly related to time with more cases being experienced early, annualization of incidence density could inflate the true incidence. Also, differences in incidence between cohorts could be partially accounted for by differences in mean age, gender, and the amount of exposure to antipsychotics among cohorts. To control for these variables in the estimation of the risk of DM, the Cox proportional hazard regression was used to determine the HR of DM for antipsychotic cohorts relative to the AdvancePCS general patient population. Using the PHREG procedure in SAS, several proportional hazards models were created using various combinations of the following covariates: age (three categories), gender (two categories), and amount of exposure (five categories). The reference categories for these covariates, represented by zero in the model, were the 18 to 44 group for age and female patients for gender. Amount of exposure was viewed as continuous days of treatment determined from the date of first antipsychotic prescription filled and the last successive prescription(s) that was not separated by more than 15 days. Individual doses were determined for each subject by sum-

ming the product(s) of strength and number of tablets for the successive prescriptions and dividing that sum by the number of continuous days of treatment. Because these doses varied widely within and among the antipsychotic cohorts, subjects within a cohort were grouped into dose quartiles. Subjects in the AdvancePCS general patient population were assigned a fifth dose "quartile" with a value of zero. Age was also standardized into the 18 to 44, 45 to 64, and 65 years of age and older categories because these ranges correspond with those cited for the incidence of diabetes in the United States general population [39]. In addition, given the wide doses observed in the antipsychotic cohorts, the HRs of DM were determined for each dose quartile relative to the AdvancePCS general patient population. The HRs of DM between selected antipsychotic cohorts were also determined. The alpha level for statistical significance was 0.05.

3. Results

The characteristics of the antipsychotic cohorts studied are summarized in Table 1. Haloperidol, thioridazine, risperidone, and olanzapine were the most commonly prescribed agents in their respective antipsychotic classes in the AdvancePCS database. Compared with the AdvancePCS general patient population, patients in the combined conventional and combined atypical antipsychotic cohorts were older. Among individual antipsychotic cohorts, the average age of the haloperidol cohort was notably older, with almost two thirds of patients over 64 years of age. There were more women than men in all cohorts, with the exception of the clozapine cohort. The average duration of antipsychotic treatment, ranging from 67 to 137 days, was longer for the atypical antipsychotic cohorts.

Separate regression analyses were performed to determine the association between the covariates and the development of DM (Table 2). A significant HR for age was found for most cohorts (excluding the thioridazine and clozapine cohorts), and a significant HR for gender was found for the AdvancePCS

Table 1
Characteristics of cohorts studied

	AdvancePCS general patient population	Conventional antipsychotic			Atypical antipsychotic				
		All agents	Haloperidol	Thioridazine	All agents	Clozapine	Olanzapine	Quetiapine	Risperidone
Number of subjects in cohort	5,816,473	19,782	8476	3133	38,969	277	13,863	4196	20,633
Age distribution, y									
18–44, %	36.5	20.8	11.9	25.7	30.2	36.8	36.6	35.8	24.6
45–64, %	39.3	26.0	15.3	26.7	23.6	25.3	28.7	28.1	19.2
65 and older, %	24.2	53.2	72.8	47.7	46.3	37.9	34.7	36.0	56.2
Mean age, y	52	64	72	61	60	55	55	55	64
Male, %	37	44	41	38	38	53	39	37	37
Average duration of antipsychotic treatment, d (SD)	NA	67 (74)	68 (70)	76 (81)	90 (83)	137 (125)	89 (85)	89 (79)	90 (82)
Mean dose of antipsychotic, mg (SD)	NA	NA	2.5 (5.2)	43.9 (54.6)	NA	183.1 (198.6)	5.1 (4.2)	79.9 (96.7)	1.2 (1.0)

Table 2
Hazard ratio of diabetes mellitus for covariates in the proportional hazard regression model stratified by antipsychotic cohorts

Variable	HR	95% CI	P value
Conventional antipsychotic cohort (n = 19,782)			
Age 45–64 y ^a	2.4	1.5–3.9	0.0003
Age ≥65 y ^a	3.4	2.2–5.3	≤0.0001
Gender (male) ^b	1.0	0.8–1.2	0.8158
Haloperidol cohort (n = 8476)			
Age 45–64 y	4.5	1.3–15.2	0.0162
Age ≥65 y	5.9	1.9–18.4	0.0025
Gender (male)	1.3	0.9–1.8	0.1218
Thioridazine cohort (n = 3133)			
Age 45–64 y	1.7	0.7–4.0	0.2061
Age ≥65 y	2.1	1.0–4.5	0.0610
Gender (male)	0.8	0.5–1.4	0.4729
Atypical antipsychotic cohort (n = 38,969)			
Age 45–64 y	2.8	2.0–4.0	≤0.0001
Age ≥65 y	6.1	4.5–8.2	≤0.0001
Gender (male)	1.3	1.1–1.6	0.0003
Clozapine cohort (n = 277)			
Age 45–64 y	3.0	0.3–33.6	0.3677
Age ≥65 y	3.4	0.4–31.3	0.2716
Gender (male)	0.7	0.2–3.2	0.6497
Olanzapine cohort (n = 13,863)			
Age 45–64 y	2.6	1.5–4.5	0.0006
Age ≥65 y	6.5	4.2–10.5	≤0.0001
Gender (male)	1.3	1.0–1.8	0.0585
Quetiapine cohort (n = 4196)			
Age 45–64 y	1.0	0.3–2.9	0.9670
Age ≥65 y	3.0	1.3–7.0	0.0095
Gender (male)	1.1	0.6–2.1	0.7649
Risperidone cohort (n = 20,633)			
Age 45–64 y	3.7	2.2–6.2	≤0.0001
Age ≥65 y	6.6	4.2–10.3	≤0.0001
Gender (male)	1.3	1.1–1.7	0.0010
AdvancePCS general patient population cohort (n = 5,816,473)			
Age 45–64 y	3.4	3.3–3.5	≤0.0001
Age ≥65 y	4.0	3.9–4.2	≤0.0001
Gender (males)	1.1	1.1–1.2	≤0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a For all cohorts, age 18–44 used as reference group.

^b For all cohorts, female gender used as reference group.

HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points.

general patient population, combined atypical antipsychotic, and risperidone cohorts. The gender effect was smaller than the age effect. Male gender was associated with a 30% increased risk of DM for the combined atypical antipsychotic cohort ($P = 0.0003$) and a 10% increased risk for the AdvancePCS general patient population cohort ($P \leq 0.0001$).

The incidence of diabetes per 1000 patient-years of antipsychotic treatment and the HR of diabetes of the various cohorts are shown in Table 3. Compared with the incidence density of the AdvancePCS general patient population, the incidences of diabetes during exposure to antipsychotics were several times higher. The Cox proportional hazards regression, adjusting for age, gender, and duration of antipsychotic exposure, showed that the risk of DM for the combined conventional and combined atypical antipsychotic cohorts was

significantly higher than in the AdvancePCS general patient population. The HRs for all individual atypical antipsychotic cohorts (clozapine, olanzapine, risperidone, and quetiapine) were significantly higher than those of the AdvancePCS general patient population.

The risk of DM for the combined conventional cohort was not significantly different from that of the combined atypical cohorts (HR 0.97, CI 0.84–1.11; $P = 0.626$) (Table 4). No significant increase in the risk of DM was observed for the olanzapine (HR 1.09, CI 0.86–1.37; $P = 0.479$) or the clozapine (HR 1.31, CI 0.60–2.86; $P = 0.496$) cohort when compared with the haloperidol cohort. The number of patients in the clozapine cohort was small ($n = 277$) and lacked power to detect a significant difference in the HR ratio within the range of the HRs observed in the other antipsychotic cohorts. The risk of DM for the quetiapine cohort was lower than the risk for the haloperidol cohort (HR 0.67, CI 0.46–0.97; $P = 0.033$). The risk of DM in the risperidone cohort, relative to the haloperidol cohort, was 1.23 (CI 1.01–1.50; $P = 0.040$). When comparing the two largest atypical antipsychotic cohorts (olanzapine and risperidone), the HR was 0.90 (CI 0.76–1.07; $P = 0.234$).

The age- and gender-adjusted HRs for the dose quartiles relative to the AdvancePCS general patient population are displayed in Table 5. A positive dose relationship for the risk of DM was observed for the thioridazine cohort because the 95% CI of the first and fourth dose quartile did not overlap. A significant dose-response relationship was not observed in the atypical antipsychotic cohorts, with the possible exception of quetiapine. Although the HR of the quetiapine cohort was not statistically significant in the first dose quartile relative to the AdvancePCS general patient population (HR 1.8, CI 0.9–3.4; $P = 0.096$), the HR was statistically significant in the fourth dose quartile (HR 3.1, CI 1.9–5.1; $P \leq 0.0001$).

4. Discussion

This large pharmacoepidemiologic study examined at least two important questions: (1) Did patients on atypical agents experience a different risk of treatment-emergent diabetes than those on conventional antipsychotics? and (2) Were there clinically significant differences in the risks of diabetes between antipsychotics? Consistently, the HRs of all antipsychotic treatment cohorts studied were significantly higher than those of the AdvancePCS general patient population. Although the risk of DM was comparable between the combined conventional cohort and the combined atypical cohort, some significant differences were observed when pairwise comparisons were made between individual antipsychotics. Of the atypical antipsychotic cohorts, only the risperidone cohort was associated with a significantly greater risk of diabetes than the haloperidol cohort. Direct comparison of the olanzapine and risperidone cohorts indicated no significant difference in the risk of diabetes during treatment with these agents.

Table 3

Incidence and hazard ratio of diabetes mellitus in patients during treatment with antipsychotics

Cohort	New cases (n)	Patients (n)	Patient-years	Incidence (per 1000 patient-years)		HR ^a		
				Rate	95% CI	Ratio	95% CI	P value
Conventional antipsychotics								
All combined	307	19,782	3645.57	84	75–94	3.5	3.1–3.9	≤0.0001
Haloperidol	133	8476	1568.39	85	70–100	3.1	2.6–3.7	≤0.0001
Thioridazine	62	3133	654.28	95	71–119	4.2	3.2–5.5	≤0.0001
Atypical antipsychotics								
All combined	641	38,969	9571.18	67	62–72	3.1	2.9–3.4	≤0.0001
Clozapine	7	277	103.95	67	16–118	3.3	1.4–8.0	0.0070
Olanzapine	194	13,863	3374.57	58	49–66	3.0	2.6–3.5	≤0.0001
Quetiapine	40	4196	1025.75	39	27–51	1.7	1.2–2.4	0.0020
Risperidone	400	20,633	5066.90	79	71–87	3.4	3.1–3.8	≤0.0001
General patient population	45,513	5,816,473	2,908,236.5	15.7	15.5–15.8			

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Cox proportional hazards regression analysis adjusted for age, gender, and duration of antipsychotic exposure.

HR and 95% CI values were rounded to the first decimal place except where such rounding obscured significance cut-off points.

For all antipsychotic cohorts, increasing age was a significant risk factor for DM. This finding is in keeping with well-established epidemiologic data indicating that the prevalence of diabetes increases with age [40], with an almost two-fold increase past age 49 [39]. Male gender was a significant predictor of increased risk of diabetes only for the combined atypical antipsychotic, the risperidone, and the AdvancePCS general patient population cohorts.

Factors related to diagnostic heterogeneity and illness severity may also underlie some of the findings in the dose quartile analysis. The antipsychotic cohorts included all subjects treated with antipsychotics, irrespective of diagnosis and illness severity. The fourth dose quartile in the antipsychotic cohorts contains patients who received the highest doses of antipsychotics that may define a subpopulation of more severely ill, diagnostically homogeneous patients. Compared with other psychiatric disorders commonly treated with an-

tipsychotics, schizophrenic patients often require higher doses of antipsychotics. Thus, the risk of DM associated with the fourth dose quartile may be particularly relevant to patients with schizophrenia.

Recently, there have been a number of reports on the prevalence [36] or the risk [37,38] of DM in subjects treated with antipsychotics. Some of these reports have been limited by relatively small sample sizes, the concurrent use of multiple antipsychotic drugs in the cohorts, or the absence of a reference (control) population. Our study presents a number of strengths: (1) The sample sizes of cohorts were large; (2) only patients who were antipsychotic free for at least 6 months and who received only a single antipsychotic during the evaluation period were included in the antipsychotic cohorts, and thus the study was not confounded by antipsychotics that were recently or concurrently administered; and (3) the use of the AdvancePCS general patient population enabled us to compare the rates of developing DM relative with a reference population that was not exposed to antipsychotic medications.

The major limitation of this study was that psychiatric diagnostic information was not available in the database. Other limitations were that only incident cases of DM that resulted in intervention with antidiabetic medications were identified and that all indications for antipsychotic prescriptions were included, regardless of psychiatric illness spectrum or severity. Furthermore, the selection of a given antipsychotic reflects clinical choices rather than randomized assignment. Potentially, certain patient attributes that influence treatment selection might also affect likelihood of developing DM. While pharmacoepidemiological studies can control for some important factors (e.g., age), others cannot be addressed with available data (e.g., severity of illness); 3) the average duration of antipsychotic treatment was not long, ranging from 68 days to 137 days; 4) the database did not

Table 4

Hazard ratio of developing diabetes comparing other antipsychotic cohorts to the haloperidol cohort

Treatment cohort	New cases (n)	Subjects in cohort (n)	HR ^a		
			Ratio	95% CI	P value
Olanzapine	194	13,863	1.09	0.86–1.37	0.479
Risperidone	400	20,633	1.23	1.01–1.50	0.040
Quetiapine	40	4,196	0.67	0.46–0.97	0.033
Clozapine	7	277	1.31	0.60–2.86	0.496

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Cox proportional hazards regression analysis adjusted for age, gender, and duration of antipsychotic exposure.

HR and 95% CI values were rounded to the first decimal place except where such rounding obscured significance cut-off points.

In the haloperidol cohort, there were 133 new cases in a total of 8476 patients.

Table 5
Hazard ratios for antipsychotic cohort dose quartiles relative to the AdvancePCS general patient population

Cohort	Mean dose/quartile ($\pm$ SD)	Mean age ($\pm$ SD)	IIR ^a Ratio	95% CI	P value
Conventional					
Haloperidol					
Q1	0.5 $\pm$ 0.3	77.1 $\pm$ 30.6	2.6	1.9–3.7	≤ 0.0001
Q2	0.9 $\pm$ 0.3	75.8 $\pm$ 31.5	2.9	2.0–4.2	≤ 0.0001
Q3	1.7 $\pm$ 0.7	72.6 $\pm$ 34.1	2.9	2.0–4.1	≤ 0.0001
Q4	7.0 $\pm$ 17.5	61.5 $\pm$ 39.5	4.3	3.1–5.9	≤ 0.0001
Thioridazine					
Q1	9.9 $\pm$ 6.3	66.1 $\pm$ 39.6	2.1	1.0–4.5	0.0453
Q2	20.1 $\pm$ 6.3	63.6 $\pm$ 38.8	3.0	1.7–5.4	≤ 0.0001
Q3	37.3 $\pm$ 14.4	60.2 $\pm$ 37.9	2.9	1.6–5.2	0.0005
Q4	110.8 $\pm$ 151.1	54.9 $\pm$ 37.0	8.9	6.2–12.7	≤ 0.0001
Atypical					
Olanzapine					
Q1	1.7 $\pm$ 0.9	60.1 $\pm$ 42.2	3.4	2.6–4.5	≤ 0.0001
Q2	3.1 $\pm$ 0.7	55.0 $\pm$ 41.0	2.6	1.9–3.6	≤ 0.0001
Q3	5.3 $\pm$ 2.0	53.4 $\pm$ 39.6	2.5	1.9–3.3	≤ 0.0001
Q4	11.3 $\pm$ 9.8	50.0 $\pm$ 37.1	3.6	2.8–4.7	≤ 0.0001
Risperidone					
Q1	0.4 $\pm$ 0.2	70.9 $\pm$ 40.6	3.7	3.0–4.5	≤ 0.0001
Q2	0.7 $\pm$ 0.1	65.1 $\pm$ 43.5	3.0	2.4–3.8	≤ 0.0001
Q3	1.1 $\pm$ 0.3	63.6 $\pm$ 43.0	3.0	2.5–3.7	≤ 0.0001
Q4	2.5 $\pm$ 2.4	56.0 $\pm$ 42.2	4.0	3.3–4.8	≤ 0.0001
Quetiapine					
Q1	17.0 $\pm$ 8.6	60.2 $\pm$ 40.7	1.8	0.9–3.4	0.0957
Q2	34.5 $\pm$ 11.3	57.1 $\pm$ 41.2	1.4	0.7–2.9	0.3347
Q3	64.5 $\pm$ 24.4	53.3 $\pm$ 37.8	0.6	0.2–1.8	0.3938
Q4	203.7 $\pm$ 245.1	49.8 $\pm$ 36.4	3.1	1.9–5.1	≤ 0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval.

^a Cox proportional hazards regression analysis adjusted for age and gender.

HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points.

The sample size of the clozapine cohort (277 subjects with 7 cases of diabetes mellitus) was too small for a meaningful quartile analysis.

contain information on well known risks for DM, including obesity, ethnic origin, or family history. Thus it was not possible to adjust for differences in these risk factors between cohorts; 5) the mean daily doses in antipsychotic cohorts were low. However, the dose quartile analysis showed that relatively higher doses were represented. Thus our findings can only be generalized to populations similar to that represented in the AdvancePCS database; 6) we did not account for exposure to other drugs that may be temporally associated with glucose dysregulation (e.g. protease inhibitors, thiazide diuretics and β -blockers). Therefore, if these drugs were not prescribed uniformly across the cohorts studied, the hazard ratio for developing diabetes may have been overestimated in individual cohorts containing patients prescribed these drugs.

Elevated HR during antipsychotic treatment may reflect a number of factors. While one possibility is an adverse glycemic effect of antipsychotics, other major considerations include (1) a vulnerability for DM which may be genetically or behaviorally linked to the disorder being treated; (2) an indirect medication effect, e.g., via an effect on diet or exercise; and (3) enhanced recognition of DM coinciding with the prescription of antipsychotic medication or illness severity, e.g., increased probability of detecting diabetes for

patients who had more frequent contact with medical professionals due to their illness. These additional factors need to be taken into account in determining the risk of developing DM during treatment with antipsychotics. Further, given that differences in background incidence and risk factors for DM might exist between populations commonly treated with antipsychotics and the general population, comparisons between antipsychotic-treated cohorts and a reference population without psychosis may overestimate the potential effect of antipsychotics on the emergence of DM.

In conclusion, our study suggests that patients treated with either conventional or atypical antipsychotics may be at higher risks of developing DM than the AdvancePCS general patient population. The risk of developing diabetes was comparable between conventional and atypical antipsychotic cohorts. What remains unclear is to what extent the observed increases in incidence and risk of DM may be related to factors intrinsic or extrinsic to those psychiatric disorders commonly treated with antipsychotic drugs. Finally, though the potential morbidity and mortality related to DM is serious, it must be evaluated in the context of the significant morbidity and mortality associated with major psychiatric illnesses. Findings from the present study suggest that the decisions regarding the choice of antipsychotic for treat-

ing major psychiatric illness should not be based solely on the relatively modest differences in DM rates observed during treatment with these agents. In patients with schizophrenia as in the general population, consideration should be given to the presence of known risk factors for diabetes [41], including obesity and glucose intolerance and psychotropic therapy should be evaluated in the context of the patient's overall response and tolerability to therapy.

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METHODS

Background: Trauma and psychosocial problems have long been reported by the healthcare staff for conventional and support psychiatric patients. However, no large-scale epidemiological studies have been carried out that systematically assessed the role of trauma and psychosocial problems in the care of patients with mental health problems. We explored the UK General Practice Research Network (GPRN) to determine the prevalence of trauma and psychosocial problems among adult outpatients compared with the general adult population in the UK.

Aims: An epidemiologic trauma sample of patients registered to both conventional and support psychiatric services was identified. The prevalence of trauma and psychosocial problems was explored in a sample of outpatients during the study period, and a general practice population cohort (Maudsley-2) defined. The GPRN database was then searched for patients with a diagnosis of trauma and psychosocial problems. The prevalence of trauma and psychosocial problems was compared between these cohorts. The research for inclusion in the GPRN of children (development) between these cohorts. The research for inclusion in the GPRN of children (development) between these cohorts.

Conclusions: Our paper is the general population sample in the UK. Patients support to psychiatric patients is a higher rate of developing distress (62% vs 15.4%). The prevalence of trauma and psychosocial problems was higher in the sample of outpatients compared with the general adult population (71% and 40% respectively). The prevalence of trauma and psychosocial problems was higher in the sample of outpatients compared with the general adult population (71% and 40% respectively). The prevalence of trauma and psychosocial problems was higher in the sample of outpatients compared with the general adult population (71% and 40% respectively).

- Limitations
 - Only party with all

- Anytype an asymptomatic culture assessment strategy of patients who need prior exposure to conventional antipsychotics
- Lack of concern or information on the family history of diabetes and of its origin
- The study did not detect any evidence that patients already treated with antipsychotics are at greater risk of developing diabetes
- Among patients receiving a typical antipsychotic therapy, the majority (71%) was taking clozapine whereas 21% received olanzapine
- Significant number of patients receiving other atypical antipsychotics

• **Diabetes: method**

- One Prospective Study of H2A/C40A1000 regression model was used to estimate the hazard of DM in patients controls
- Covariates were age, gender, race, plasma glucose
- The hazard of DM was 1.50 in patients receiving study drugs between the period 0-9999 patients population cohort and
- a 4 treatment antipsychotic cohort

GPRD - SUMMARY

- Among individual antipsychotic cohorts that were adequately represented in this analysis of the GPRD database, a significantly elevated risk for DM versus the GPRD was observed in the thioridazine and risperidone monotherapy cohorts.

- This study is consistent with previous observations of statistical risk of diabetes in patients treated with antipsychotic drugs.
- The statistical association between treatment with ODM or DM may be relative to factors such as: genetic vulnerability, a lifestyle, drug treatment, eating disorders, psychosocial distress, drug severity limited with antipsychotic drugs.
- Additional factors which were not consistently available in the GPRD database would need to be evaluated regarding this association with the use of antipsychotic DM (e.g. ethnic background, family history of DM).
- Several years of cumulative clinical use of a given antipsychotic drug are needed for the required number of patients to be available for this type of epidemiological assessment. The number of patients available for this type of comparison regarding the presence or absence of an increased risk of DM in patients treated with each agent introduced or have previously been reported.

	Univariate Descriptive Population	Controlled Descriptive Antipsychotic Subgroup
Number of subjects	272	451
Mean age, years (SD)	50.9 (17.5)	50.7 (23.4)
18 to 44 years of age	41%	31%
45 to 54 years of age	30%	23%
55 years of age and older	29%	46%
Proportion male	65%	56%
Proportion obese	33%	15%

PROPORTIONAL HAZARD ANALYSIS OF DIABETES MELLITUS FOR COVARIATES IN THE COX REGRESSION MODEL: STRATIFIED BY COHORT

REGRESSION MODEL, STRATIFIED BY GENDER
93%
10/10/2000

Variable	Mean and SD	Confidence Interval	P value
Community Antipsychotic Outpatient (N=46,119)			
Presence of Obesity	3.1	1.9–5.1	<0.0001
Age 15–24 years*	4.0	2.2–11.0	<0.0001
Age 45–64 years*	4.9	1.7–8.1	0.001
Gender (Male)	5.0	2.4–1.5	0.98
General Adult Primary Population (N=308,272)			
Presence of Obesity	4.7	3.9–5.7	<0.0001
Age 25–34 years	8.62	8.7–8.7	<0.0001
Age 45–64 years	3.3	3.1–4.6	<0.0001
Gender (Male)	1.8	1.8–1.9	<0.0001

*Ag = 18-44 years used as reference

INCIDENCE AND HAZARD RATIO OF DIABETES IN PATIENTS DURING ANTIPSYCHOTIC THERAPY

	No. of patients	Mean age (SD)	Mean duration of illness (SD)	Mean duration of hospital stay (SD)	Mean duration of follow-up (SD)	First episode (%)	Second episode (%)
All schizophrenic patients	179	30.1 (11.1)	30.0 (20.0)	12.7 (8.7)	16.0 (10.6)	1.0 (0.5)	98.9 (5.7)
Subtypes							
Paranoid	55	34.6 (8.5)	1.9 (3.0)	7.7 (5.1)	14.7 (8.8)	1.0 (0.5)	98.9 (5.6)
Disorganized	56	27.0 (8.1)	10.1 (10.7)	12.0 (8.1)	14.7 (8.8)	0.0 (0.0)	100.0 (0.0)
Undifferentiated	68	29.4 (10.4)	14.0 (12.1)	12.7 (8.1)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Residual	6	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Unsubtyped	12	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Subtypes with subtypes							
Paranoid	16	37.0 (8.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Disorganized	7	28.0 (8.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Undifferentiated	10	30.0 (10.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Residual	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Unsubtyped	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Subtypes with subtypes							
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Undifferentiated	10	30.0 (10.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Residual	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Unsubtyped	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
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Subtypes with subtypes							
Paranoid	16	37.0 (8.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Disorganized	7	28.0 (8.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Undifferentiated	10	30.0 (10.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Residual	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Unsubtyped	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Subtypes with subtypes							
Paranoid	16	37.0 (8.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Disorganized	7	28.0 (8.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Undifferentiated	10	30.0 (10.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Residual	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Unsubtyped	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Subtypes with subtypes							
Paranoid	16	37.0 (8.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Disorganized	7	28.0 (8.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Undifferentiated	10	30.0 (10.0)	0.0 (0.0)	0.0 (0.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Residual	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Unsubtyped	1	33.0 (10.7)	1.0 (1.0)	4.0 (2.0)	15.0 (9.0)	0.0 (0.0)	100.0 (0.0)
Subtypes with subtypes							

* Results from OAR group-based analysis are shown with age, gender and ethnicity as covariates. Reference group was the general and not population cohort. Some age categories were not used as a variable in the model for the "heterophyllum" treatment, but only two age categories (45-64 and 65 and older) for individual anthropometric measurements.

- GPBD pre-selection claim that base is comprised of 8 million UK residents created by selected geospatial coordinates with had equal to other patient data sets no comparison provided by VAMP in lack of prospective evidence research hypothesis. The longitudinal database contains patient information on sex, age, weight, height, smoking, prescription, hospitalisation, age decomposition, the geospatial coordinates information was chosen to ensure that they were representative of the UK population.

- Study Design

- This retrospective population epidemiological study addresses the historical and social context of the use of LSD in the United Kingdom who received a single or multiple doses, frequency of medication.
- **Design** of the study
 - This study had been a comprehensive diagnosis of bipolar type I schizophrenia (as defined by any one of the **Output** Institute Information System diagnostic criteria) and a clinical history of the patients, including the use of psychiatric medication indicated by the treatment of doctors who was considered as **Primary Outcome**.
- **Research Population**
 - The study included population criteria considered as a random sample of subjects registered continuously during January 1st, 1954 and December 31st 1997 who had been prescribed at least one antipsychotic medication other than an antipsychotic in antipsychotics; apart during the two-year period.
- **Analysis**
 - **Inclusion criteria**
 - **Age**: included 16 years of age or 16 years old in 1954, who were registered in standard population register for 3 years after 1954 up to the study period.
 - **Use of the national system antipsychotic system**: patients were included even if they had been meeting with conventional antipsychotics.
 - **Exclusion criteria**
 - **Age**: those under 16 years
 - **Prevalence history of DSM**
 - **Patients enrolled in conventional antipsychotics** and **applied antipsychotic** after diagnosis.

REFERENCES

- [illegible]

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CLINICAL EXPERIENCE

Retrospective Cohort Study of Diabetes Mellitus and Antipsychotic Treatment in a Geriatric Population in the United States

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Objectives: The objective of this study was to investigate risk of diabetes among elderly patients during treatment with antipsychotic medications.

Design: We conducted a longitudinal, retrospective study assessing the incidence of new prescription claims for antihyperglycemic agents during antipsychotic therapy.

Setting: Prescription claims from the AdvancePCS claim database were followed for 6 to 9 months.

Participants: Study participants consisted of patients in the United States aged 60+ and receiving antipsychotic monotherapy. The following cohorts were studied: an elderly reference population (no antipsychotics: $n = 1,836,799$), those receiving haloperidol ($n = 6481$) or thioridazine ($n = 1658$); all patients receiving any conventional antipsychotic monotherapy ($n = 11,546$), dozapine ($n = 117$), olanzapine ($n = 5382$), quetiapine ($n = 1664$), and risperidone ($n = 12,244$), and all patients receiving any atypical antipsychotic monotherapy ($n = 19,407$).

Measurements: We used Cox proportional hazards regression to determine the risk ratio of diabetes for antipsychotic cohorts relative to the reference pop-

ulation. Covariates included sex and exposure duration.

Results: New antihyperglycemic prescription rates were higher in each antipsychotic cohort than in the reference population. Overall rates were no different between atypical and conventional antipsychotic cohorts. Among individual antipsychotic cohorts, rates were highest among patients treated with thioridazine (95% confidence interval [CI], 3.1–5.7), lowest with quetiapine (95% CI, 1.3–2.9), and intermediate with haloperidol, olanzapine, and risperidone. Among atypical cohorts, only risperidone users had a significantly higher risk (95% CI, 1.05–1.60; $P = 0.016$) than for haloperidol. Conclusions about dozapine were hampered by the low number of patients.

Conclusion: These data suggest that diabetes risk is elevated among elderly patients receiving antipsychotic treatment. However, causality remains to be demonstrated. As a group, the risk for atypical antipsychotic users was not significantly different than for users of conventional antipsychotics. (*J Am Med Dir Assoc* 2004; 5: 38–46)

Keywords: Antipsychotics; diabetes mellitus; geriatrics; prescriptions; drug

Use of antipsychotic medications among the elderly is substantial, with as much as half of all repeat prescriptions for antipsychotics being accounted for by patients over age 65.¹ It

has been estimated that 38% to 43% of all elderly patients residing in skilled care facilities receive antipsychotic medication,^{2,3} although as many as 60% to 80% of elderly patients at facilities for the mentally ill could be receiving such treatment.^{4,5} Fully 20% of the population aged 80 and older are affected by dementia,⁶ and approximately one fourth to one half of these develop psychotic features that require the use of an antipsychotic agent.^{7,8} In addition to being prescribed for this condition, however, a considerable proportion of antipsychotic prescriptions for the elderly are for use as a tranquilizer or anxiolytic.^{9,10}

Use of conventional high-potency antipsychotics such as

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haloperidol is associated with high levels of extrapyramidal symptoms,^{11,12} to which elderly patients are particularly vulnerable.^{13,14} In contrast, extrapyramidal symptoms in patients treated with atypical antipsychotics are less common.¹⁵ Nevertheless, an issue has been raised recently regarding the safety of both conventional and atypical antipsychotics, as it has been suggested that their use could be associated with induction of insulin resistance and an increased risk of type 2 diabetes mellitus.¹⁶⁻¹⁸ For example, one study¹⁹ reports that 12% of patients treated with clozapine developed type 2 diabetes compared with a prevalence in the general population of 5.1%.²⁰ Some studies appear to associate the use of specific antipsychotic medications with a higher rate of new-onset hyperglycemia or type 2 diabetes.^{16,17,19} This is still a point of controversy, however, because such studies have largely relied on case reports and chart reviews and might not accurately reflect the actual incidence of hyperglycemia among antipsychotic users relative to the general population, let alone the population of patients with mental illness. Moreover, the contribution of undiagnosed diabetes or impaired glucose tolerance among patients before their use of antipsychotics is unknown.²¹ By contrast, other studies have concluded that antipsychotic use is merely coincidental to an underlying predisposition to diabetes among patients with schizophrenia.²²

Many attempts to investigate the potential link between antipsychotic use and an increased risk of diabetes have been hampered by limited sample size, and studies have yielded largely inconclusive results. However, a recent analysis²¹ has been conducted using a drug prescription claim database maintained by AdvancePCS (Scottsdale, AZ), the United States' largest health plan provider, with more than 75 million members linked to 58,000 pharmacies throughout the country. The analysis suggested that there is a statistically significant increase in the risk of diabetes during treatment with either conventional or atypical antipsychotics. However, large-scale studies of this sort that focus on an elderly population have received little attention. Accordingly, the current analysis was undertaken, using the AdvancePCS prescription claim database, to investigate the risk of diabetes among patients aged 60 and older who had been receiving either conventional or atypical antipsychotic medications.

METHODS

Study Design and Patient Sample

This longitudinal study was conducted retrospectively to compare the risk of new development of diabetes mellitus among selected antipsychotic cohorts drawn from the AdvancePCS prescription claim database. The validity and reliability of their prescription database has been verified independently. Over 300 million prescription claims per year are processed in this database for more than 50 million members covered by over 2000 managed care plans and employers. Most claims were submitted by pharmacies handling the outpatient prescription needs for these patients, although some prescriptions were filled in long-term care settings. Only patients who maintained coverage with AdvancePCS were fol-

lowed; if patients discontinued their coverage, they were censored from the analysis. This analysis examines the data from patients aged 60 and older, amounting to a total patient sample of nearly two million patients. Because this was an examination of only the potential effects of exposure to antipsychotic medications, diagnostic information was not captured. Information regarding patients' ethnicity was also not available. For the purposes of this analysis, patients were examined both together as a single geriatric population (all patients aged ≥ 60 years) and stratified as two separate subgroups, a younger one consisting of patients aged 60 to 74 and an older one of patients aged 75 and older.

Inclusion/Exclusion Criteria

Patients who were qualified for prescription claims through AdvancePCS for the entire 12 months before enrollment were eligible for inclusion in the analysis. No obvious differences were seen in the number of patients using a diabetes medication when comparing a 12-month preenrollment period versus a 24-month preenrollment period; thus, the 12-month preenrollment period was used.²¹ The exclusion criteria applicable to all cohorts included (1) a preexisting history of diabetes mellitus, as evidenced by a prescription claim for any antihyperglycemic medication during the 12-month period before enrollment; (2) a prescription claim for any antipsychotics within the 6-month period before the enrollment date; and (3) absence of information on sex or year of birth.

Cohort Studies

A "general patient population" cohort, consisting of all subjects who had made any AdvancePCS-covered prescription claim during a 2-month enrollment window (January 1 to February 29, 2000), was used as a standard reference population. Patients in the general population cohort must not have made a claim for any diabetes drug for at least 12 months before enrollment. In addition, they must not have received a prescription for an antipsychotic for at least 6 months before and 6 months after enrollment.

Only patients who were prescribed a single antipsychotic were included in the antipsychotic cohorts for this study, regardless of indication for antipsychotic therapy. The antipsychotic cohorts studied consisted of the following: (1) patients receiving haloperidol monotherapy; (2) patients receiving thioridazine monotherapy; (3) all patients receiving monotherapy with any single conventional antipsychotic, referred to as the "combined conventional antipsychotic" cohort; (4) patients receiving clozapine monotherapy; (5) patients receiving olanzapine monotherapy; (6) patients receiving quetiapine monotherapy; (7) patients receiving quetiapine monotherapy; (8) patients receiving risperidone monotherapy; and (9) all patients receiving monotherapy with any single atypical antipsychotic, referred to as the "combined atypical antipsychotic" cohort. Antipsychotic agents included both conventional antipsychotics (chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, prochlorperazine, promazine, thioridazine, thiothixene, trifluoperazine, and triflupromazine) and atypical antipsychot-

ics (clozapine, olanzapine, quetiapine, and risperidone). Haloperidol and thioridazine were chosen as separate cohorts from among the conventional antipsychotics as a result of their sufficient numbers, whereas the remaining conventional antipsychotics individually formed less than 10% of the total prescriptions for typical antipsychotics, yielding cohorts that were too small for analysis. Clozapine was included as a separate cohort from among the atypical antipsychotics as a result of the intense focus it has received for a possible association with diabetes risk.

The enrollment window for subjects in the antipsychotic cohorts was December 1, 1998, through February 29, 2000. Subjects who started therapy during this period and continued treatment with the same single antipsychotic were included in the antipsychotic cohorts. Patients receiving antipsychotics were studied for as long as they had continuous therapy and did not terminate AdvancePCS coverage. The data cutoff point for this study was August 31, 2000. For all antipsychotic cohorts, patients who received more than one antipsychotic during the enrollment window were excluded. The earliest date during the enrollment window that any patient filed a prescription claim, either an antipsychotic agent in the case of the antipsychotic cohorts or a nonantipsychotic agent in the case of the general patient population, was considered the enrollment date for that subject.

Incidence of Diabetes Mellitus

New onset of diabetes mellitus during antipsychotic exposure was identified by claims for any medication indicated for the treatment of diabetes regardless of the route of administration. For the purposes of this analysis and of the language in this report, the incidence of new prescriptions for antihyperglycemic medications is equated with the incidence of new-onset diabetes without regard to clinicians' standards for diagnosis or choices of treatment. To identify the timing of onset of new cases of diabetes, the date of the first antihyperglycemic agent prescribed after the enrollment date was considered the start of antidiabetic therapy. Each patient in the antipsychotic cohort was tracked for new onset of diabetes from the enrollment date to the time that the antipsychotic was discontinued for more than 15 days, or until the data cutoff point, whichever came first.

Comparison of Risk Between Cohorts

To compare the risk of developing diabetes among cohorts, both incidence density and risk ratios were determined. Incidence of diabetes for antipsychotic cohorts might not be linearly related to time, with more cases being experienced earlier during treatment exposure. Annualization of incidence density might therefore be likely to inflate the true incidence. Also, differences in incidence between cohorts could be partially accounted for by differences in mean age, sex, and the amount of exposure to antipsychotics among cohorts. To control for these variables in the estimation of the risk of diabetes, the Cox proportional hazards regression was used to determine the risk ratio of diabetes for antipsychotic cohorts relative to the general AdvancePCS population, matching the antipsychotic cohort with the reference population by age

(≥ 60 years, 60–74 years, or ≥ 75 years). Several Cox proportional hazard models were analyzed with the "PHREG" (proportional hazards regression) procedure in SAS (Statistical Analysis Systems, SAS Institute, Cary, NC) using covariates for sex and duration of exposure. For comparisons of diabetic risk among the atypical antipsychotic treatment groups, the haloperidol cohort was used as a reference standard because of its status as the most widely used conventional antipsychotic agent. The alpha level for statistical significance was 0.05.

RESULTS

Observational Results

A total of 30,953 elderly outpatients who had received prescriptions for antipsychotic treatment were included in this analysis (Tables 1 and 2), and an additional 1,836,799 outpatients from the general population who had received prescriptions for other, nonantipsychotic medications were used as the standard for comparison. Prescriptions for atypical antipsychotic medications (Table 2) outnumbered those for conventional antipsychotics (Table 1) by nearly 70%. In terms of raw numbers of patients, relative rates of prescribing for the atypical agents were as follows: risperidone > olanzapine > quetiapine > clozapine. For conventional antipsychotic agents, prescription rates were highest for haloperidol, followed by thioridazine, and finally by all other conventional agents. It was noted that, in terms of chlorpromazine equivalents (doses converted to an equivalent daily dose of chlorpromazine, based on minimum effective doses²³) and relative to dose recommendations for older patients with schizophrenia, the mean administered doses were low for thioridazine (36.1 mg chlorpromazine equivalents), risperidone (75.0 mg), quetiapine (87.2 mg), haloperidol (90.0 mg), and clozapine (90.3 mg), but moderate to high for olanzapine (165.0 mg). Mean durations of treatment were, for the most part, in the vicinity of 70 to 100 days. The one exception was clozapine, which was administered for a mean duration of over 140 days.

As shown in Tables 1 and 2, a higher proportion of patients in the older group of patients had prescriptions for antipsychotics compared with the younger group (≥ 75 years: 21,742 patients compared with a corresponding general population of 690,545 patients, or an equivalent frequency of 32 per thousand; 60–74 years: 9211 of 1,146,254 patients, or an equivalent frequency of 8 per thousand). The older group of patients had a higher proportion of females relative to the younger subgroup, both overall and within each drug cohort, presumably reflecting age-related changes in demographics. Mean doses of each drug were lower among the older patients relative to their corresponding drug-matched younger counterparts. Mean treatment durations were much longer among the clozapine-treated patients relative to the other drug cohorts, both overall and within each of the two age subgroups.

Comparison of Antipsychotic Users and Nonusers

Compared with the general patient population of patients aged 60+ who received only nonantipsychotic prescriptions, an increased risk of development of diabetes was seen in every antipsychotic cohort (Table 3). The risk was lowest for the

Table 1. Characteristics of Patients Receiving Conventional Antipsychotics versus the General Patient Population

Characteristic	General Patient Population	Conventional Antipsychotics		
		All Agents	Haloperidol	Thioridazine
All patients, aged ≥ 60				
No. of subjects	1,836,799	11,546	6481	1658
Age, mean (SD)	72.1(8.3)	78.4(9.1)	80.8(8.4)	77.8(9.1)
Percent males	39.2	43.1	39.8	35.3
Treatment duration days (SD)		70.2(75.9)	68.5(69.8)	84.7(87.2)
Dose (mg/day)				
mean (SD)			1.8(3.4)	36.1(43.4)
CPZ equivalents			90.0	36.1
Patients aged 60–74				
No. of subjects	1,146,254	3778	1389	564
Age mean (SD)	66.7(4.4)	67.8(4.4)	68.6(4.4)	67.4(4.4)
Percent males	41.1	47.6	46.2	34.0
Treatment duration days (SD)		69.7(80.0)	67.4(71.4)	83.9(88.5)
Dose (mg/day)				
mean (SD)			2.7(6.0)	48.7(58.7)
CPZ equivalents			135.0	48.7
Patients aged ≥ 75				
No. of subjects	690,545	7768	5092	1094
Age mean (SD)	81.0(5.0)	83.5(5.7)	84.2(5.7)	83.1(5.6)
Percent Males	36.1	40.9	38.0	35.9
Treatment duration days (SD)		70.4(73.8)	68.8(69.4)	85.1(86.5)
Dose (mg/day)				
mean (SD)			1.5(2.3)	29.6(30.9)
CPZ equivalents			75.0	29.6

SD, standard deviation; CPZ, chlorpromazine.

quetiapine cohort, with patients nevertheless being approximately twice as likely to have received a new prescription for antihyperglycemic medication as patients in the general patient population, whereas patients receiving thioridazine had the greatest risk, being four times as likely to have received new antidiabetic treatment. Risk did not appear to be related to dose, however, because the two groups with the highest risk ratios, thioridazine and risperidone, were also associated with the lowest relative doses.

A comparison of patients within each of the stratified age groups (Table 3) showed the risk ratio (RR) among younger patients (60–74 years of age) to be highest for the risperidone (RR = 5.1) and haloperidol (RR = 5.0) cohorts. It should be pointed out, however, that the number of younger patients in the clozapine cohort was too low to permit a meaningful statistical analysis, and therefore no comparisons could be made regarding the risk ratio in patients treated with clozapine compared with the other antipsychotics. Among older patients (75+), diabetes risk was highest for the clozapine and thioridazine cohorts. In fact, older patients receiving clozapine had the highest risk of any subgroup, being 5.8 times as likely as older patients in the reference population to have received new antidiabetic treatment. This figure takes into account the longer duration of exposure in the clozapine cohort, because the Cox proportional hazards regression analysis was adjusted for duration of exposure as well as sex. However, this figure must nevertheless be regarded as tentative, again as a result of the

large confidence interval associated with this small group of patients. Younger patients receiving quetiapine were unique in being the only subgroup not to have a significantly higher risk of diabetes (95% confidence interval [CI], 0.5–2.7; $P = 0.794$) than their age-matched general reference population; similarly, among older patients, quetiapine use was temporally associated with the lowest risk of any cohort compared with their age-matched general patient population.

Comparison of Atypical Antipsychotic Users and Conventional Antipsychotic Users

The risk for patients receiving prescriptions for atypical antipsychotics was not significantly different from that for patients taking conventional antipsychotics (Table 4). This was true for the overall patient sample (95% CI, 0.92–1.25; $P = 0.382$) and within each age-stratified group (aged 60–74: 95% CI, 0.74–1.22; $P = 0.686$; aged ≥ 75 : 95% CI, 0.97–1.44; $P = 0.104$). For a comparison of diabetes risk among the different drug cohorts, risk ratios were calculated using the haloperidol drug cohort as the reference population (Table 4). Of the atypical antipsychotics, only the risperidone cohort had a significantly higher diabetes risk relative to haloperidol. This was seen both overall (95% CI, 1.05–1.60; $P = 0.016$) and among the older patients (95% CI, 1.05–1.75; $P = 0.019$). Among younger patients (60–74 years of age), the quetiapine cohort was again seen to have the lowest risk of diabetes, with an incidence rate

TABLE 2. Characteristics of Patients Receiving Atypical Antipsychotics versus the General Patient Population

Characteristic	General Patient Population	Atypical Antipsychotics				
		All Agents	Clozapine	Olanzapine	Quetiapine	Risperidone
All Patients aged ≥60						
No. of subjects	1,836,799	19,407	117	5382	1664	12,244
Age mean (SD)	72.1 (8.3)	79.2 (8.8)	75.2 (7.2)	77.4 (9.1)	76.9 (8.5)	80.4 (8.4)
Percent males	39.2	35.2	45.3	34.2	40.4	34.8
Treatment duration days (SD)		97.6 (89.8)	141.2 (124.3)	102.0 (96.1)	99.2 (86.9)	95.1 (86.6)
Dose (mg/day)						
mean (SD)			77.9 (120.9)	4.4 (3.8)	64.6 (83.5)	1.0 (0.8)
CPZ equivalents			90.3	165.0	87.2	75.0
Patients aged 60–74						
No. of subjects	1,146,254	5433	52	1961	619	2801
Age mean (SD)	66.7 (4.4)	68.1 (4.4)	68.6 (4.3)	67.7 (4.5)	68.0 (4.4)	68.5 (4.4)
Percent Males	41.1	38.7	48.1	38.0	42.2	38.2
Treatment duration days (SD)		91.4 (86.9)	149.0 (131.7)	93.9 (91.2)	95.9 (83.4)	87.7 (83.1)
Dose (mg/day)						
mean (SD)			114.0 (160.1)	5.1 (4.3)	75.8 (86.9)	1.2 (1.0)
CPZ equivalents			132.2	191.3	102.3	90.0
Patients aged ≥75						
No. of subjects	690,545	13,974	65	3421	1045	9443
Age mean (SD)	81.0 (5.0)	83.6 (5.7)	80.5 (3.9)	83.0 (5.7)	82.3 (5.3)	83.9 (5.7)
Percent males	36.1	33.8	43.1	32.1	39.4	33.8
Treatment duration days (SD)		100.0 (90.7)	135.0 (118.8)	106.6 (98.5)	101.1 (88.8)	97.3 (87.6)
Dose (mg/day)						
mean (SD)			49.1 (64.4)	4.0 (3.4)	58.0 (80.7)	0.9 (0.7)
CPZ equivalents			57.0	150.0	78.3	67.5

SD, standard deviation; CPZ, chlorpromazine.

in this younger subgroup of 0.97% and a risk ratio significantly lower than that of haloperidol. The older subgroup of quetiapine users, however, showed no significant difference from haloperidol. The risk ratio for the olanzapine group was not significantly different from that of the haloperidol reference group, either overall or in either age subgroup. Relative to the risperidone cohort, the olanzapine group had a risk ratio of 0.97 (95% CI, 0.76–1.24; $P = 0.814$). The risk for clozapine also was not different overall from that of the haloperidol

reference group. In terms of incidence rates, however, clozapine had the highest percentage of new cases of diabetes, both overall (5 of 117 [4.27%]) and in the older subgroup (4 of 65 [6.15%]), but this must again be taken in the context of the low overall numbers of patients in the clozapine cohort.

DISCUSSION

This analysis is consistent with earlier reports that patients who receive antipsychotic medications could be at increased

Table 3. Development of Diabetes Mellitus During Treatment With Antipsychotics, Relative to the General Population of the Same Age Group*

Cohort	All Patients (aged ≥60)			Patients (aged 60–74)			Patients (aged ≥75)		
	Risk Ratio	95% CI	P Value	Risk Ratio	95% CI	P Value	Risk Ratio	95% CI	P Value
Conventional antipsychotics									
All combined	3.6	3.1–4.1	<0.001	4.5	3.7–5.6	<0.001	3.2	2.7–3.8	<0.001
Haloperidol	3.2	2.7–3.9	<0.001	5.0	3.6–6.8	<0.001	2.8	2.2–3.5	<0.001
Thioridazine	4.2	3.1–5.7	<0.001	4.1	2.4–6.9	<0.001	4.3	3.0–6.3	<0.001
Atypical antipsychotics									
All combined	3.5	3.2–3.8	<0.001	4.1	3.5–4.8	<0.001	3.3	3.0–3.7	<0.001
Clozapine	3.1	1.0–9.5	0.051	†	†	†	5.8	1.9–17.8	0.002
Olanzapine	3.6	3.0–4.2	<0.001	3.8	2.9–5.0	<0.001	3.5	2.8–4.3	<0.001
Quetiapine	1.9	1.3–2.9	0.001	1.1	0.5–2.7	0.0794	2.5	1.6–3.9	<0.001
Risperidone	3.7	3.3–4.2	<0.001	5.1	4.2–6.3	<0.001	3.4	2.9–3.9	<0.001

* Cox proportional hazards regression analysis adjusted for sex and duration of exposure.

† Too few patients in cohort to yield meaningful comparison.

CI, confidence interval.

Table 4. Development of Diabetes Mellitus Among Selected Antipsychotic Cohorts*

Cohort	No. of Patients in Cohort	New Cases No. (%)	Risk Ratio	95% CI	P Value
All patients (aged ≥ 60)					
All conventionals	11,546	238 (2.1)	(1.0)		
Haloperidol	6481	118 (1.8)	(1.0)		
All atypicals†	19,407	515 (2.7)	1.1	0.9–1.3	0.382
Clozapine‡	117	5 (4.3)	1.4	0.6–3.5	0.464
Olanzapine§	5382	142 (2.6)	1.2	0.9–1.5	0.209
Quetiapine¶	1664	29 (1.7)	0.7	0.5–1.1	0.136
Risperidone‡	12,244	339 (2.8)	1.2	1.1–1.6	0.016
Patients aged 60–74					
All conventionals	3778	100 (2.7)	(1.0)		
Haloperidol	1389	39 (2.8)	(1.0)		
All atypicals†	5433	159 (2.9)	1.0	0.7–1.2	0.686
Clozapine‡	52	1 (1.9)	§	§	§
Olanzapine§	1961	53 (2.7)	0.8	0.5–1.2	0.297
Quetiapine¶	619	6 (1.0)	0.3	0.1–0.7	0.003
Risperidone‡	2801	99 (3.5)	1.1	0.8–1.7	0.481
Patients aged ≥ 75					
All conventionals	7768	138 (1.8)	(1.0)		
Haloperidol	5092	79 (1.6)	(1.0)		
All atypicals†	13,974	356 (2.6)	1.2	1.0–1.4	0.104
Clozapine‡	65	4 (6.2)	§	§	§
Olanzapine§	3421	89 (2.6)	1.3	1.0–1.8	0.065
Quetiapine¶	1045	23 (2.2)	1.1	0.7–1.7	0.807
Risperidone‡	9443	240 (2.5)	1.4	1.1–1.8	0.019

* Cox proportional hazards regression analysis adjusted for sex and duration of exposure.

† Versus all conventional antipsychotics.

‡ Versus haloperidol.

§ Too few patients in cohort to yield a meaningful comparison.

CI, confidence interval.

risk of hyperglycemia or diabetes mellitus. Even among the patients who received quetiapine, the cohort that had the lowest risk ratio of any of the antipsychotic cohorts, the likelihood of receiving a new prescription for antidiabetic treatment was seen to be nearly twice that of the general reference population of geriatric patients, whereas a greater than fourfold risk was seen among patients receiving thioridazine. In the middle of the spectrum of risk in our study were patients who received the remaining antipsychotics, consisting of, in descending order of risk, risperidone, olanzapine, and haloperidol. The results from the clozapine cohorts were inconclusive as a result of the considerably lower numbers of patients involved, which prevented a reliable assessment of clozapine's relative risk.

Further analysis of risk among the atypical antipsychotic cohorts, using the haloperidol cohort as the reference population, appeared to corroborate this relative order of risk, because quetiapine was uniquely found to have a significantly lower risk relative to the haloperidol cohort among younger patients (aged 60–74), whereas the risperidone cohort was uniquely found to have a significantly higher risk both overall and among the older patients (aged 75+). However, it is possible that this latter finding is simply a reflection of the substantially larger size of the patient cohort. In this analysis, the risk of diabetes in the olanzapine cohort was not significantly different from that of patients treated with haloperidol.

This, in itself, is a noteworthy finding, because studies have reported an increased risk of diabetes^{24,25} or glucose dysregulation²⁶ in patients treated with olanzapine compared with patients treated with haloperidol or other conventional antipsychotics. Clozapine had the highest risk ratio in the subgroup of patients aged 75 and older, on the order of nearly six times that of the reference population. However, the findings for clozapine throughout the rest of this analysis were inconclusive as a result of the small size of the clozapine cohort and low number of prescriptions for antihyperglycemic medications that were reported.

The prevalence of diabetes has been reported to be two to four times greater in patients with schizophrenia than in the general population,²⁷ and numerous analyses have concluded that patients with schizophrenia who receive antipsychotics, particularly the atypical antipsychotics, could have an increased risk of hyperglycemia.^{17,28,29} For example, outpatients with schizophrenia who received atypical antipsychotics were, as a whole, 9% more likely to have an International Classification of Diseases, 9th revision, diagnosis of diabetes than those receiving conventional antipsychotics.²⁵ Moreover, patients receiving treatment with clozapine, olanzapine, or quetiapine have been reported to have significantly higher prevalences of diabetes relative to those receiving conventional antipsychotics, whereas patients receiving risperidone did not.²⁵ Glucose tolerance tests, too, have shown that

patients receiving clozapine, olanzapine, or risperidone could have higher plasma glucose levels than patients receiving haloperidol or chlorpromazine.²⁶ As a consequence, differences in diabetes medication prescription rates in this study could be the result of differences in the characteristics of the populations for which the antipsychotics were prescribed, for example, differences in the percentage of patients with schizophrenia or dementia.

Large-scale studies of the hypothesized link between diabetes and antipsychotic use have until recently been lacking. Many analyses that have been reported have relied on isolated case reports that are lacking matched controls of healthy subjects from the general population.^{18,30-33} Such results have been largely inconclusive as a result of various methodologic limitations, and causality remains an issue. Previous analyses of information from claims databases typically have merely examined the overall incidence of diabetes, rather than the onset of new diagnoses of diabetes,²⁵ or have omitted use of a reference cohort of patients not receiving antipsychotics.³⁴ For their part, tests of glucose metabolism in patients receiving antipsychotics have typically used healthy, untreated control subjects but no healthy subjects exposed acutely to antipsychotics,³⁵ which might have provided information regarding the effect of the treatment itself rather than simply about differences between the patients being tested. Some have interpreted these results as indicative that antipsychotics themselves could induce hyperglycemia either through direct effects on pancreatic mechanisms³⁶ or secondarily through induction of body weight increases.³⁷ With respect to the latter, nearly all of the atypical antipsychotics have been reported to be associated with increased appetite and weight gain.³⁸ This appears to be an unlikely explanation of the changes occurring in the present analysis, because the incidence of weight gain in response to antipsychotic treatment among elderly patients, particularly those with dementia, tends to be overshadowed by a greater incidence of weight loss.^{39,40} Moreover, weight gain is more highly associated with use of the atypical antipsychotics, whereas increased risk of hyperglycemia was also seen in the current analysis among patients receiving conventional antipsychotics. On the other hand, others have proposed that antipsychotics could merely exacerbate an underlying predisposition to diabetes in patients with schizophrenia⁴¹; alternatively, the use of antipsychotics could be entirely coincidental to a preexisting comorbidity for diabetes among the schizophrenic population.^{22,42} The association between schizophrenia and diabetes was reported as early as the 1920s,⁴³ well before the development of modern antipsychotic medications, and it has been suggested that schizophrenia is itself the clinical manifestation of a metabolic disorder that can be thought of as "cerebral diabetes."⁴⁴ On the other hand, although there could be an association between the clinical condition of schizophrenia and risk of diabetes, the contribution of any schizophrenia-linked predisposition to hyperglycemia in the current analysis was likely to have been minimal, because neuroleptics are more frequently prescribed to the elderly for agitation or psychosis associated with dementia, not for schizophrenia.⁹ Unfortunately, important information on patients' baseline glucose

levels, underlying comorbidities, and risk factors was not available. As a result, the contribution of patients' preexisting conditions to the observed increases in the incidence of antihyperglycemic prescriptions is not known, and caution should certainly be exercised in equating "new" prescriptions for antihyperglycemic medications with the appearance of new-onset diabetes.

These findings extend the recent work of Buse and coworkers,²¹ who reported the results of an analysis from the AdvancePCS database, of which the present results represent a subset. Their analysis involved 58,751 patients aged 18 and older who had received prescriptions for antipsychotics. The results of the present analysis largely reflect their findings in the broader patient population,²¹ with higher risks occurring during treatment with all antipsychotics relative to the reference population but no difference in risk between conventional and atypical antipsychotics. Risk ratios for the various cohorts were quite similar between the two analyses, despite the differences in patient ages. Both studies showed the highest risk to be found in the thioridazine cohort and the lowest in the quetiapine cohort. One notable difference, however, was the finding by Buse that patients aged 65+ who received atypical antipsychotics had higher risks of diabetes than did patients aged 45 to 64, implying that, at least among patients receiving atypical agents, increasing age could be a risk factor for diabetes. By contrast, the present analysis showed that, for haloperidol and risperidone, the confidence intervals were in fact lower among patients aged ≥ 75 years than among those aged 60 to 74 years. It would appear, then, that any age-related increase in risk could have already reached a maximum by the time patients had entered their seventh decade of life. Alternatively, it could be that the older patients, having received considerably lower doses of antipsychotic, could merely have been exposed to a correspondingly lower risk of pharmacologically induced hyperglycemia. Both of these possibilities are, of course, entirely speculative. However, this latter hypothesis seems less likely, because weight increase with olanzapine and risperidone treatment appears uncorrelated with dose.⁴⁵ Moreover, hyperglycemic and euglycemic clamp studies failed to show a direct effect of risperidone or olanzapine on insulin production and/or sensitivity. Finally, it is likely that there are differences in the diagnostic mix of the two age groups, with the younger group containing a higher percentage of patients with schizophrenia and the older group containing a higher percentage of patients with dementia. Eventual differences in diabetes risk between these diagnostic groups could explain the differences between the two age groups.

A number of limitations of this analysis warrant mention. For example, no psychiatric diagnostic data were available, and no assessment was possible to determine the confounding effects of other nonantipsychotic drugs that could have hyperglycemic potential such as beta-adrenergic antagonists, thiazide diuretics, corticosteroids, or protease inhibitors.⁴⁶ In addition, no data were available on patients' baseline body mass index or family histories of diabetes, which might have provided crucial information regarding preexisting risk, and patients were not systematically randomized to their drug

cohort; rather, assignments were made based on the clinical choices of attending physicians. Finally, treatment exposures were of limited duration, lasting for the most part for just 2½ to 3 months. These relatively short treatment-exposure periods may not have been sufficient to fully evaluate potential treatment effects, although some reports have suggested that the majority of cases of new-onset diabetes incurred during treatment with antipsychotics occur within 3 to 6 months.^{32,47,48} The short period in which an acute need for antihyperglycemic medications does appear to increase in the present analysis is therefore somewhat surprising. One explanation could be that the development of hyperglycemia is not entirely the result of the administration of antipsychotic agents, but could in fact be the result of a threshold effect in an already impaired patient population. Possibly ameliorating some of the concerns over the limitations of this analysis is the fact that it involved nearly 31,000 antipsychotic-treated patients and a control population of nearly two million patients, and it might therefore be reasonably expected that, with such a large sample, a fair degree of balancing took place between drug cohorts for such possible risk factors as obesity, family histories of diabetes, and the relative proportions of the different conditions for which these medications were being prescribed.

CONCLUSION

These data indicate that the incidence of new cases of diabetes could be higher among elderly patients who receive prescriptions for antipsychotic medications than among those not receiving antipsychotics. The risk of developing diabetes was highest overall for patients treated with thioridazine. Risk in the overall atypical antipsychotic cohort was not significantly higher than that for the overall conventional antipsychotic cohort. Among the individual atypical antipsychotic cohorts, the risperidone group's risk uniquely was significantly higher than haloperidol's. In conclusion, the risk of diabetes could be higher for patients using any antipsychotic, and clinicians must be cognizant of it, regardless of the antipsychotic selected.

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to 4 days following the transition from the IM to the oral formulation, olanzapine is comparable to the typical antipsychotic haloperidol in sustaining alleviation of agitation, with a more favorable safety profile.

METHODS: Acutely agitated inpatients with schizophrenia who had been treated with IM olanzapine (n=122) or IM haloperidol (n=116) over a 24-hour period were entered into a 4-day oral treatment period with the same medication (5 to 20 mg/day). Baseline to endpoint change on the PANSS-EC was the primary efficacy measurement. Safety was assessed by collecting adverse events, baseline to endpoint change and treatment-emergent extrapyramidal symptoms, anticholinergic use, and ECG QTc interval changes.

RESULTS: Significant and similar baseline to endpoint reductions in agitation were observed for IM olanzapine and IM haloperidol during the 24-hour IM period on the PANSS-EC. Continued PANSS-EC score improvement was observed over the 4-day oral period for both treatment groups, with no significant between-group difference. Significantly more oral haloperidol-treated patients spontaneously reported treatment-emergent acute dysonia, extrapyramidal syndrome, and akathisia compared with oral olanzapine-treated patients. There were no significant between-group differences in baseline to endpoint EPS change. Criteria for akathisia was met significantly more for oral haloperidol than oral olanzapine, and significantly more haloperidol patients used anticholinergic medications. There were no between-group significant differences in QTc interval changes.

CONCLUSIONS: IM olanzapine and IM haloperidol effectively reduced acute agitation in schizophrenia over 24 hours. The reduction in agitation was sustained for up to 4 days following the transition to oral therapy with both olanzapine and haloperidol. During the oral treatment period, olanzapine demonstrated a more favorable safety profile than haloperidol.

247E. Nizatidine may ameliorate weight gain during olanzapine treatment. Alan Breier, M.D., Yoko Tanaka Ph.D., Suraj Roychowdhury Ph.D., W. Scott Clark, Ph.D., Virginia L. Stauffer, Pharm.D.; Eli Lilly and Company, Indianapolis, IN.

Presented at the Annual Meeting of the College of Psychiatric and Neurologic Pharmacists, San Antonio, TX, March 24-27, 2001.

248E. A pharmacoepidemiological study of diabetes mellitus and antipsychotic treatment in the United States. Patricia Cavazzoni, M.D., Kenneth Kwong, M.D., Kenneth Hornbuckle, Ph.D., David Hutcheson, MHA, Lois Jovanovic, M.D., John Buse, M.D., Ph.D., Angela Hill, Pharm.D.; Eli Lilly and Company, Indianapolis, IN; University of Ottawa, Ottawa, ON, Canada; Advance PCS, Scottsdale, AZ; Sansum Medical Research Institute, Santa Barbara, CA; University of North Carolina, Chapel Hill, NC.

Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

249. Use of atypical antipsychotics and the incidence of diabetes: evidence from a claims database. Maureen J. Lage, Ph.D., Jason E. Kemner, MPH, Angela Hill, Pharm.D.; Eli Lilly and Company, Indianapolis, IN.

OBJECTIVE: Compare the incidence of diabetes between patients initiating treatment with typical or atypical antipsychotics.

METHODS: Retrospective analysis of the IMS LifeLinkTM claims database identified 6,758 enrollees with the following characteristics: (1) age 18-65; (2) initiated on typical (n=3,381) or atypical (n=3,377) between October 1996 and December 1998; (3) no use of antipsychotics for six months prior initiation; (4) not classified as diabetic (i.e. no diagnosis of diabetes or receipt of any diabetic medication for one year prior initiation).

Logistic regressions were used to estimate odds ratios (OR) of a diagnosis of diabetes or use of any diabetic medication in the one year post-initiation, controlling for age, gender, and regional differences.

RESULTS: Higher probability of becoming diabetic was not evident following initiation on atypicals (mean duration of therapy 135 days) compared to typicals (mean duration of therapy 84 days; OR=1.032; p=0.825) or initiation on olanzapine (OLZ) or risperidone (RIS) compared to typicals (OR=0.977, 1.170; p=0.899, 0.35, respectively). The probability of developing diabetes was less in patients treated with OLZ (mean dose 9.01 mg/day) than in patients treated with RIS (mean dose 2.37 mg/day; OR=0.834; p=0.277), although the difference was not statistically significant.

CONCLUSION: The probability of developing diabetes was no more likely following treatment with atypicals than typicals. Within atypical use, the probability of developing diabetes was less during treatment with OLZ than with RIS, although the difference was not statistically significant.

250. Concomitant use of antipsychotics and cytochrome P450 3A4-metabolized medications in the treatment of schizophrenia. Iluyi Ascher-Svanum, Ph.D., John S. Kennedy, M.D., David Lee, Ph.D., Merle Haberman, MHA, Shonda Fuster, Pharm.D.; Eli Lilly and Company, Indianapolis, IN; Carenmark/Proctor Sciences, Herndon, VA.

PURPOSE: Antipsychotics are extensively metabolized by cytochrome P450 enzymes, thus establishing the potential for pharmacokinetic drug-drug interaction when coadministered with other drugs. The purpose of this analysis was to assess the prevalence and utilization pattern of concomitant

CYP3A4-metabolism inhibiting medications in schizophrenia patients who were treated with antipsychotics.

METHODS: This retrospective cohort study is based on proprietary managed care claims database representing a large, geographically diverse US population. Health care administrative claims, covering 1-year period (1999), were used to identify schizophrenia patients (n=1938) who were treated with antipsychotics and co-prescribed medications that were CYP3A4 inhibitors.

RESULTS: 26% of the patients experienced concomitant use of at least one CYP3A4 inhibitor medication. Most (73%) of the concurrent inhibitors were confined to four drugs (fluoxetine, erythromycin, nefazodone and nifedipine). Utilization patterns differed across gender and age categories but were similar for patients treated with classical and novel antipsychotics.

CONCLUSIONS: One fourth of the schizophrenia patients in this study used concomitant CYP3A4 inhibitor medications and antipsychotic drugs. A number of atypical antipsychotics (e.g., ziprasidone, quetiapine) are dependent for clearance upon metabolism by CYP3A4 enzymes. The combined therapies of such antipsychotics with CYP3A4 inhibitors could alter their pharmacological effects and potentially lead to various adverse effects. Further studies are needed to determine whether dosing antipsychotic medications that are metabolized by the CYP3A4 enzyme will require added monitoring and slow titration in order to minimize potential adverse drug-drug interactions when concurrent CYP3A4 inhibitors are present.

251E. The Texas Medication Algorithm Project (TMAP): outcomes for persons with major depressive disorder. M. Lynn Crismon, Pharm.D., Madhukar H. Trivedi, M.D., A. John Rush, M.D., T. Michael Kashner, Ph.D., Marcia C. Toprac, Ph.D., Melanie M. Biggs, M.D., Kathy Shores-Wilson, Ph.D., Thomas J. Carwoody, Ph.D., Steven P. Shoa, M.D.; University of Texas, Austin, TX; University of Texas Southwestern Medical Center, Dallas, TX; Texas Department of Mental Health and Mental Retardation, Austin, TX.

Presented at the 39th Annual Meeting of the American College of Neuropsychopharmacology San Juan, Puerto Rico, December 12, 2000.

252E. A comparison of expenditures by indigent patients continuously treated with atypical antipsychotic agents within a behavioral health organization in Texas. Michael R. Johnson, Ph.D., M. Lynn Crismon, Pharm.D., Ann Thompson, MBA, BSN, Amy Grogg, Pharm.D.; The University of Texas at Austin, Austin, TX; Janssen Pharmaceutica, Titusville, NJ.

Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

253. Increased lithium dose requirement in patient with hyperglycemia. Monika Cyr, Pharm.D., Melanie Guin, M.D., S. Casey Lainez, Pharm.D.; Lakeland Regional Medical Center, Lakeland, FL; VAMC, Memphis, TN; University of Tennessee, Memphis, TN.

PURPOSE: Lithium is filtered by the kidneys and reabsorbed exclusively in the proximal tubule. Thus, drugs that affect proximal tubule fluid dynamics such as thiazide and osmotic diuretics will alter lithium renal clearance. The purpose of this case is to alert clinicians to the fact that hyperglycemic states can also alter proximal tubule fluid dynamics resulting in a change in the renal clearance of lithium.

METHODS: Data was collected from a persistently hyperglycemic patient in whom lithium plasma concentrations (C_{pl}) were low despite receiving doses that normally achieved therapeutic lithium plasma concentrations. The lithium doses, lithium plasma concentrations, and blood glucose concentrations occurring over a 56 day hospital admission were evaluated to determine if high blood glucose concentrations appeared to affect the lithium plasma concentration. The lithium dose required to increase the lithium plasma concentration by 0.1 mEq/L was calculated (LiDose_{0.1} = (0.1) (LiDose/C_{pl}). A linear regression was performed with LiDose_{0.1} as the dependent variable and blood glucose concentration as the independent variable.

Day	LiDose	C _{pl}	BGC	LiDose _{0.1}
8	900	0.30	255	300
16	1800	0.33	253	545
26	2400	1.03	250	233
32	2400	0.60	177	400
39	2400	1.16	106	188
43	2400	1.28	136	188
50	1800	0.90	263	200

RESULTS: Over the course of the patient's hospitalization 50 blood glucose concentrations and 8 lithium plasma concentrations were determined. The lithium dose was increased from 900 mg/day up to a maximum of 2400 mg/day. The table gives the lithium doses (LiDose) and blood glucose concentrations (BGC) associated with each of the 8 lithium plasma concentration determinations (C_{pl}) and the calculated lithium dose required to increase the plasma concentration by 0.1 mEq/L (LiDose_{0.1}). A linear regression of LiDose_{0.1} versus blood glucose concentration resulted in an r²=0.58.

CONCLUSIONS: Though there is a theoretical basis for hyperglycemia causing an increased renal clearance of lithium due to hyperglycemic-induced

Treatment Outcomes

No Significant Difference in Diabetes Risk During Treatment With Typical Versus Atypical Antipsychotics: Results From a Large Observational Study

David W. Lee, PhD, Robert B. Fowler, Pamela J. Kadlubeck, MPH, Merle Haberman, MHA

Case reports and other evidence have indicated a possible causal relationship between atypical antipsychotic agents and diabetes mellitus (DM). This study estimates the 1-year relative risk of DM onset for a large cohort of treatment-naïve patients who initiated therapy with any typical antipsychotic, any atypical antipsychotic, olanzapine, or risperidone. Data from a US MCO were used to select a cohort of nondiabetic patients aged 18 to 65 years who initiated typical or atypical antipsychotic therapy between September 30, 1997, and December 31, 1999 (N = 2315). Logistic regression was used to compare the odds of patients in selected antipsychotic treatment groups (atypical vs typical, olanzapine vs typical, risperidone vs typical, and olanzapine vs risperidone) developing DM in the year following initiation of therapy after controlling for age, sex, geographic region, mental health disorder, length of therapy, and hypertension/heart disease comorbidities.

Key words: Atypical antipsychotics • Diabetes mellitus • Olanzapine • Risperidone • Typical antipsychotics

Typical and atypical antipsychotic agents comprise the armamentarium for treating patients with schizophrenia.¹ Typical antipsychotics (eg, chlorpromazine, haloperidol) are older agents that primarily act by blocking dopamine receptors. Atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, and ziprasidone) are newer drugs that have a higher affinity for dopamine receptors.

Both typical and atypical antipsychotic agents are effective treatments of schizophrenia and are differentiated primarily by their safety profiles. Adverse events commonly reported to varying degrees during treatment with typical or atypical antipsychotics include sedation, postural hypotension, hyperprolactinemia, and a lowering of the seizure

threshold.² The primary differentiating features of atypical antipsychotics are that they have a more favorable extrapyramidal symptoms profile and are generally better tolerated than typical antipsychotics.

Atypical agents, however, have unique safety profiles that distinguish one from another. For example, clozapine has been associated with high rates of sedation, hypersalivation, and tachycardia. Weight gain has been associated with clozapine, olanzapine and, to a lesser extent, risperidone.²⁻⁴ Also, ziprasidone has been shown to prolong the QTc interval on ECG. This agent is contraindicated in patients who take other QTc-prolonging drugs, who have had a recent acute myocardial infarction, or who have uncompensated heart failure. Finally, clozapine,

Acknowledgment

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quetiapine, olanzapine, and ziprasidone generally are considered to be prolactin-sparing⁵; risperidone's association with prolactin appears to be dose-dependent.⁶

Some reports have suggested that diabetes mellitus (DM) may be an additional adverse effect of atypical antipsychotics.^{7,8} The relationship between atypicals and DM may be indirect. Certain atypicals have been associated with weight gain, and weight gain is a known risk factor for diabetes. Other research has suggested that atypicals may directly affect insulin levels.⁹⁻¹³

Numerous case reports of DM onset among patients who took atypical antipsychotics have been published, and several of these reports cite cases of DM or diabetic ketoacidosis with relatively quick onset (within 1 year) after initiation of atypical antipsychotic therapy.^{8,14-21} These case reports are difficult to interpret, however, because patients with schizophrenia are known to have an elevated risk of DM irrespective of medication use.²²⁻²⁶ In addition, case reports do not compare DM onset rates between patients taking typicals and atypicals or between atypical agents.

This study's purpose is to provide additional evidence on the 1-year relative risk of DM onset after initia-

Dr Lee is senior consultant, Mr Fowler and Ms Kadlubeck are consultants, and Ms Haberman is associate vice president for analytic and data operations, all at Protocare Sciences, Herndon, Va.

tion of therapy with selected antipsychotics. Specifically, medical claims data were used to compare the odds of developing DM in a large cohort of patients who initiated antipsychotic therapy with any atypical agent, with any atypical agent, or with the most commonly used atypical agents—olanzapine and risperidone.

Methods

Data were obtained from Protocare Sciences' database of administrative claims and enrollment information from a large MCO in the United States that provides services to approximately 3 million members each year. From these data, a cohort of treatment-naïve patients with no history of DM was created. Specifically, patients who filed a claim for either a typical or an atypical antipsychotic in the 27-month period between September 30, 1997, and December 31, 1999, were identified.

Using the date of the first antipsychotic prescription as the "index" date, we excluded those patients who filed a claim for an antipsychotic in the 180-day period before their index date; who were not continuously eligible for medical and pharmacy benefits for 365 days before and after their index date; who were not between the ages of 18 and 65 years (inclusive); and who filed a prescription for a diabetes medication or who had either a medical or facility claim with a diabetes diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 250.xx) in the 365 days before their index date. Patients who were prescribed multiple antipsychotics concomitantly on the index date were excluded. Patients who used multiple antipsychotic agents after their index date,

either concomitantly or consecutively, were included.

Separate logistic regression models were used to estimate odds ratios (ORs) for DM onset in the 365-day period on or after the index date for patients who initiated typical versus atypical; typical versus olanzapine; typical versus risperidone; and olanzapine versus risperidone. DM onset was considered to have occurred if a patient filed a claim for a diabetes medication in the 365-day period on or after their index date or if a patient had 2 medical or facility claims with a diabetes diagnosis on different dates of service in that same period.

Explanatory variables in the models included age and its square, sex, geographic region, mental health condition (schizophrenia [ICD-9-CM codes 295.xx], bipolar disorder [ICD-9-CM codes 296.4x or 296.8x], other depression [ICD-9-CM codes 296.2x to 296.23, 296.25, 296.26, 296.3x to 296.33, 296.35, 296.36, 300.4x, 309.0x, 309.1x, or 311.xx]), evidence of hypertension (ICD-9-CM codes 401.xx to 405.xx), evidence of heart disease (ICD-9-CM codes 410.xx to 414.xx or 420.xx to 429.xx), and length of antipsychotic therapy.

Evidence of hypertension and/or heart disease was identified by examining the diagnoses on medical or facility claims filed during the 27-month study period. Length of antipsychotic therapy was calculated as the total number of unique (non-overlapping) days supplied for all index drug prescriptions filled on or after the index date. Controls for duration of exposure to specific antipsychotics (ie, any typical, any atypical, olanzapine, or risperidone) were not included.

Parameter-estimate robustness was assessed by comparing the OR

estimates under separate analyses for those who did and those who did not use multiple antipsychotic agents in the postindex period. Results from these models are not reported because they did not materially affect the OR estimate. All analyses and estimates were performed using SAS version 8.1 software.

Results

Descriptive statistics for the 2315 patients who met the inclusion criteria are reported in Table 1. There were 981 patients (42.4%) who started therapy with typicals, and 1334 (57.6%) who started therapy with atypicals. Among the atypical group, 513 patients (38.5%) initiated therapy with olanzapine and 750 (56.2%) initiated therapy with risperidone. Of the remaining 71 patients (5.3%) who took atypical antipsychotic agents, 5 (0.4%) started therapy with clozapine and 66 (4.9%) started therapy with quetiapine. Seventy-nine percent of patients were only prescribed the index antipsychotic during the study period.

Patients initially prescribed atypicals were significantly younger, more likely to be female, and more likely to have a diagnosis of depression or bipolar disorder than patients initially prescribed typical antipsychotic drugs. Length of therapy in the atypical group was longer than that for patients in the typical group (126.10 days vs 108.34 days, respectively; $P < .0001$). Hypertension ($P = .0192$) and heart disease ($P = .0097$) were significantly less likely to occur among patients in the atypical treatment group compared with those in the typical treatment group. Statistically significant differences in the number of patients taking antipsychotic agents in the East North Central region compared

Treatment Outcomes

with the Mountain/Pacific region were also observed ($P = .0002$ and $P = .0075$, respectively).

Patients in the olanzapine and risperidone groups differed in the number of patients who had bipolar disorder and in their regional composition. Specifically, 18.32% of olanzapine patients were bipolar, compared with 12.67% of risperidone

patients ($P = .0056$). Risperidone patients were significantly more likely to be from the East Coast than olanzapine patients ($P = .0068$). Patients taking olanzapine were significantly more likely than patients taking risperidone to be located in the West North Central ($P < .0001$) and East South Central ($P < .0001$) regions.

Table 1 also compares the per-

centages of patients in each group who experienced DM onset in the 365-day period following initiation of antipsychotic therapy. The 1-year rate of DM onset for patients in the atypical group (3.00%) was nearly identical to the rate observed in the typical group (3.16%) ($P = .8237$). The unadjusted 1-year rates of DM onset between the olanzapine

Table 1
Characteristics of Study Participants

Variable	Atypical vs Typical				Olanzapine vs Risperidone		
	Total	Atypical	Typical	P Value	Olanzapine	Risperidone	P Value
Sample size	2315	1334	981	N/A	513	750	N/A
DM onset after 1 y	3.07%	3.00%	3.16%	.8237	2.53%	3.33%	.4142
Mean age	44.05 y	42.37 y	46.34 y	<.0001	42.19 y	42.65 y	.4795
Male sex	41.38%	38.46%	45.36%	.0009	38.21%	38.80%	.8315
Length of therapy	118.57 d	126.10 d	108.34 d	<.0001	126.83 d	123.94 d	.6368
Psychiatric Diagnosis							
Schizophrenia	14.69%	14.99%	14.27%	.6280	15.79%	14.40%	.4866
Bipolar disorder	12.35%	15.74%	8.56%	<.0001	18.32%	12.67%	.0056
Depression	45.27%	52.17%	35.88%	<.0001	54.78%	40.67%	.0864
Comorbid Condition							
Hypertension	22.04%	25.19%	20.56%	.0192	26.12%	25.07%	.6725
Heart disease	16.24%	14.54%	18.88%	.0097	12.67%	16.73%	.1288
Region							
East Coast	33.65%	32.48%	35.27%	.1572	28.46%	35.73%	.0068
East North Central	25.96%	28.86%	22.02%	.0002	25.73%	30.87%	.0568
West North Central	6.35%	5.85%	7.03%	.2473	9.16%	3.80%	.0001
East South Central	13.17%	13.79%	12.83%	.3051	20.47%	8.53%	<.0001
West South Central	16.46%	17.32%	16.88%	.1161	15.01%	19.60%	.0380
Mountain/Pacific	2.46%	1.72%	3.47%	.0075	1.17%	1.87%	.3298

N/A, not applicable; DM, diabetes mellitus.

Table 2
Odds Ratios for Comparison Groups

Group	Sample Size	Odds Ratio	95% Confidence Interval	P Value
Atypical vs Typical	2315	1.010	0.612-1.668	.9685
Olanzapine vs Typical	1494	0.864	0.437-1.732	.6796
Risperidone vs Typical	1731	1.074	0.612-1.885	.8024
Olanzapine vs Risperidone	1263	0.788	0.384-1.610	.5109

(2.53%) and risperidone (3.33%) treatment groups were also similar ($P = .4142$).

Table 2 presents ORs, and Table 3 lists logistic regression parameter estimates. The results show that the risk of diabetes onset was statistically indistinguishable between patients who started therapy with any atypical agent compared with any typical agent; olanzapine compared with any typical agent; risperidone compared with any typical agent; and olanzapine compared with risperidone.

Statistically significant covariates in the atypical versus typical group included bipolar disorder, length of therapy, hypertension, heart disease, and location in the West South Central region. Specifically, patients with bipolar disorder had a lower risk of DM onset ($P = .0425$), as did patients in the West South Central region ($P = .0371$). Length of therapy ($P = .0019$), hypertension ($P = .0116$), and heart disease ($P = .0453$) were each positively associated with DM risk. None of the covariates in the model comparing olanzapine with all typical antipsychotics were statistically significant. Length of therapy ($P = .0013$) and West South Central region ($P = .0181$) were the only statistically significant covariates in the model comparing risperidone with all typ-

ical antipsychotics. Finally, length of therapy ($P = .0219$), hypertension ($P = .0048$), and heart disease ($P = .0058$) were positively associated with DM risk in the model comparing olanzapine with risperidone.

Discussion

This study found no detectable difference in the 1-year risk of DM onset among patients who initiated atypical antipsychotic therapy compared with those who initiated therapy with typical antipsychotics. Furthermore, no differences in the 1-year risk of DM onset were found between patients who initiated therapy with olanzapine versus any typical antipsychotic, risperidone versus any typical antipsychotic, or olanzapine versus risperidone.

Two other published studies utilized medical claims data to investigate differences in risk of DM onset between typical and atypical antipsychotics. The first study employed the same cohort design used in this study and found no significant difference in the risk of diabetes onset for patients treated with clozapine compared with those treated with typical antipsychotics.²⁷ The second study used a cross-sectional design to compare diabetes prevalence rates between patients who took typical and atypical antipsychotics.²⁸ The

second study found diabetes to be more prevalent among patients younger than 60 years who took atypical antipsychotics compared with those who took typical antipsychotics. Results from the second study and those reported here are not directly comparable, however, because the second study evaluated prevalence and did not allow for a temporal association between exposure to an antipsychotic agent and DM.

Two factors may reconcile our finding of no increased risk of DM onset between atypical and typical antipsychotics with case reports suggesting that atypical antipsychotics are linked to increased risk of DM. First, case reports do not compare the risk of one treatment with that of another. Instead, they focus on an event in 1 person temporally associated with the use of a given medication. Second, length of therapy was found to be strongly correlated with DM onset. Because therapy was longer for patients in the atypical antipsychotic group, case reports of DM among patients taking atypical antipsychotics may be reflecting duration of exposure rather than an inherent difference in the risk of DM from treatment with atypical versus typical antipsychotics. Patients with longer therapy durations may also

Treatment Outcomes

Variable	Atypical vs Typical			Diazepam vs Typical			Estimate
	Estimate	SE	P Value	Estimate	SE	P Value	
Intercept	6.045	1.871	.0012	5.982	2.353	.0227	7.000
Atypical	0.010	0.256	.9685	N/A	N/A	N/A	N/A
Olanzapine	N/A	N/A	N/A	-0.147	0.255	.5798	N/A
Risperidone	N/A	N/A	N/A	N/A	N/A	N/A	0.0722
Male Sex	0.053	0.232	.8158	0.333	0.216	.1144	0.040
Age	-0.069	0.084	.4282	-0.062	0.103	.5555	-0.134
Age Squared	-0.001	0.001	.3187	-0.001	0.001	.6982	-0.001
Schizophrenia	0.339	0.814	.6815	0.049	0.258	.9142	0.0567
Bipolar Disorder	-1.221	0.603	.0425	-1.033	0.743	.1641	-1.231
Depression	-0.101	0.263	.7010	-0.208	0.837	.8382	-0.155
Length of Therapy	0.003	0.001	.0019	0.002	0.001	.1704	0.004
Hypertension	0.888	0.273	.0016	0.598	0.347	.0958	0.560
Heart Disease	0.580	0.230	.0459	0.269	0.382	.4820	0.394
East North Central	0.330	0.318	.2711	0.771	0.480	.1084	0.398
West North Central	-0.288	0.500	.5675	-0.023	0.525	.9632	-0.943
East South Central	0.190	0.337	.5817	-0.016	0.448	.9708	-0.187
West South Central	0.888	0.425	.0371	-0.721	0.61	.1580	-1.167
Mountain/Pacific	-0.042	0.751	.9550	0.338	0.49	.7047	0.097
N/A not applicable							

have had more physician contact and, as a result, were more likely to have had DM detected or an adverse event report filed.

These findings should be interpreted in the context of the limitations of the study. First, the results may not be generalizable to the US population overall because they are based on a nonrandom sample. Second, the administrative claims data-

base and, hence, the logistic regression models lack certain variables that are well-known risk factors for DM (eg, family history, ethnicity, and weight). The results presented here are biased to the extent that these missing variables are correlated with therapy choice.

Also, the study did not directly control for specific antipsychotic exposure. Rather, it used an intent-to-

treat methodology and controlled for overall duration of the index antipsychotic therapy. However, more than three fourths of this sample had exposure to only the 1 index antipsychotic agent during the 1-year follow-up, and diabetes onset was tracked over a 1-year period irrespective of duration of index antipsychotic treatment or whether the antipsychotic agent was changed

during the study. This limitation for controlled with risk of possible bias by index risk for more than at

Treatment Outcomes

Risperidone vs. Typical			Olanzapine vs. Risperidone		
P Value	Estimate	SE	P Value	Estimate	SE
0.027	-7.000	2.335	0.027	-5.120	1.2272
N/A	N/A	N/A	N/A	N/A	N/A
0.796	N/A	N/A	N/A	0.240	0.366
N/A	0.072	0.287	0.023	N/A	N/A
0.214	0.040	0.285	0.887	0.344	0.364
0.555	0.134	0.103	0.831	0.040	0.104
0.982	0.001	0.081	0.210	0.000	0.001
0.142	0.367	0.455	0.039	0.473	0.491
0.164	-1.231	0.736	0.947	1.189	0.751
0.564	0.155	0.297	0.025	0.276	0.355
0.704	0.004	0.001	0.012	0.003	0.002
0.856	0.560	0.310	0.710	1.077	0.382
0.820	0.384	0.305	0.240	1.067	0.387
0.1084	0.398	0.350	0.2546	0.159	0.402
0.9652	-0.943	0.753	0.2104	0.449	0.679
0.3708	0.187	0.474	0.8331	0.779	0.766
0.1586	-1.187	0.494	0.0181	-0.573	0.678
0.7047	0.097	0.760	0.8987	0.685	1.097

controlled during the follow-up period. Another limitation was that the time frame for conducting the analysis coincided with concerns about the potential risk of atypical antipsychotics. It is possible, therefore, that the results are biased because of confounding by indication—that is, patients at risk for diabetes may have been more likely to receive typical rather than atypical antipsychotics. This

may have been counterbalanced, however, by patients who were prescribed atypical antipsychotics having been screened more frequently for diabetes.

These limitations notwithstanding, however, this study does provide important new evidence regarding medication selection. It suggests that concerns about diabetes should not be an important differen-

tial in choosing between atypical or typical antipsychotic therapy, or specifically between olanzapine and risperidone. □

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Risk of Diabetes in Medi-Cal Patients Prescribed Atypical Antipsychotics

Amy Grogg¹ PharmD, Jeffrey S. Markowitz² DrPH, Ramy Mahmoud¹ MD

¹Janssen Pharmaceuticals, Inc., L.P., Titusville, NJ; ²Health Data Analytics, Princeton, NJ

INTRODUCTION

- Diabetes and ketoacidosis are growing and under-investigated concerns with atypical antipsychotics
- Multiple case series¹⁻⁴ and large-scale epidemiological studies^{1,5,6} have consistently indicated that two atypical antipsychotics, clozapine and risperidone, are most commonly associated with the induction or exacerbation of type II diabetes and ketoacidosis
- Speculation about the mechanism of action of this effect is still unknown. However, one potential mechanism focuses on weight gain⁷⁻⁹ which is believed to be highest for clozapine and risperidone (relative to risperidone)¹⁰⁻¹²
 - Hypothetical: clozapine is a structural analog of dopamine*¹³
- We evaluate relative risk of new-onset diabetes for different serotonin-dopamine antagonists in a very large US Medicaid population

OBJECTIVES

- To determine rates and risk factors of new-onset diabetes in a Medicaid population of individuals taking three different atypical antipsychotics as monotherapy based on a large, administrative claims database

METHODS

- Retrospective cohort study (See Figure)
- Subjects included all California Medicaid patients under age 65 initiating monotherapy with risperidone (RIS), quetiapine (QUET) or olanzapine (OLZ) after 12/31/99
- Continuous enrollment in Medi-Cal for > 6 months prior to antipsychotic treatment
 - No diabetes > 3 months during this period

Observation Period

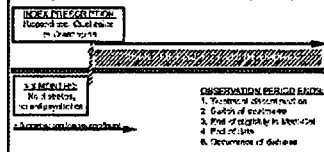
- Began with initiation of antipsychotic monotherapy
- Ended with first of any of the following:
 - Disenrollment from Medi-Cal
 - New onset diabetes (diagnostic claim or an antidiabetic prescription)
 - Antipsychotic treatment switch or discontinuation
 - End of the data
- Minimum two weeks in duration
- Occurrence of diabetes and possible risk factors examined*

*Diabetes (diagnostic claim or antidiabetic prescription) was used as the primary outcome measure

Outcome

- New-onset (incident) diabetes based on:
 - Diabetes-related ICD-9 diagnosis
 - Diabetes-related prescription (including insulin)

Figure: Retrospective Cohort Study Design



Other Potential Risk Factors

- Demographics (age, gender and race)
- Insurance: Drug Use (antipsychotics, antidepressants, mood stabilizers)
- Clinical: Hypertension, antipsychotic-related disorder, # of comorbid conditions based on Charlson Index¹⁴
- Antipsychotic dose
 - Within-subject average dose compared
 - Average dose standardized within each antipsychotic treatment
 - Three doses were combined into a single distribution

Statistical Analysis Plan

- Cohort rates of diabetes
 - Number of diabetes cases over number of subjects
- Incidence density rates
 - Number of diabetes cases over number of antipsychotic exposure days
- Unadjusted logistic regression predicting diabetes
- Adjusted multivariate logistic regression (saturated model) predicting diabetes

RESULTS

- Alpha level = 0.05 (2-tailed)
- Sample size (total n = 18,223)
 - 7,895 (43.8%), 1,578 (8.6%) and 8,550 (47.6%) RIS, QUET and OLZ respectively
- Background Variables (Table 1)
 - More than two-thirds were less than 45 years of age
 - About half were male and about half were Caucasian
 - More than half took antidepressants and more than 25% took mood stabilizers
 - > 10% had hypertension; about 16% had bipolar disorder

Table 1. Patient Characteristics

Variable	%	Variable	%
Treatment (within dose)		Antipsychotic Drug Use	
Risperidone (1-6 mg)	43.8%	Atypical	43.9%
Quetiapine (50-750 mg)	8.6%	Antidepressants	51.6%
Olanzapine (5-16 mg)	47.6%	Mood stabilizers	36.7%
Demographics		Clinical	
Age < 45 years	65.2%	Hypertension	22.0%
Female gender	40.1%	Bipolar Disorder	16.4%
Caucasian	47.7%	Atypical Antipsychotics	17.8%

Table 2. Rates and Risk Factors of Diabetes in Patients Taking Three Types of Antipsychotics

Variable	BIVARIATE RESULTS			MULTIVARIATE RESULTS	
	Incidence Rate*	Rate Ratio	95% Confidence Interval	Adjusted Odds Ratio	95% Confidence Interval
Treatment (Dose)		Index Reference		Group	
Risperidone	1.1%	1.0	(0.8, 1.2)		
Quetiapine	1.5%	0.9	(0.6, 1.4)	0.72	(0.46, 1.12)
Olanzapine	4.5%	1.5	(1.2, 1.9)*	1.30	(1.0, 1.62)*
Age		Index Reference		Group	
< 45 years	1.0%	1.0	(0.8, 1.2)		
45-64 years	5.8%	1.9	(1.7, 2.1)*	1.89	(1.36, 2.10)*
65-84 years	1.2%	1.2	(0.8, 1.8)		
Gender		Index Reference		Group	
Male	1.2%	1.0	(0.8, 1.2)		
Female	4.3%	1.3	(1.0, 1.8)*	1.04	(0.85, 1.28)
Race		Index Reference		Group	
Caucasian	1.1%	1.0	(0.9, 1.1)		
Black	4.7%	1.9	(1.7, 2.1)*	1.22	(0.90, 1.63)
Other	4.6%	1.4	(1.0, 1.9)*	1.40	(1.12, 1.76)*
Diabetes		Index Reference		Group	
Yes	1.0%	1.0	(0.8, 1.3)		
No	1.6%	1.6	(1.4, 1.8)*	1.03	(0.79, 1.33)
Insurance Status		Index Reference		Group	
Medicaid	4.3%	1.2	(1.0, 1.5)*		
Non-Medicaid	1.7%	1.0	(0.8, 1.2)	1.28	(1.03, 1.59)*
Mood Stabilizers		Index Reference		Group	
Yes	4.1%	1.7	(1.5, 1.9)*		
No	2.7%	1.0	(0.8, 1.2)	1.35	(1.07, 1.70)*
Hypertension		Index Reference		Group	
Yes	0.1%	1.6	(1.2, 1.8)*		
No	1.5%	1.0	(0.8, 1.2)	2.51	(1.92, 3.33)*
Risperidone (within dose)		Index Reference		Group	
Bipolar	4.3%	1.7	(1.5, 1.9)*		
Major Depressive	1.5%	1.1	(0.8, 1.5)	1.20	(0.91, 1.59)
Major Anxiety	4.6%	1.4	(1.0, 1.9)*	1.32	(0.83, 2.13)
Other Disorders	1.9%	1.2	(0.8, 1.8)		
Comorbidities		Index Reference		Group	
Low comorbidity	1.1%	1.0	(0.8, 1.2)		
Medium comorbidity	4.2%	1.3	(1.0, 1.7)*	1.50	(1.19, 2.05)*
High comorbidity	5.3%	1.6	(1.4, 1.9)*	2.30	(1.58, 3.34)*
Antipsychotic Dose		Index Reference		Group	
Low dose	1.2%	1.0	(0.8, 1.2)		
Medium dose	2.2%	1.9	(1.7, 2.1)*	1.44	(1.09, 1.89)*
High dose	4.4%	1.2	(0.9, 1.6)	2.00	(1.54, 2.60)*

*Significant difference between treatment groups (p < 0.05) based on multivariate logistic regression. All other risk factors were included in the model. Incidence rates are per 100 person-years.

The following results are shown in Table 2:

- Incidence Rates of Diabetes**
 - Cohort Rates: 1.80%, 1.52%, and 2.82% for RIS, QUET and OLZ respectively
 - Incidence Density Rates Per Year of Exposure: 3.15%, 3.04%, and 4.74% for RIS, QUET and OLZ respectively
- Risk Ratios (Table 2)**
 - Unadjusted Odds Ratios (95% Confidence Intervals)
 - QUET vs RIS = 0.67 (0.63, 1.49)
 - OLZ vs RIS = 1.50 (1.22, 1.86)
 - Adjusted Odds Ratios (95% Confidence Intervals)
 - QUET vs RIS = 0.72 (0.46, 1.12)
 - OLZ vs RIS = 1.30 (1.05, 1.62)
- Significant Multivariate Risk Factors for Diabetes**
 - Age 45-64 years (index = 1.0), other race (index = white) antidepressants, mood stabilizers, hypertension, one comorbidity, comorbidities, medium antipsychotic dose, high antipsychotic dose (index = low dose)

CONCLUSIONS

- Rates of diabetes were significantly higher for subjects prescribed olanzapine compared to risperidone
- No significant differences were observed in rates of diabetes between quetiapine and risperidone
- Diabetes was also associated with higher doses, mood stabilizer use, and both psychiatric & medical comorbidity
- Clinicians should exercise caution in prescribing olanzapine to patients with pre-existing diabetes and to individuals with strong family histories

LIMITATIONS

- No data on weight gain
- Relatively small number of subjects taking quetiapine not all potential confounding variables were measured
- Effects of monotherapy only were assessed
- Family histories of subjects unknown

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ICGP Abstracts 2002

treatment on wandering, and the impact of wandering on the risk reduction for falls.

Results: Of 625 patients who participated in the trial, 537 (86%) were ambulatory (placebo $n = 139$, RIS 0.5 mg $n = 133$, RIS 1 mg $n = 126$, RIS 2 mg $n = 139$). Of those, 109 patients (20.3%) fell during the trial. The RIS 1-mg group showed statistically significant lower rate of falls than placebo (12.7% vs. 22.3%; $p = .04$). Fall rates for the RIS 0.5-mg group (18.0%) and RIS 2-mg group (27.3%) were not significantly different from placebo. Eight fractures occurred; none in patients receiving the 1-mg dose. Among behavioral symptoms, only wandering was associated with an increased risk of falls. Of the 393 patients who had a wandering score > 0 at baseline, 83 (21.1%) fell. Among these patients, RIS 1 mg significantly reduced the wandering score by 1 point ($p < .01$ versus placebo and led to an even larger reduction in risk for falls (Hazard ratio = 0.36; $p = .01$). Among 205 patients at the highest 2 wandering levels at baseline, RIS 1 mg was associated with approximately a 70% reduction in risk for falls compared to placebo (Hazard ratio = 0.28; $p < .01$).

Conclusions: Risperidone titrated to a dose of 1 mg per day reduces the risk of falls in ambulatory patients with behavioral disturbances due to dementia. This effect is especially important in patients who exhibit wandering, where the magnitude of risk reduction increases with the severity of wandering. This result has important quality of life and economic implications, as falls are resource intensive and one of the leading causes of injuries and accidental death in the elderly.

The Effect of Olanzapine on ADAS-COG Performance in Mild Alzheimer's Disease Without Psychosis or Behavioral Disorders

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Introduction: Olanzapine 5 mg per day has been previously reported to nonsignificantly improve ADAS-COG-assessed cognitive performance in Alzheimer's disease patients with psychosis and agitation/aggression (Kennedy JS et al., 2001). We report the effect of olanzapine in patients with baseline Mini-Mental State Examination (MMSE) scores of 23 to 26 from a randomized, prospective 24-week placebo-controlled study to determine if olanzapine would improve cognition in this mildly impaired subgroup or more impaired patients.

Method: Patients diagnosed with NINCDS-Research Criteria. Alzheimer's disease without psychosis or behavior disorder ($N = 268$; entry MMSE 14-26) were randomized in a 2:1 ratio to olanzapine (2.5 mg for 2 weeks then a fixed dose of 5 mg for the remainder of the study) or placebo for a 24-week study. ADAS-COG and CIBIC-plus assessments occurred at baseline, week 12, and week 24. A subgroup of patients with mild cognitive impairment (olanzapine $n = 78$ and placebo $n = 43$) was also examined.

Results: In the overall study, olanzapine produced a mild but statistically significant decline in ADAS-COG performance compared with placebo at week 24: ADAS-COG placebo worsening 1.39 points, olanzapine ADAS-COG worsening 4.07 points ($p = .004$). Examining the CIBIC-plus, differences between placebo and olanzapine were not significant at week 12 or week 24. In the subgroup with MMSE scores of 23 to 26, mean ADAS-COG scores improved 0.68 points at week 12 and 1.27 points at week 24 for placebo patients and worsened 0.15 points at week 12 and 0.36 point at week 24 for olanzapine patients. Means were not significantly different between therapies and did not significantly differ from baseline scores.

Conclusion: We do not understand the reason underlying the worsening of ADAS-COG scores in the olanzapine group. Olanzapine

was initially suggested to have potent anticholinergic activity. The results of this study, in a population understood to be very sensitive to the adverse effects of anticholinergic medications, suggest that olanzapine has little if any anticholinergic effects *in vivo*. The improvement observed in the placebo group over this 24-week study is similar to that reported for some medications that act as acetylcholinesterase inhibitors. Most of the patients who entered this study were defined by the investigators as resistant to any beneficial effects of such medication therapy.

Funding provided by Eli Lilly and Company.

The Use of Antipsychotics and the Incidence of Diabetes in a Geriatric Population: Evidence From a Claims Database

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Introduction: The objective of this study is to compare the incidence of diabetes for elderly patients who have initiated treatment on various antipsychotic medications, during the time period prior to broad public attention to this public health concern.

Method: A retrospective analysis of the IMS Lifeline claims database was undertaken. 4009 enrollees with the following characteristics were identified: (1) Age ≥ 65 ; (2) Initiated on conventional or atypical antipsychotic between September 30, 1996, and December 31, 1998; (3) No use of antipsychotics for 6 months prior to initiation; (4) Use of antipsychotics for at least 1 month; (5) Use of only one antipsychotic medication in 12 months post-initiation; and (6) Not classified as diabetic (i.e., did not receive 2 or more diagnoses of diabetes and did not receive any diabetic medication) for 1 year prior to initiation and 1 month post-initiation on antipsychotics. Logistic regressions were used to estimate odds ratios associated with a patient being classified as diabetic, controlling for age, gender, regional differences, mental and physical health comorbidities, length of antipsychotic use, and type of antipsychotic medication.

Results: There was no evidence of any type of antipsychotic medication being associated with an elderly individual having a higher likelihood of being classified as diabetic. Specifically, patients who initiated therapy on atypicals compared with typicals (odds ratio = 1.262; $p = .3514$), olanzapine compared with typicals (odds ratio = 1.084; $p = .8344$), risperidone compared with typicals (odds ratio = 1.391; $p = .2838$), or haloperidol compared with atypicals (odds ratio = 0.981; $p = .9454$) did not have statistically significant different probabilities of being classified as diabetic.

Conclusion: The likelihood of developing diabetes was not significantly different following treatment with atypicals than typicals. Moreover, a comparison of the use of haloperidol, olanzapine, and risperidone also showed no significant difference in the incidence of diabetes associated with these medications compared to other antipsychotics. These results indicate that a 1-year difference in diabetes risk is not a clinically important differentiator among the most widely used antipsychotic medication in the elderly patient population.

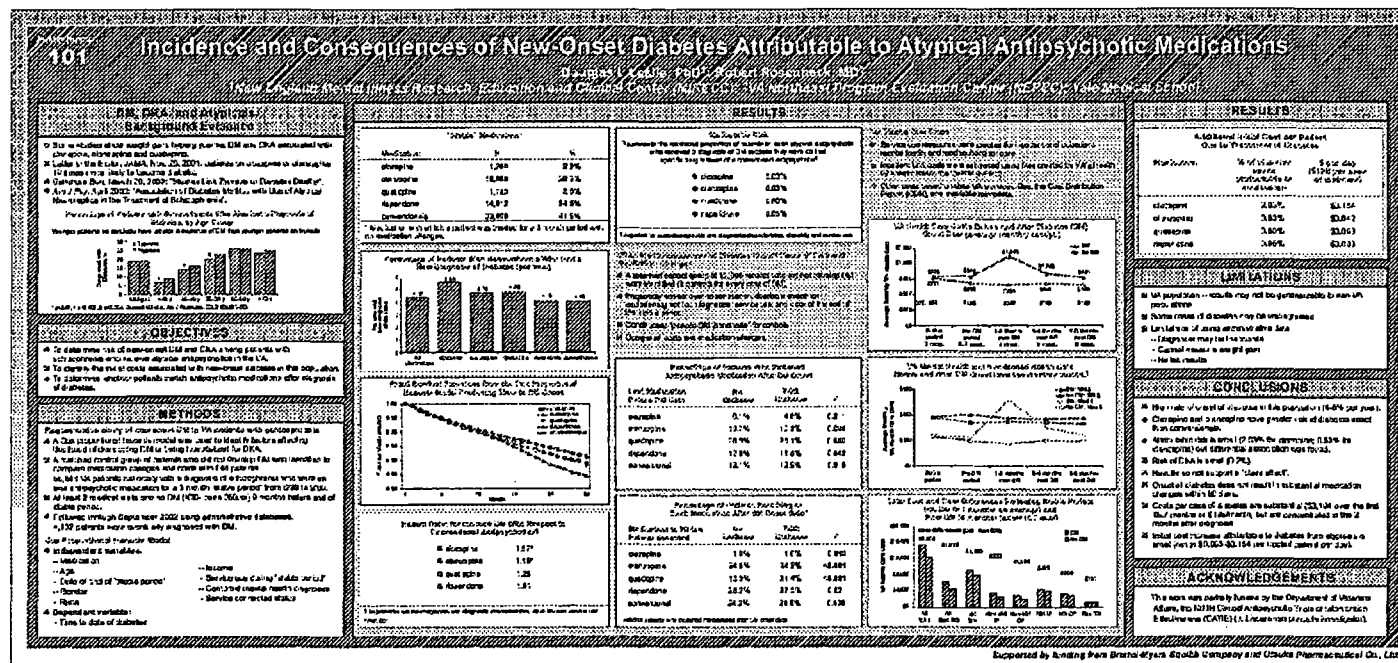
Source of funding: Eli Lilly and Company.

Duloxetine for the Treatment of Major Depressive Disorder in Patients Age ≥ 55 , 1: Efficacy

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The rate of major depressive disorder (MDD) in the > 65 age group varies from 5% in the general community to as high as 15%



Metabolic Adverse Events Among Schizophrenics Exposed to Antipsychotics in the General Practice Research Database

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INTRODUCTION

newer class of antipsychotic exhibits superior safety in terms of pyramidal side effects compared to conventional antipsychotics.

ent evidence from the literature has tested an association between the of these agents and the development of metabolic adverse events such as diabetes and lipidemia.

the majority of these studies are reports, we sought to determine independent contribution of these agents to the incidence of metabolic events using a large healthcare base.

DEFINING ANTIPSYCHOTIC EXPOSURE

posure to antipsychotic was defined as receipt of at least one prescription for antipsychotic within three months prior to the index date (date of adverse event or last date of follow-up).

following agents were included in study:

conventional antipsychotics
atypical antipsychotics
risperidone
olanzapine

METHODS

The study population was derived from the UK-based General Practice Research Database (GPRD), comprising some 8,000,000 patients followed between 1987 and 2000.

A total of 19,837 patients with a diagnosis of schizophrenia, but no diagnosis of diabetes or hyperlipidemia prior to the designated study period, were identified.

Patient eligibility begins from the time that Up To Standard data is provided to the GPRD. Up To Standard refers to data recording that reaches an appropriate standard for use in research. For patients identified as schizophrenics prior to Up To Standard medical records, the start of the study period is defined as the date when the practice began submitting Up To Standard data for the patient up to the date when the patient transferred out, died, or provided the last data submission to the GPRD. For all other patients, the start of the study period is defined as the earliest date of diagnosis with schizophrenia. To be eligible for the current study, patients must have contributed at least three months of Up To Standard data.

Incidence rates were calculated from the number of patients who developed a metabolic adverse event within three months of exposure to the drug of interest divided by the person-time exposure for the drug of interest. The person-time exposure is calculated from the number of prescriptions of the drug of interest divided by twelve (the typical prescription in the GPRD is written for one month).

RESULTS

During a mean follow-up 4.2 ± 2 years, 1,544 metabolic adverse events were recorded.

The incidence rate for metabolic adverse events among conventional antipsychotic users was 25.2/1,000 person-years (95% CI: 22.4-28.3). For patients exposed to risperidone, incidence rates were 38.6/1,000 person-years (95% CI: 26.8-55.5), and for patients exposed to olanzapine, rates were 17.3/1,000 person-years (95% CI: 12.1-24.7). (See Figures 1, 2, 3.)

The relative risk for metabolic adverse events for olanzapine patients versus risperidone patients was 2.23 (95% CI: 1.35-3.7, $p < 0.001$).

Figure 1
Incidence of Diabetes According to Antipsychotic Drug Use Among Schizophrenic Patients in the GPRD

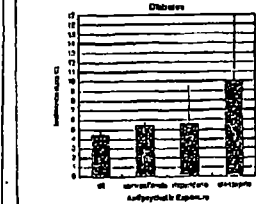


Figure 2
Incidence of Hyperlipidemia According to Antipsychotic Drug Use Among Schizophrenic Patients in the GPRD

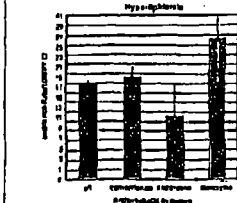
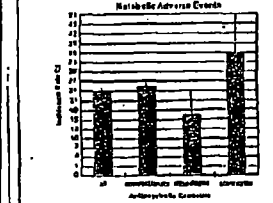


Figure 3
Incidence of Metabolic Adverse Events According to Antipsychotic Drug Use Among Schizophrenic Patients in the GPRD



DISCUSSION/CONCLUSION

Our study consistently demonstrates a 2.3-fold higher incidence of diabetes, hyperlipidemia, or metabolic adverse events among olanzapine-naïve patients with schizophrenia. The increased risk of metabolic events among subjects prescribed olanzapine in the current analysis raises serious questions about the risk-to-benefit ratio for olanzapine use among schizophrenic patients. This is particularly true as schizophrenic patients also tend to exhibit other major risk factors for cardiovascular events, such as smoking, sedentary lifestyle, and weight gain. All such factors contribute to the subsequent development of cardiovascular disease.

The metabolic consequences of olanzapine therapy should therefore be given serious consideration by treating physicians.

METABOLIC EFFECTS OF ATYPICAL ANTIPSYCHOTICS IN MONGREL DOGS

Interim Report

Marilyn Ader, Ph.D. and Richard N. Bergman, Ph.D.

October 10, 2003

I. Study Rationale

Introduction of atypical antipsychotics in psychopharmacology represented an major advance in the treatment of schizophrenia, providing an effective therapy for both positive and negative symptoms of psychosis while minimizing the extrapyramidal effects characteristic of earlier therapeutic options. Indeed, these medications are widely prescribed (~3% of the U.S. population) for treatment of schizophrenia, as well as bipolar disorder, depression, and dementia.

In the face of their widespread use, concern is growing that some atypical antipsychotics are associated with pronounced increases in body weight (1,2), although it is unclear whether weight gain is a direct effect of drug or secondary to behavioral changes such as increased sedation associated with pharmacotherapy. Regardless of its causality, obesity is a significant public health concern, and represents a major risk factor for chronic diseases such as Type 2 diabetes, cancer, and atherosclerosis (3-5).

More recently, some atypical antipsychotics have been linked to severe metabolic dysregulation. Although conventional neuroleptics were reported to impair glucose tolerance when introduced over 50 years ago (6), case reports and retrospective analyses have noted a disproportionate number of patients developing fasting hyperglycemia and new-onset diabetes or exhibiting exacerbation of pre-existing

diabetes soon after initiation of atypical antipsychotic treatment (7-12). Of particular concern are reports of diabetic ketoacidosis (DKA) (7-9,13), a complication resulting primarily from severe insulin deficiency not typical in the diabetes associated with obesity. However, while published clinical studies provide a suggestive link between many atypical antipsychotics and the development of obesity or diabetes, there are significant obstacles to proving causation. Most notably, underlying mental illness (e.g. schizophrenia) has been associated with glucose intolerance and diabetes independent of pharmacotherapy (14,15), but few studies have been performed in drug naïve individuals, thus making it difficult to determine pure effects of drug versus that of underlying disease. Polypharmacy is also common in this patient population, making it difficult to determine direct effect of atypical medications from those of co-medications such as valproate, which itself has been associated with pronounced weight gain and fasting hyperinsulinemia (16,17). Furthermore, substance abuse (e.g. nicotine, cannabis, cocaine) is extremely common in patients with schizophrenia and bipolar disorder, and alterations in such use during treatment can obscure the assessment of metabolic effects of psychotropic medication *per se* (18,19). Finally, most studies have been conducted on an outpatient basis, making it difficult to ensure compliance in taking medications and maintaining adequate records of food intake and activity.

We performed a placebo-controlled study in a canine model to directly test whether chronic treatment with atypical antipsychotics results in obesity and glucose dysregulation. Experiments were performed in normal conscious dogs, tested before and after 4-6 weeks daily treatment with olanzapine (OLZ), risperidone (RIS), or placebo. These drugs were chosen because they collectively account for >80% of all

drugs prescribed of their class of atypical antipsychotics. An extensive array of reliable metabolic experiments were performed in all animals before and after treatment to characterize the physiologic basis for clinically observed derangements in glucose homeostasis, including diabetes and DKA.

This study represents the first direct comparison of the metabolic effects of the two most widely prescribed atypical antipsychotics *in the absence of underlying disease*, and demonstrates clear differential effects of these two agents on body composition and carbohydrate metabolism.

II. Study Design and Experimental Protocols

A. Rationale

The ability of an organism to dispose of glucose during the day depends upon several physiological factors. Very briefly, fasting glucose levels are dependent primarily upon the basal rate of liver glucose output. This rate may be measured using the tracer dilution approach, which is included in this protocol. The change in glucose during and after meals depends primarily upon 1) the ability of the β -cells of the pancreas to respond to changes in plasma glucose and 2) the sensitivity of the tissues to insulin ("insulin sensitivity"). In particular, the liver and skeletal muscle insulin sensitivity are most important to disposal of a carbohydrate meal. Diminished insulin secretory function is a critical component in the pathogenesis of diabetes, and severe β -cell defects are required for development of diabetic ketoacidosis.

Thus, to investigate the underlying physiologic mechanisms which may contribute to the development of fasting hyperglycemia, overt diabetes, and DKA, we

performed studies in the dog to determine the effects of chronic (4-6 wk) treatment of atypical antipsychotics on 1) pancreatic insulin secretion, 2) liver insulin sensitivity, and 3) peripheral (i.e., skeletal muscle) insulin sensitivity.

B. Surgical Preparation and Feeding Procedures

Repetitive procedures were performed on 26 male mongrel dogs (mean: 28.8 ± 0.6 kg) in the conscious, relaxed state. Dogs were outfitted with chronic indwelling catheters in the jugular vein, advanced into the right atrium (for blood sampling) and in the femoral vein (for infusions). Daily food intake was carefully monitored. All dogs were fed ad libitum: one can Hill's Prescription Diet (10% carbohydrate, 9% protein, 8% fat) and a known quantity of standard dry chow (37% carbohydrate, 26% protein, 15% fat) once per day. Throughout the study period, any dog that completely consumed its daily meal on two consecutive days was provided with an increased amount of chow for all subsequent days. This feeding regimen enabled daily measures of food intake to determine its contribution to any observed changes in body weight.

C. Study Design

The study was divided into two phases: 1) baseline testing ("pre-drug"), and 2) "post-drug" period. Prior to study entry, dogs were randomly assigned to one of three treatment arms: olanzapine, risperidone, or placebo. Pre-drug testing was performed to quantify insulin sensitivity and trunk adiposity (see below for details). The order of experiments was randomized, and studies were performed in each animal over a 10-d period, with ≥ 2 d between experiments. After pre-drug testing, dogs were placed on drug (or placebo) regimen for 4-6 wk, after which all procedures performed during pre-drug phase were repeated ("post-drug") under conditions identical to pre-drug testing.

Drug (or placebo) treatment was continued during the entire post-drug testing period. Body weight was measured twice weekly between pre- and post-drug testing.

Dogs were assigned to receive either OLZ (Zyprexa, Lilly; n=10), RIS (Risperdal, Janssen Pharmaceutica; n=10), or placebo (gelatin capsules, Monterey Bay Spice Co; n=6). Drugs were administered orally once per day, 6-8 hr after daily presentation of food (~ 2 pm). Doses were based on those used in typical treatment of patients, as well as on reported dopamine D₂ receptor binding in the caudate nucleus (20). To simulate clinical use, doses of each drug were stepped up to target dose by day 4 of treatment. Target dose for OLZ was 15 mg/d, and target dose for RIS was 5 mg/d.

D. Experimental Procedures

During pre-drug and post-drug periods, all animals underwent three procedures, performed in random order: [1] the euglycemic hyperinsulinemic clamp (EGC), to quantify hepatic and peripheral insulin sensitivity, [2] β -cell stepwise stimulation test (STEP test), to quantify glucose-stimulated insulin secretion, and [3] abdominal MRI, to assess treatment-induced changes in adiposity. Oral glucose tolerance tests were also performed before and after treatment in all animals, but data is not fully analyzed and will not be presented in this Interim Report. All procedures were performed in overnight fasted animals; during all clamps, dogs were fully conscious, rested comfortably in a Pavlov sling, and were given free access to water.

1) Euglycemic Hyperinsulinemic Glucose Clamp (EGC): A primed infusion of 3-³H-glucose was initiated to permit calculation of rates of glucose uptake (R_d) and endogenous glucose production (HGO). After basal blood sampling, hyperinsulinemia was induced by systemic infusion (1 mU/min per kg) beginning at time 0 and continued

for the 180-min clamp duration. Blood samples were drawn at 10-15 min intervals, and centrifuged immediately for on-line assay of plasma glucose. Euglycemia was maintained by variable rate glucose infusion, spiked with 3-³H-glucose.

2) Stepwise β -cell Stimulation Test ("STEP Test"): After basal blood sampling, glucose was clamped at 3 successive glycemic levels by exogenous glucose infusion. Glucose was maintained at target concentrations of 100 mg/dl (t = 0 to 59 min), 150 mg/dl (t = 60 to 149 min), and 200 mg/dl (t = 150 to 240 min).

3) Abdominal MRI: MRIs were performed as previously described by us (21), with minor modifications. After an overnight fast, dogs were pre-anesthetized and sedated. Thirty 1-cm axial abdominal images were obtained using a General Electric 1.5 Tesla Horizon magnet. Images were analyzed by a laboratory technician who was blinded to treatment group and phase of study (pre-drug, post-drug). Analysis was performed using ScionImage software, which quantified fat tissue (pixel value: 0-120) and other tissues (pixel value: 121-256) in each slice. Total trunk fat and tissue were estimated as the integrated fat or tissue across all 30 slices. Visceral fat was defined as fat within the peritoneal cavity at ± 5 images from the slice at the level where the left renal artery branches from the abdominal aorta (i.e. from 11-cm abdominal range). All adiposity data are expressed in units of cm³ normalized to volume (in cm³) of non-fat tissue.

E. Data Analysis

1) Insulin Sensitivity: Peripheral insulin sensitivity was defined as $\Delta R_d / (\Delta INS \times GLU_{ss})$, where ΔR_d is the change in R_d from basal to steady state, ΔINS is

the increment of plasma insulin engendered by exogenous infusion (i.e. steady state minus basal), and GLU_{ss} is the steady state glucose concentration (22). Hepatic insulin sensitivity was calculated as the absolute value of $\Delta HGO/(\Delta INS \times GLU_{ss})$, where ΔHGO is the observed change in HGO (basal minus steady state).

2) Insulin secretion and β -cell sensitivity: From STEP tests, the sensitivity of pancreatic β -cells to glucose was calculated from the glucose-insulin dose-response relationship. However, since circulating insulin response to hyperglycemia reflects both pancreatic insulin secretion and insulin clearance by the liver, we also calculated insulin secretion directly using deconvolution methods (23). Insulin and C-peptide dynamics were analyzed by deconvolution to obtain a time course of insulin secretion during the STEP test. Pancreatic β -cell sensitivity to glucose was characterized by the dose response between glucose and insulin secretion, using the area under the curve (AUC) for each glycemic period for each variable (i.e. 0-60 min, 61-150 min, and 151-240 min).

3) β -cell compensation for insulin resistance: The effect of drug (or placebo) treatment on the ability of β -cells to compensate for insulin resistance was quantified by the disposition index, or DI (24). The DI was calculated as $(SI_{clamp} \times \text{secretion AUC}_{0-240 \text{ min}})$, where SI_{clamp} was assessed from euglycemic hyperinsulinemic clamps also performed on each animal before and after drug treatment. Whole-body insulin sensitivity (SI_{clamp} ; combined actions of insulin to stimulate glucose uptake and suppress endogenous glucose production) was defined as $\Delta GINF/(\Delta INS \times GLU_{ss})$, where $\Delta GINF$ and ΔINS are the increments in glucose infusion rate and plasma insulin measured during exogenous insulin infusion (i.e. steady state minus SRIF period), and GLU_{ss} is the steady state glucose concentration. Calculated values (insulin secretion;

β -cell sensitivity to glucose, DI, and SI_{damp}) were non-normally distributed, and are reported as median value, with first and third quartiles for each variable in brackets.

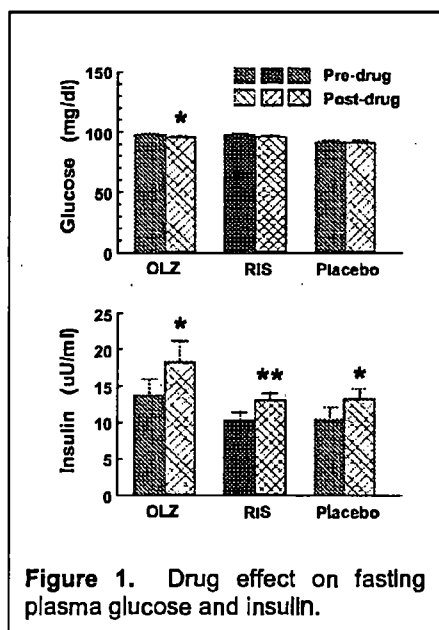
III. Effect of Drugs on Basal Fasting Plasma Concentrations

Pre-drug characteristics of each treatment group are shown in Table 1. Fasting glucose was not different between OLZ and RIS (97.7 $\pm$ 0.9 and 97.8 $\pm$ 1.4 mg/dl), but was slightly lower in the placebo group (92.2 $\pm$ 1.6 mg/dl; p=0.015 by ANOVA). There were

	OLZ	RIS	Placebo
Glucose [mg/dl]	97.7 $\pm$ 0.9	97.8 $\pm$ 1.4	92.2 $\pm$ 1.6*
Insulin [uU/ml]	13.7 $\pm$ 2.3	10.3 $\pm$ 1.1	10.5 $\pm$ 1.6
FFA [mM]	0.62 $\pm$ 0.07	0.73 $\pm$ 0.07	0.54 $\pm$ 0.07
Glycerol [mM]	0.103 $\pm$ 0.010	0.115 $\pm$ 0.010	0.094 $\pm$ 0.009
Triglycerides [mM]	0.291 $\pm$ 0.025	0.351 $\pm$ 0.026	0.366 $\pm$ 0.029
Body Weight [kg]	29.1 $\pm$ 0.8	27.9 $\pm$ 0.8	29.8 $\pm$ 1.8

Table 1. Fasting plasma concentrations at study entry. (* p=0.015 vs OLZ and RIS, by ANOVA)

no differences in fasting insulin, FFA, glycerol, triglycerides, lactate, or body weight among groups (p>0.14).

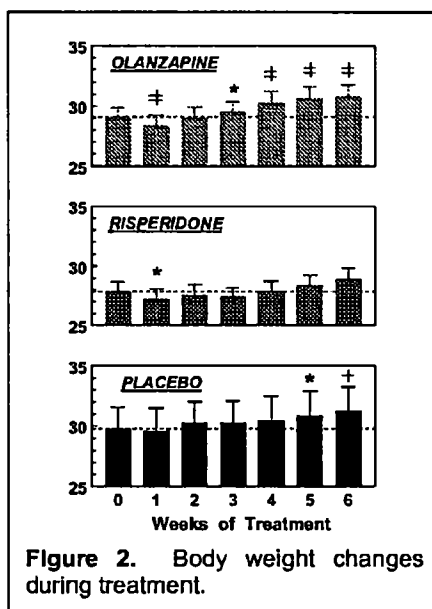


The effects of drug (or placebo) treatment on basal plasma glucose and insulin are shown in Figure 1. Fasting hyperglycemia did not develop in any dog. Rather, glucose was marginally lower after OLZ (p=0.05), but clearly remained in the physiologic range within which counterregulatory responses are absent. In contrast, fasting insulin was elevated from pre-drug in all groups (p=0.033, p=0.01, and p=0.02

for OLZ, RIS, and placebo, respectively). FFA, glycerol, and lactate concentrations were not appreciably changed in any treatment group, although there was a trend towards reduced FFA after treatment with RIS ($p=0.078$). Triglycerides were unchanged by OLZ ($p=0.44$), but significantly reduced by RIS ($p=0.011$). Except for insulin, fasting plasma values were not changed significantly by placebo treatment.

IV. Body Weight Gain and Food Intake

There were modest changes in body weight in all groups (Figure 2). OLZ-treated dogs exhibited a paradoxical initial drop in weight of 0.7 ± 0.2 kg ($-2.5 \pm 0.6\%$ pre-drug weight) within 1 week of drug treatment ($p=0.001$), which occurred despite increased food intake during that time ($p=0.015$; Table 2). Significant weight gain was observed by week 3 and sustained for the remainder of the treatment period, reaching maximum of $+1.7 \pm 0.4$ kg ($+5.9 \pm 1.2\%$ of pre-drug weight) at week 6 ($p=0.001$ vs pre-drug). Overall weight gain during OLZ may at least in part be explained by increased food intake; dogs consumed a significant excess of calories during the entire treatment period (AUC: 14745 ± 5765 kcal; $p=0.031$).



Body weight changes during RIS smaller in magnitude compared to OLZ (Figure 2). Following weight loss after 1 wk of RIS (0.7 ± 0.2 kg, $-2.4 \pm 0.8\%$ pre-drug weight; $p=0.016$), weight showed a marginal, non-significant upward trend to maximum

recorded weight by week 6 ($p=0.09$). Food intake was not appreciably altered by RIS

(AUC: -8219 ± 5499 ;

$p=0.17$; Table 2), but

was significantly

lower than that

observed during OLZ

treatment even after

	Weeks of Treatment							AUC
	Pre-drug	1	2	3	4	5	6	
Olanzapine	3211 ± 195	3761 ± 238	5484 ± 206	3304 ± 162	3798 ± 247	3405 ± 211	3296 ± 181	14745 ± 5765
Risperidone	2800 ± 257	2687 ± 178	2574 ± 248	2496 ± 150	2719 ± 214	2648 ± 142	2426 ± 150	-8219 ± 5499
Placebo	2772 ± 114	3345 ± 394	5185 ± 480	3212 ± 513	3091 ± 354	3183 ± 335	3081 ± 49	18099 ± 11988

Table 2. Food intake during drug treatment. During OLZ, food intake was significantly increased at wks 2 and 4 ($p<0.05$)

accounting for differences in pre-drug food intake (AUC, post-drug: OLZ: 14745 ± 5765 ,

RIS: -8219 ± 5499 kcal; $p=0.01$).

Placebo-treated ad lib-fed dogs exhibited steady upward trend in body weight.

Weight gain averaged $+1.5 \pm 0.3$ kg, or $+4.8 \pm 1.0\%$ of pre-drug weight by wk 6 ($p=0.006$).

There was a trend towards increased food intake (Table 2), although intra-group

variability precluded statistical significance (AUC: 18099 ± 11988 kcal; $p=0.19$).

V. Differential Effects of Treatment on Adiposity

A. MRI Results

In contrast to very modest changes in body weight, abdominal MRI images reveal that adiposity was profoundly increased over the 4-6 wk of drug treatment (Figure 3). Placebo-treated dogs exhibited a modest, but significant increase in

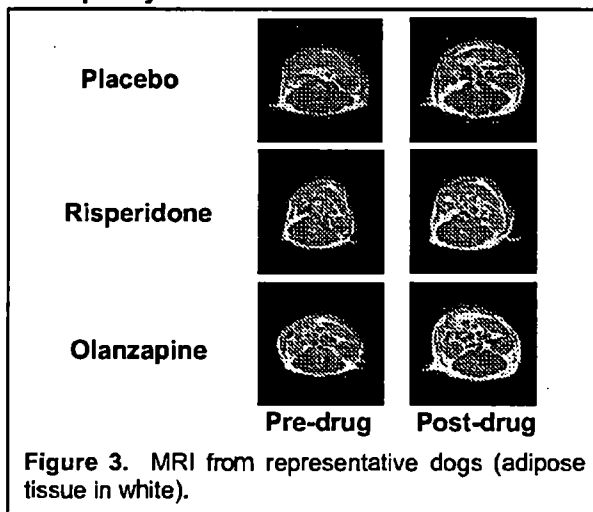
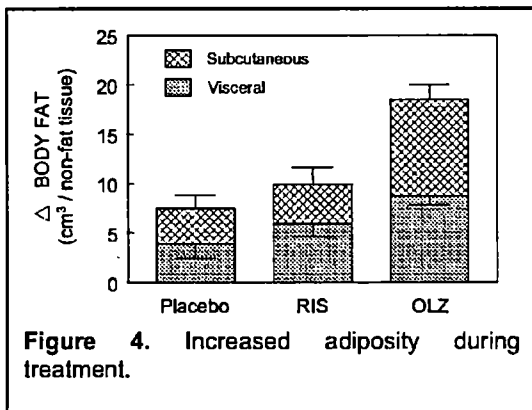


Figure 3. MRI from representative dogs (adipose tissue in white).



adiposity (Figure 3). Dogs exhibited increases of 27-30% in total ($p=0.042$), visceral ($p=0.046$), and subcutaneous ($p=0.044$) fat depots after 4-6 wk of placebo (Figure 4).

RIS treatment resulted in 45% increase in total fat volume, from

21.9 ± 3.0 to 31.8 ± 2.8 cm^3 ($p=0.005$; Figure 4). Visceral fat was increased in the majority of dogs (pre: 11.4 ± 0.8 , post: 17.3 ± 1.2 cm^3 ; $p=0.001$), whereas the subcutaneous adipose depot was enlarged 37% after 4-6 wk treatment with RIS (pre: 10.5 ± 2.4 , post: 14.4 ± 1.8 cm^3 ; $p=0.053$). Overall, adiposity changes due to RIS were not different from those observed in placebo-treated dogs ($p>0.33$).

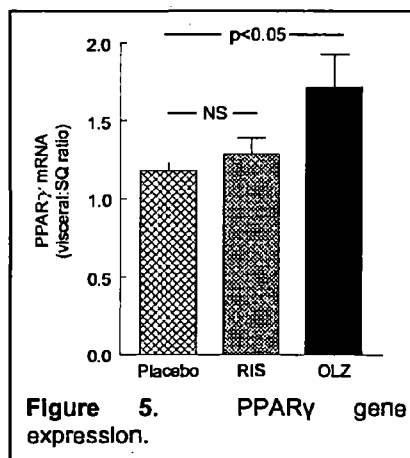
Fat deposition was most dramatic in OLZ-treated dogs, where total trunk fat increased in all dogs, from 24.9 ± 3.2 to 43.4 ± 3.9 cm^3 ($p<0.001$). This increase represents a profound enlargement of both fat depots: the visceral adipose compartment expanded by 66% (pre: 13.1 ± 1.3 , post: 21.8 ± 1.1 cm^3 ; $p<0.001$), while subcutaneous fat increased 83% (pre: 11.8 ± 2.0 , post: 21.6 ± 3.1 cm^3 ; $p=0.001$).

OLZ-induced changes were markedly greater than that observed in placebo-treated animals (total: $p=0.0088$; visceral: $p=0.025$; subcutaneous: $p=0.0078$). Fat accumulation during OLZ was 2-fold greater than that observed after RIS treatment in total ($p=0.018$) and subcutaneous ($p=0.024$) compartments, and was marginally greater than RIS in visceral fat accumulation (OLZ: 8.7 ± 0.9 ; RIS: 5.9 ± 1.3 cm^3 ; $p=0.091$).

Moreover, for a given observed change in body weight, OLZ-treated dogs exhibited greater total fat deposition than dogs treated with either RIS or placebo.

B. Adipose Tissue Gene Expression

We measured mRNA gene expression of key factors involved in lipid turnover and fat accumulation. Upon completion of post-drug procedures, biopsies were taken of visceral and subcutaneous fat, and gene expression analysis was performed. Preliminary data from 4 dogs from each treatment group are shown in Figure 5. Adipose tissue from OLZ-treated dogs exhibited nearly 50% greater expression of PPAR γ when compared to either RIS- or placebo-



treated animals. These data suggest that OLZ acts, at least in part, to markedly increase fat cell accumulation, which would contribute to expansion of the adipose tissue compartment in these animals. Interestingly, PPAR γ was not different between RIS and placebo groups, which is consistent with the fact that these groups did not differ in the degree of fat deposition induced by their respective treatments (Figure 4).

VI. Treatment Effects on Glucose Uptake and Peripheral Insulin Sensitivity

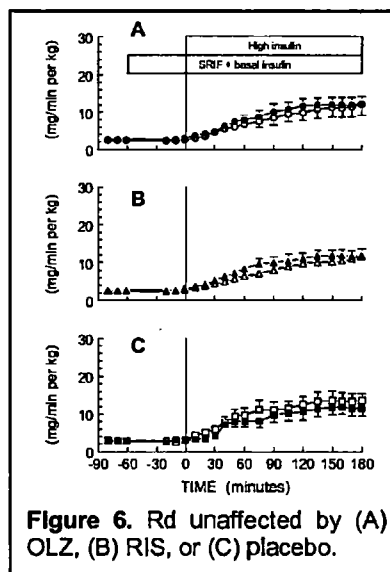
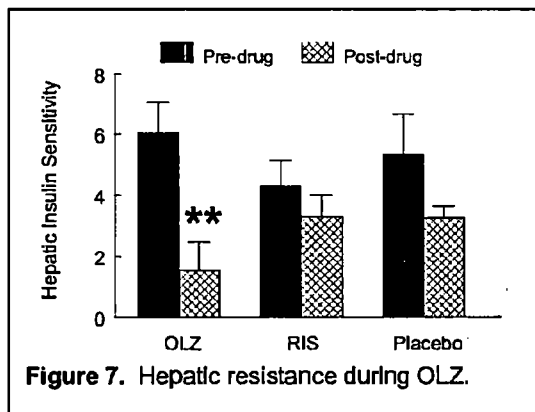
Prior to drug treatment, basal glucose uptake (R_d) was similar across groups ($p=0.81$ by ANOVA). The ability of insulin to stimulate R_d during clamps is depicted in Figure 6. Neither drug nor placebo treatment had any effect on either basal or steady-state R_d ($p>0.23$). Peripheral insulin sensitivity was similar before treatment (OLZ 24.3 ± 4.4 , RIS: 24.7 ± 6.3 , placebo: 20.1 ± 4.2 dl/min per kg per μ U/ml), and not

significantly altered by treatment in any group (OLZ, 23.3 ± 6.4 ; RIS, 19.9 ± 1.9 ; placebo, 25.3 ± 5.7 dl/min per kg per $\mu\text{U/ml}$; $p > 0.3$ compared to respective pre-drug value).

VII. Differential Effects of Treatment on Hepatic Insulin Sensitivity

Insulin-mediated suppression of glucose production from the liver was impaired by OLZ (Figure 7). Prior to OLZ treatment, HGO was suppressed $>90\%$ during clamps (basal: 2.5 ± 0.2 ,

steady state: 0.2 ± 0.5 mg/min per kg; $p < 0.0001$). However, after OLZ treatment, hyperinsulinemia failed to significantly suppress HGO (basal: 2.3 ± 0.1 , steady state: 1.8 ± 0.4 mg/min per kg; $p = 0.12$). Hepatic insulin sensitivity was markedly diminished by OLZ, declining from 6.1 ± 1.0 to 1.5 ± 0.9 dl/min per kg per $\mu\text{U/ml}$ ($p = 0.009$; Figure 7). We did not observe a significant reduction in liver insulin sensitivity with RIS (pre: 4.3 ± 0.8 ,



development of resistance was also observed in this group.

VIII. Insulin Secretion and the Ability of β -cells to Compensate for Insulin Resistance

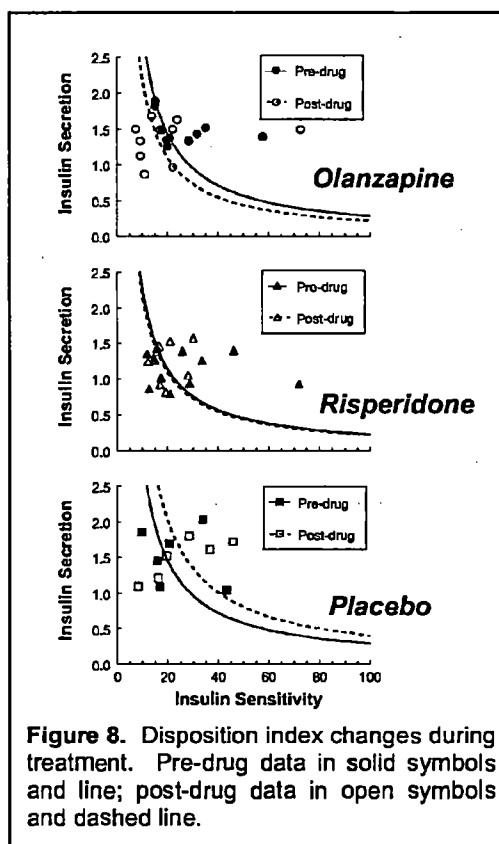
Clinically, atypical antipsychotics have been associated with development of fasting hyperglycemia and weight gain. More disturbing are reports of diabetic ketoacidosis, which is seen in Type 1 diabetes, but less in the Type 2 diabetes associated with obesity. Few studies have accurately quantified insulin secretion in subjects receiving antipsychotic treatment. We exploited our canine model to determine if insulin secretory function is impaired by chronic administration of atypical antipsychotics.

Circulating insulin response to hyperglycemia is the end results of glucose-stimulated pancreatic insulin secretion and that proportion of insulin which survives first-pass extraction by the liver. To distinguish these two processes, we quantified insulin secretion rates directly by deconvolution of the plasma C-peptide response to hyperglycemia.

The secretion dose response relationships indicate no apparent difference among treatments to alter the ability of the pancreas to secrete insulin in response to hyperglycemia (not shown). However, to determine if insulin secretory function during drug (or placebo) treatment was appropriate for the prevailing insulin sensitivity, euglycemic hyperinsulinemic clamps were performed on all dogs before and after treatment. Prior to treatment, SI_{clamp} was not different among groups ($p=0.81$). OLZ treatment caused a significant reduction in SI_{clamp} (pre: 20.70 [17.11, 32.48], post: 16.89 [9.12, 22.46] dl/min per kg per μ U/ml; $p=0.021$). RIS treatment resulted in a highly

variable, non-significant decline in SI_{clamp} (pre: 23.42 [14.02, 36.73], post: 16.79 [15.26, 22.78] dl/min per kg per $\mu U/ml$; $p=0.16$). There was no change in SI_{clamp} in placebo-treated animals (pre: 18.70 [14.17, 36.10], post: 23.92 [14.18, 38.92] dl/min per kg per $\mu U/ml$; $p=0.68$).

The ability of β -cells to compensate for fluctuations in insulin sensitivity, quantified by the disposition index (DI) is depicted in the sensitivity-secretion relationships in Figure 8. Despite the apparent preservation of β -cell secretory function during OLZ treatment from secretion dose response relationships, we observed significant reduction in the DI after 4-6 wk drug treatment (pre: 28.5 [26.4, 47.3], post 22.1 [10.9, 34.4]; $p=0.021$). In contrast, the DI was not altered by either RIS (pre: 22.7 [16.4, 47.6], post: 21.8 [15.7, 30.2]; $p=0.45$) or placebo (pre: 28.8 [18.1, 50.9], post: 40.3 [16.9, 63.9]; $p=0.80$) treatment.



IX. Study Conclusions

A. Adiposity and Hepatic Insulin Sensitivity

This study is the first demonstration of the intrinsic effects of two popular atypical antipsychotics on body weight, adiposity, and insulin sensitivity of the

liver and peripheral tissues. We observed clear differences in the effects of OLZ and RIS. OLZ caused significant weight gain and profound increases in total trunk adiposity, reflecting marked expansion of both visceral and subcutaneous adipose depots. In addition, severe hepatic insulin resistance developed after 4-6 weeks of olanzapine treatment. In contrast, RIS had more modest effects on adiposity that did not differ from the effects of placebo; RIS did not adversely affect hepatic insulin sensitivity. These results underscore the extreme value of comparing effects of these drugs in the absence of other risk factors. Significant questions remain as to the mechanisms by which these drug effects occur.

B. Pancreatic Insulin Secretory Function

These studies suggest a significant effect of one of these agents – olanzapine – to impair β -cell function (i.e. compensation for insulin resistance) that was not evident in dogs treated with RIS. Furthermore, these studies emphasize the need to assess insulin secretory function in the context of concomitant quantitative measures of insulin sensitivity, as the present secretory defects were only manifest when secretion was observed to be inadequate for the prevailing degree of insulin resistance. The mechanisms by which these actions of atypical antipsychotics occur are not known, but proposed studies will attempt to examine the underlying processes by which diabetes and diabetic ketoacidosis may develop in the vulnerable psychiatric population.

X. Overall Conclusions from Dog Study

These experiments indicate that two of the most widely prescribed atypical antipsychotics exert very different metabolic effects after 1-month chronic treatment in the canine model. Oral administration of OLZ induced profound visceral and

subcutaneous adiposity. Hepatic sensitivity was drastically reduced after OLZ. RIS exerted more modest effects on fat deposition that were not different from placebo-treated dogs. There was a small, but highly variable increase in body weight during RIS, but the cause of this weight change is not known, since RIS-treated dogs actually consumed fewer calories during treatment compared to pre-drug caloric intake. Unlike OLZ treatment, RIS treatment did not alter hepatic insulin sensitivity.

Of particular potential clinical relevance is the effects of these drugs on insulin secretion. It is necessary to express β -cell function in the context of prevailing insulin sensitivity (c.f. ref. (24)). OLZ caused modest, but significant insulin resistance. Such a reduction in insulin sensitivity *should* elicit an increase in insulin secretory response. That OLZ treatment resulted in unchanged insulin sensitivity in the face of insulin resistance means that pancreatic β -cell function was impaired with OLZ, as the disposition index declined. Again, the two drugs exert differential effects -- the disposition index was unaffected by RIS or placebo treatment.

Finally, in contrast to clinical reports that use of atypical antipsychotics are associated with the development of diabetes in the treated patient population, none of the dogs treated with OLZ or RIS in our studies developed either fasting hyperglycemia or frank diabetes, despite the above-described metabolic damage. While the reasons for this are not known, we speculate that underlying risk factors must exist for antipsychotic-induced diabetes to develop.

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Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

General Medical Report

**Evaluation of the Effects of Risperidone on Glucose Metabolism in Phase 2-4
Clinical Trials**

R064766 (Risperidone)

Issue/Report Date: 26 March 2004
Department: Drug Development
Document No.: EDMS-PSDB-1647076: 6.0

Compliance: The studies described in this report were performed according to the principles of Good Clinical Practice (GCP).

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DEFINITIONS OF TERMS

Random blood sample	Blood sample retrieved at any time of day without regard to time since last meal. This can also be called a "casual" sample.
Glucose levels suggestive of diabetes	For purposes of this report, classification was made based on random blood glucose concentration ≥ 11.1 mmol/L (without confirmation by clinical symptoms of diabetes, fasting plasma glucose, or oral glucose tolerance test), or by fasting blood glucose concentration ≥ 7 mmol/L.
Glucose levels suggestive of impaired glucose tolerance	For purposes of this report, classification was made based on random blood glucose concentration ≥ 7.8 and < 11.1 mmol/L or fasting blood glucose concentration ≥ 6.1 mmol/L and < 7 mmol/L. The classification was not based on results of a glucose tolerance test.

FUNCTIONAL ROLES

Sponsor's Responsible:

Physician:	Sally Berry, M.D., Ph.D.
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1. ABSTRACT

The data from over 12,000 patients treated in short-term and over 7500 treated in long-term Phase 2, 3 and 4 trials conducted and analyzed by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD; formerly Janssen Research Foundation) were collected for a review of adverse events associated with abnormalities in glucose metabolism and abnormal glucose levels. The trials were not specifically designed to measure the impact of risperidone on glucose metabolism. Information was derived from adverse event reports and routine laboratory tests.

Adverse events

The following were considered glucose-related adverse events: metabolic acidosis, decreased blood sugar, increased blood sugar, diabetic coma, hyperosmolar, diabetes mellitus, diabetes mellitus aggravated, diabetes mellitus deteriorated, new onset diabetes mellitus, diabetes mellitus precipitated, diabetes mellitus reactivated, diabetic ketoacidosis, abnormal glucose tolerance, glucose tolerance decreased, abnormal glucose tolerance test, glycosuria, hyperglycaemia, hypoglycemia, hypoglycemic reaction, ketoacidosis, and ketonuria. For all age groups combined, in short-term trials (≤ 3 months) the incidence of reported glucose-related adverse events was low among risperidone-treated patients (0.72% of 8458 patients) and comparable to the incidence among placebo-treated patients (0.88% of 1825 patients) and olanzapine-treated patients (0.93% of 536 patients). In the long-term trials (≥ 6 months), the incidence of glucose-related adverse events was comparable between risperidone treatment (1.49% of 6590 patients) and the typical agent, haloperidol (1.55% of 579 patients), and was lower than in olanzapine-treated patients (1.66% of 300 patients). There were no placebo-controlled long-term trials.

In the short-term trials, there were no glucose-related adverse events in the pediatric population. In adults, the incidence of glucose-related adverse events was very low with risperidone treatment (0.52% of 7169 subjects) and comparable to placebo (0.43% of 935 subjects). The incidence in olanzapine-treated patients was 0.87% of 458 patients. Disturbances in glucose metabolism appeared to be age dependent regardless of study treatment. Elderly subjects had a higher incidence of glucose-related adverse events compared to younger subjects. The incidence of glucose-related

adverse events was slightly higher with risperidone treatment (2.17% of 1105 patients) than with placebo (1.70% of 707 patients) among the elderly.

In long-term trials, the incidence of glucose-related adverse events was 0.13% of 782 pediatric patients, 1.51% of 4982 adults, and 2.66% of 826 elderly among risperidone-treated patients. The incidence was 1.58% among 569 haloperidol-treated adults and 1.68% among olanzapine-treated adults.

Serious adverse events

Among all risperidone-treated patients, there was one fatal case in which, among other symptoms, a glucose-related adverse event was present. This was an elderly patient with hyperglycemia and hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

The incidence of serious adverse events related to abnormalities in glucose metabolism with short-term (0.11% of 8458 patients) or long-term (0.26% of 6590 patients) risperidone treatment was comparable to short-term placebo (0.22% of 1825 patients) or short-term haloperidol treatment (0% of 920 patients), and lower than with long-term haloperidol treatment (0.52% of 579 patients). No serious glucose-related adverse events were reported in patients treated with olanzapine (536 and 300 patients in short-term and long-term trials, respectively) or patients treated with neuroleptics other than haloperidol (293 and 234 patients in short-term and long-term trials, respectively).

Discontinuations due to adverse events

The incidence of discontinuations due to adverse events related to abnormalities in glucose metabolism with risperidone treatment in short- and long-term trials (0.02% and 0.05%, respectively) was comparable to that of placebo treatment (0.05%, short-term only) and lower than for long-term haloperidol treatment (0.17%). No discontinuations were related to abnormalities of glucose metabolism with short-term haloperidol treatment, or in smaller groups with olanzapine or other neuroleptics.

Glucose levels

Results were treated according to the fasting or non-fasting status of the patient at the sampling time. Samples obtained from patients not known to be fasting were considered random samples. Random glucose levels of

≥ 11.1 mmol/L were categorized as suggestive of diabetes; levels ≥ 7.8 and < 11.1 mmol/L were characterized as suggestive of impaired glucose tolerance in patients with random glucose levels < 7.8 mmol/L at baseline. These criteria were based on recommendations of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus according to which random levels ≥ 11.1 mmol/L are diagnostic for diabetes in the presence of clinical symptoms; results of oral glucose tolerance tests 2 hours post-load (75 g glucose) or fasting plasma glucose levels ≥ 7.8 and < 11.1 mmol/L are diagnostic of impaired glucose tolerance. Fasting glucose levels were categorized as follows: normal (< 6.1 mmol/L), suggestive of impaired glucose tolerance (≥ 6.1 mmol/L but < 7 mmol/L), or suggestive of diabetes (≥ 7 mmol/L). Glucose was not typically measured in the pediatric trials.

Among risperidone-treated adults with normal baseline glucose levels in short-term trials, the incidences of glucose levels suggestive of diabetes or impaired glucose tolerance during treatment (0.4% and 3.1% of 3131 subjects, respectively) were comparable to those with placebo (0.5% and 6.4% of 598 subjects), haloperidol (0% and 5.7% of 158 subjects), and other antipsychotic treatments (0.2% and 2.8% of 464 subjects). Elderly patients in the short-term trials had slightly higher incidences of glucose levels suggestive of impaired glucose tolerance (15.6% of 743 subjects) with risperidone relative to placebo (10.8% of 464 subjects) and other antipsychotic treatments (8.5% of 142 subjects). In the elderly, levels suggestive of diabetes were similar in the risperidone (6.5%) and placebo (6.9%) groups. Incidence was 2.1% in the small elderly group treated with other antipsychotics.

Among risperidone-treated adults with normal baseline in long-term trials (1424 patients), 1.6% had levels suggestive of diabetes and 7.3% suggestive of impaired glucose tolerance, lower than the 2.4% and 12.7% of 245 olanzapine-treated patients, and 3.0% and 8.3% (of 230 patients) incidences of diabetic and hyperglycemic levels observed for patients who received other antipsychotic treatments in the long-term trials. Among elderly patients with normal baseline in the long-term trials, 4.1% of 292 had levels suggestive of diabetes, and 25.0% of 292 had levels suggestive of impaired glucose tolerance. There were only 2 elderly subjects with normal baseline in comparator groups in the long-term trials.

Prior history of diabetes

Analysis of the subgroup of subjects in which presence or absence of prior diabetes was clinically determined (5298 in short-term trials, 2572 in long-term trials) suggest that abnormalities of glucose metabolism in this clinical database (as reflected in adverse event reports and glucose levels) mainly represented poorly controlled existing diabetes rather than new-onset diabetes. In the short-term trials, among patients without pre-existing diabetes, 0.5% of the risperidone-treated and 0.5% of the placebo-treated patients had glucose-related adverse events; glucose levels were suggestive of diabetes for 1.4% of the risperidone-treated and 3.1% of the placebo-treated patients, and suggestive of impaired glucose tolerance for 4.3% of the risperidone patients and 8.6% of the placebo patients. Among subjects with no prior history of diabetes in long-term trials, 0.7% of risperidone-treated and 1.4% of olanzapine-treated patients had glucose-related adverse events. Of patients with normal baseline glucose, 0.8% of risperidone-treated patients and 2.8% of olanzapine-treated patients had glucose levels suggestive of diabetes, and 5.0% of risperidone-treated and 12.6% of olanzapine-treated patients had glucose levels suggestive of impaired glucose tolerance.

Among subjects with pre-existing diabetes, in the short-term trials the rates of glucose-related adverse events were 6.2% of risperidone patients and 6.5% of the placebo patients. Among patients with pre-existing diabetes and normal glucose levels at baseline, postbaseline glucose levels were suggestive of diabetes for 14.3% of risperidone patients and 20.5% of placebo patients, and suggestive of impaired glucose tolerance in 19.6% and 15.4% of risperidone- and placebo-treated patients, respectively. Among subjects with pre-existing diabetes in the long-term trials, 14.3% of risperidone-treated patients had glucose-related adverse events. There were few subjects with pre-existing diabetes who had normal baseline glucose in the long-term trials.

Weight Gain

The J&JPRD clinical database reflects the rank-order of antipsychotic weight gain reported by Allison in the American Journal of Psychiatry.¹ That is, in the J&JPRD database, olanzapine was associated with the highest weight gain, risperidone with moderate weight gain, and haloperidol with low weight gain. This rank order (olanzapine>risperidone>haloperidol) was generally true in each analysis of weight gain including short-term and

long-term trials, elderly population, pediatric population, and in the percentage of patients gaining a clinically significant amount of weight.

Conclusion

The information derived from a large number of clinical trials reporting on more than 12,000 subjects in short-term trials and over 7500 subjects in long-term trials supports the conclusion that disturbances of glucose metabolism during risperidone treatment are not very common. Overall, the incidence of glucose-related adverse events was lower with risperidone than placebo or olanzapine. Serious glucose-related adverse events were rare and were not more frequent with risperidone than with placebo. One fatal case resulted from urosepsis. In the pediatric and adult populations, risperidone was similar to, if not lower than, placebo, and lower than olanzapine in terms of percentage of individuals with abnormalities in glucose metabolism. Elderly patients showed a higher incidence of some abnormalities in glucose metabolism with risperidone compared to placebo in short-term trials. Most observations were hyperglycemia and poorly controlled glucose levels in patients with a history of diabetes; new-onset diabetes and blood levels suggestive of diabetes were infrequent among subjects with no prior history of diabetes. The J&JPRD clinical database is consistent with the rank order of antipsychotic-induced weight gain reported by Allison et al (olanzapine>risperidone>haloperidol.)¹

2. INTRODUCTION AND OBJECTIVE OF THE REPORT

RISPERDAL[®] (risperidone) is a benzisoxazole derivative with potent serotonin 5-HT_{2A} and dopamine D₂ receptor-blocking properties.^{2,3}

RISPERDAL[®] (risperidone) has been marketed world-wide in more than 70 countries since 1993. Risperidone is approved for the treatment of a broad range of patients with schizophrenia, including first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia, and other psychotic conditions. In addition, risperidone alleviates affective symptoms such as depression, guilt feelings, and anxiety associated with schizophrenia. It is also indicated in maintenance therapy in schizophrenic patients. In some countries, it is indicated for the treatment of manic episodes associated with bipolar disorder and for the treatment of behavioral disturbances in patients with dementia who are aggressive, psychotic or have activity disturbances, and for conduct and other disruptive behavior disorders in children and adults with subaverage IQ. Based on extensive clinical experience including short-and long-term use, risperidone is well tolerated.

An evaluation of available adverse event data related to abnormalities of glucose metabolism from Phase 2-4 risperidone trials sponsored and analyzed by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (formerly Janssen Research Foundation) from 1 December 1985 to 1 April 2000 was performed in August 2000. This was done upon request by the regulatory authorities to follow the effects of novel antipsychotic treatment on glucose metabolism. This report cumulatively updates the previous information about adverse events with data from recent trials, and provides a cumulative analysis of glucose levels and weight gain.

3. SUBJECTS AND METHODS

3.1. Subjects

3.1.1. Subjects Evaluated for Glucose-Related Adverse Events in Phase 2, 3 and 4 Trials

All Phase 2, 3, and 4 trials in the risperidone program conducted and analyzed by J&JPRD, that were completed and for which data were fully analyzed as of 1 September 2003, were reviewed (Table 1). In addition, 4 ongoing follow-up trials in subjects treated with risperidone long-acting injectable were included (cutoff date, 28 March 2003). The program consisted of trials with oral (tablet and solution) and long-acting injectable formulations of risperidone. The trials were not specifically designed to measure the impact of risperidone on glucose metabolism. Information was derived from adverse event reports and routine laboratory and safety tests.

Trials listed in bold in Table 1 are those in which at least one glucose-related adverse event occurred in any treatment group.

Those trials with adverse event data in a format that could be merged with the other trials were included, as shown in the table. Data from 4 of the trials (GBR-17, GER-11, BEL-6, and BEL-9, italicized in the table) were not available in an appropriate format for inclusion because they were among the oldest trials. These data were not included in the analyses. This exclusion is not expected to influence the overall conclusions of this report since a relatively small percentage (approximately 2.5%) of patients were involved.

Information about seriousness of adverse events was not captured in the electronic databases for the following trials: AUT-1, BEL-11, BEL-14, BEL-21, BEL-22, BEL-24, BEL-5, BEL-7, BEL-17, FIN-1, FRA-3, GER-3, GER-5, INT-2, INT-3, INT-7, INT-4, INT-8, INT-8/INT-4, KOR-1, NED-2, USA-1, USA-5, USA-5/USA-7, USA-6, USA-6/USA-7, USA-9, USA-9/USA-7. However, information about serious glucose-related adverse

events was retrieved from other sources and is included in summaries of serious adverse events presented in this report.

Indications studied included schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar mania, dementia and behavioral disturbances (mainly in elderly patients), and conduct or other disruptive behavior disorders (mainly in children and adolescents). Trial medication doses given for indications other than schizophrenia and bipolar disorder were generally lower.

Data from patients treated in 83 of the Phase 2-4 trials listed in Table 1 (non-italicized) were evaluated for glucose-related adverse events (data in the electronic database). Based on short-term trials (≤ 3 months), 1,825 patients were treated with placebo, 8458 with risperidone, 920 with haloperidol, 536 with olanzapine, and 293 with other neuroleptics. Because BEL-11 was a cross-over trial, 37 patients provided data for both risperidone and placebo analysis and therefore were counted twice in the total number of patients evaluated for glucose-related adverse events in short-term trials.

In long-term trials (≥ 6 months), there were no patients with placebo, 6590 with risperidone, 579 with haloperidol, 300 patients with olanzapine, and 234 patients with other neuroleptics. These totals include patients who also participated in short-term trials, and continued into long-term extension trials.

Table 1: Phase 2-4 Risperidone Trials (As of 28 March 2003)

Trial design	Other					
Trial no.	Total patients	Risperidone	Haloperidol	neuroleptics ^a	Olanzapine	Placebo
TRIALS IN ADULT SUBJECTS (18-65 yrs)						
Double-blind						
short-term trials						
AUT-1	67	34	0	33	0	0
BEL-5 ⁴	44	22	22	0	0	0
BEL-7	60	28	32	0	0	0
FIN-1 ⁵	98	48	0	50	0	0
FRA-3 ⁶	62	21	20	21	0	0
GER-5 ⁷	59	39	0	20	0	0
IND-2	290	146	0	0	0	144
INT-10 ⁸	211	211	0	0	0	0
INT-2 ⁹	1362	1136	226	0	0	0
INT-3 ¹⁰	523	348	87	0	0	88
INT-5	183	99	84	0	0	0
INT-7 ¹¹	107	55	0	52	0	0
INT-9	149	75	0	74	0	0
INT-39/GBR-28	77	39	0	0	0	38
INT-45	490	247	0	0	243	0
INT-46 ^c	150	75	0	0	0	75
INT-61 ^j	779	779	0	0	0	0
KOR-1 ¹²	39	19	20	0	0	0
SUI-1 ¹³	86	43	0	43	0	0
USA-1 ¹⁴	160	53	53	0	0	54
USA-60	441	441	0	0	0	0
USA-72	246	163	0	0	0	83
USA-102 ^c	156	52	53	0	0	51
USA-112	407	202	0	0	205	0
USA-121 ^j	507	400	0	0	0	107
USA-239	259	134	0	0	0	125
USA-240 ^d	39	14	0	0	0	25
INT-69 ^k	438	154	144	0	0	140
INT-69 ^k	227	163	64	0	0	0
Open short-term trials						
GBR-17	192	192	0	0	0	0
GER-3	13	13	0	0	0	0
GER-11	254	254	0	0	0	0
INT-1	121	121	0	0	0	0
INT-32 ^j	86	86	0	0	0	0
INT-85 ^f	166	166	0	0	0	0
ITA-1	31	31	0	0	0	0
USA-54	935	935	0	0	0	0
USA-241 ^d	17	17	0	0	0	0
INT-69 ^k	146	146	0	0	0	0
USA-259	141	141	0	0	0	0
INT-81	283	283	0	0	0	0

(Continued)

Risperidone: Effects on Glucose Metabolism

Table 1: Phase 2-4 Risperidone Trials as of 28 March 2003 (Continued)

Trial design Trial no	Total patients	Risperidone	Haloperidol	Other neuroleptics ^a	Olanzapine	Placebo
Double-blind long-term trials						
INT-6	190	91	99	0	0	0
USA-79	395	192	203	0	0	0
INT-35	555	278	277	0	0	0
Open long-term trials						
BEL-17	116	116	0	0	0	0
INT-4 ¹⁵	386	386	0	0	0	0
INT-8	109	109	0	0	0	0
INT-12	483	483	0	0	0	0
INT-17	492	258	0	234 ^b	0	0
INT-47/GBR-29	58	58	0	0	0	0
INT-57 ^{c,i}	762	762	0	0	0	0
ISR-1	135	135	0	0	0	0
NED-2	40	40	0	0	0	0
USA-5	7	7	0	0	0	0
USA-6	265	265	0	0	0	0
USA-7	105	105	0	0	0	0
USA-9	107	107	0	0	0	0
INT-62	618	318	0	0	300	0
INT-63 ¹	810	810	0	0	0	0
REDACTED						
USA-265 ¹	100	100	0	0	0	0
INT-80 ¹	315	315	0	0	0	0
TOTAL^j	16315	12726	1384	527	748	930
TRIALS IN ELDERLY SUBJECTS (>65 yrs)						
Double-blind short-term trials						
AUS-5 ⁸	337	167				170
BEL-14	39	20	0	0	0	19
INT-24 ⁸	344	115	115	0	0	114
INT-50	175	87	0	0	88	0
USA-63 ⁸	625	462	0	0	0	163
USA-232 ⁸	473	235	0	0	0	238
INT-83 ⁸	18	10	0	0	0	8
Open short-term trials						
BEL-6	50	50	0	0	0	0
Double-blind long-term trials						
None						

(Continued)

Table 1: Phase 2-4 Risperidone Trials as of 28 March 2003 (Continued)

Trial design Trial no.	Total patients	Risperidone	Haloperidol	Other neuroleptics ^a	Olanzapine	Placebo
Open long-term trials						
BEL-9	9	9	0	0	0	0
INT-23	180	180	0	0	0	0
INT-26	83	83	0	0	0	0
USA-34	22	22	0	0	0	0
USA-64	103	103	0	0	0	0
USA-70	330	330	0	0	0	0
TOTALⁱ	2788	1873	115	0	88	712
TRIALS IN PEDIATRIC SUBJECTS (<18 yrs)						
Double-blind short-term trials						
BEL-11 ^h	37 ^h	37 ^h	0	0	0	37 ^h
BEL-24	13	6	0	0	0	7
NED-9	38	19	0	0	0	19
CAN-19	110	53	0	0	0	57
USA-93	118	55	0	0	0	63
Open short-term trials						
BEL-21	6	6	0	0	0	0
BEL-22	7	7	0	0	0	0
Double-blind long-term trials						
NA						

(Continued)

Table 1: Phase 2-4 Risperidone Trials as of 28 March 2003 (Continued)

Trial design				Other		
Trial no.	Total patients	Risperidone	Haloperidol	neuroleptics ^a	Olanzapine	Placebo
Open long-term trials						
CAN-20	77	77	0	0	0	0
INT-41	504	504	0	0	0	0
INT-70	48	48	0	0	0	0
HUN-4	35	35	0	0	0	0
USA-97	107	107	0	0	0	0
TOTAL^j	1100	953	0	0	0	183
OVERALL						
TOTAL	20203ⁱ	15553	1499	527	836	1825

- Clinical trial reports for all trials are available upon request. In addition, as indicated by reference numbers, some trials have been reported in the literature.

- Trials marked in bold are those in which one or more patients in any treatment group reported a glucose-related adverse event.

- Trials marked in italics are those that were not included in the evaluation of glucose-related adverse events because their databases were not in an appropriate format for merging electronically at the time of this report. This accounted for 505 patients, all of whom received risperidone. These patients are included in the calculation of the total number of patients and the total number treated with risperidone in this table, but are not included in the numerator or denominator of percentages shown in the summary tables.

^a Other neuroleptics include zuclopenthixol (FIN-1), perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

^b Only conventional neuroleptics were used. Specific drug names are unavailable.

^c Patients in the risperidone group were simultaneously receiving a mood stabilizer. Patients in the placebo groups were taking mood stabilizer alone.

^d In trials RIS-USA-240 and RIS-USA-241 divalproate treatment is considered as concomitant therapy. Only the taper phase of RIS-USA-241 is included in the analysis because it is part of the treatment phase.

^e RIS-INT-57 permitted inclusion of elderly patients (n=75).

^f The run-in phase of RIS-INT-85 during which subjects received 2 cycles of conventional neuroleptics is not included in the analyses. For this analysis, the visit at the end of run-in was used as baseline.

^g Patients enrolled had to be 55 years or older. Median age in these trials ranged from 81 to 87 years.

^h BEL-11 was a cross-over study; the same patients were counted in the risperidone as well as the placebo group. Of the 37 patients in trial BEL-11, 2 were under the age of 18.

ⁱ Includes patients counted in more than one group. Also includes patients counted in both a short-term and long-term trial.

^j Adverse events that occurred during run-in treatment with oral risperidone were included in summary tables.

^k Trial RIS-INT-69 consisted of two treatment periods. During the first period, 438 subjects were randomized to risperidone, haloperidol or placebo. Subjects who completed this 3 weeks of double-blind treatment then either continued double-blind treatment during 9 weeks (227 subjects, placebo subjects in part I received risperidone) or received open-label risperidone treatment (146 subjects). Subjects who participated in both periods of the trial were counted twice.

^l Open label follow-up trials that are ongoing. Cut-off date for subject inclusion was 28 March 2003.

Source: Display GAE.2 and Clinical Trial Reports

Patients could be exposed to risperidone during double-blind trials and could continue to open-label treatment in subsequent trials. The relationship of the trials is shown in Table 2.

The open-label, long-term trial, USA-7 (n=105 with 5 patients having glucose-related adverse events) was an extension of several other open-label, long-term trials. These 105 patients in USA-7 were counted only once, in the first open-label, long term trial (USA-6, USA-5, or USA-9) in which they participated. The 48 patients in INT-70 and 35 patients in HUN-4 were counted as separate patients from those in the preceding long-term trial, INT-41. The same procedure was followed for subjects in follow up trials INT-63, INT-80 **REDACTED** and USA-265.

Table 2: Relationship Between Double-Blind and Open-Label Extension Trials

Double-blind, controlled (N)	Open-label (N)	Open-label (N)
GBR-28 (23) →	GBR-29 (19)	
INT-39 (54) →	INT-47 (39)	
INT-24 (334) →	INT-26 (83)	
INT-2 & INT-3 (1362 & 523) →	INT-4 (386)	
INT-3 (523) →	USA-6 (265) →	USA-7 (71)
USA-1 (160) & USA-3 (Phase I) →	USA-5 (4+3) →	USA-7 (3)
USA-8 (not included) →	USA-9 (107) →	USA-7 (31)
USA-63 (625) →	USA-70 (330)	
USA-93 (118) →	USA-97 (107)	
CAN-19 (110) →	CAN-20 (77) + INT-41 (23)	
	INT-41 (504) →	INT-70 (48)
	INT-41 (504) →	HUN-4 (35)
USA-240 (39) →	USA-241 (17)	
	INT-57 & INT-61 (762 & 779) →	INT-63 (810)
	INT-62 & INT-85 (618 & 166) →	INT-80 (315)
	INT-121 (507) →	REDACTED
	USA-259 (141) →	USA-265 (100)

Numbers in parentheses are the numbers of patients included.

3.1.2. Subjects Evaluated for Laboratory Glucose Data

Analysis of glucose levels was based on trials for which the protocol specified the collection of glucose laboratory data (Table 3). The trials were not designed to measure the impact of risperidone on glucose metabolism. Data were derived from routine laboratory tests. Fasting was required per protocol only in trials RIS-USA-232 and RIS-INT-83 (although fasting or nonfasting state for each sample was not recorded in the database), and recommended in trial RIS-INT-62. In none of the pediatric trials were glucose levels determined.

Risperidone: Effects on Glucose Metabolism

Table 3: Trials With Glucose Data Available

Trial Design Trial no.	Total patients	Risperidone	Haloperidol	Other neuroleptic ^a	Olanzapine	Placebo
TRIALS IN ADULT SUBJECTS (18-65 yrs)						
Double-blind short-term trials						
FIN-1	98	48	0	50	0	0
INT-10	211	211	0	0	0	0
IND-2	290	146	0	0	0	144
INT-2	1362	1136	226	0	0	0
INT-3	523	348	87	0	0	88
INT-5	183	99	84	0	0	0
INT-9	149	75	0	74	0	0
INT-46 ^b	150	75	0	0	0	75
SUI-1	86	43	0	43	0	0
USA-1	160	53	53	0	0	54
USA-60	441	441	0	0	0	0
USA-72	246	163	0	0	0	83
USA-102 ^b	156	52	53	0	0	51
USA-239	259	134	0	0	0	125
USA-240	39	14	0	0	0	25
INT-69 ^f	438	154	144	0	0	140
INT-69 ^f	227	163	64	0	0	0
Open short-term trials						
USA-241	17	17	0	0	0	0
INT-85 ^e	166	166	0	0	0	0
INT-69 ^f	146	146	0	0	0	0
USA-259	141	141	0	0	0	0
INT-81	283	283	0	0	0	0
Double-blind long-term trials						
INT-6	190	91	99	0	0	0
USA-79	395	192	203	0	0	0
Open long-term trials						
INT-12	483	483	0	0	0	0
NED-2	40	40	0	0	0	0
USA-5	7	7	0	0	0	0
USA-6	265	265	0	0	0	0
USA-7 ^c	105	105	0	0	0	0
USA-9	107	107	0	0	0	0
INT-62	618	318	0	0	300	0
USA-265 ^g	100	100	0	0	0	0
INT-80 ^g	315	315	0	0	0	0
TOTAL^d	8291	6026	1013	167	300	785

(Continued)

Table 3: Trials With Glucose Data Available (Continued)

Trial design Trial no.	Total patients	Risperidone	Haloperidol	Other neuroleptic ^a	Olanzapine	Placebo
TRIALS IN ELDERLY SUBJECTS (>65 yrs)						
Double-blind short-term trials						
<i>AUS-5^c</i>	337	167	0	0	0	170
<i>INT-24^c</i>	344	115	115	0	0	114
<i>INT-50</i>	175	87	0	0	88	0
<i>USA-63^c</i>	625	462	0	0	0	163
<i>USA-232^c</i>	473	235	0	0	0	238
<i>INT-83^c</i>	18	10	0	0	0	8
Open long-term trials						
<i>INT-23</i>	180	180	0	0	0	0
<i>INT-26</i>	83	83	0	0	0	0
<i>USA-70</i>	330	330	0	0	0	0
TOTAL^d	2565	1669	115	0	88	693
OVERALL TOTAL^d	10856	7695	1128	167	388	1478

Trials marked in italics are those with medical history information available.

^a Other neuroleptics include zuclopenthixol (FIN-1), remoxipride (INT-9), clozapine (SUI-1), and olanzapine (INT-50).

^b In trials INT-46 and USA-102, patients who received placebo/haloperidol during the double-blind phase and then received risperidone during the open-label phase were counted in both the risperidone and placebo/haloperidol groups for this analysis.

^c Patients enrolled had to be 55 years or older. Median age in these trials ranged from 81 to 87 years.

^d Includes patients counted in more than one group. Also includes patients counted in both a short-term and long-term trial.

^e The run-in phase of RIS-INT-85 during which subjects received 2 cycles of conventional neuroleptics is not included in the analyses. For this analysis, the visit at the end of run-in was used as baseline.

^f Trial RIS-INT-69 consisted of two treatment periods. During the first period, 438 subjects were randomized to risperidone, haloperidol or placebo. Subjects who completed this 3 weeks of double-blind treatment then either continued double-blind treatment during 9 weeks (227 subjects, placebo subjects in part I received risperidone) or received open-label risperidone treatment (146 subjects). Subjects in the different parts of the trial were counted twice.

^g Open-label follow-up trials that are ongoing. Cut-off date for subject inclusion is March 28 2003.

3.1.2.1. Patients With Medical History Information

A subset of patients in the glucose laboratory database had specific information recorded about their medical history. The short-term trials with this data available were AUS-5, IND-2, INT-2, INT-24, INT-46, INT-5, INT-50, INT-85, USA-102, USA-239, USA-240, USA-241, INT-69, INT-81, USA-259, and USA-232, with a total of 5298 patients. Long-term trials were INT-6, INT-12, INT-23, INT-26, INT-62, INT-80, USA-265, as well as INT-35 and INT-70 (neither of which had glucose level data), with a total of 2572 patients. In Table 3, trials with medical history information are italicized.

3.2. Methods of Analysis

3.2.1. Glucose-Related Adverse Events

In the population described in Section 3.1.1, the incidence of adverse events related to abnormalities of glucose metabolism (glucose-related adverse events) was determined. The events summarized are worsenings of pre-existing conditions, or newly diagnosed diabetes or abnormalities in glucose metabolism. The following were considered glucose-related adverse events: metabolic acidosis, decreased blood sugar, increased blood sugar, diabetic coma, hyperosmolar, diabetes mellitus, diabetes mellitus aggravated, diabetes mellitus deteriorated, new onset diabetes mellitus, diabetes mellitus precipitated, diabetes mellitus reactivated, diabetic ketoacidosis, abnormal glucose tolerance, glucose tolerance decreased, abnormal glucose tolerance test, glycosuria, hyperglycemia, hypoglycemia, hypoglycemic reaction, ketoacidosis, and ketonuria.

Pre-trial adverse events and post-trial/follow-up non-serious adverse events were excluded from the summary tabulations.

Patients in placebo/risperidone crossover trials were included in the total number of patients to determine the incidence for both placebo and risperidone treatment. The incidence of adverse events was attributed to the treatment at onset of each event.

The incidence of glucose-related adverse events in the placebo and active treatment groups (risperidone, haloperidol, olanzapine, other neuroleptics) was summarized by treatment, by trial design (short- and long-term trials), and by age. Glucose-related adverse events were described in detail if they were serious or if death or discontinuation occurred due to a glucose-related adverse event. In addition, the incidence of glucose-related adverse events among the population described in Section 3.1.2.1 was summarized by history of pre-existing diabetes.

3.2.2. Glucose Levels

Glucose levels were examined in the subject sample described in Section 3.1.2. In the majority of trials, fasting conditions were not required or recommended; results from those trials were treated as random samples. Subjects with a glucose level <7.8 mmol/L at baseline were considered to have a normal value. Levels ≥ 7.8 mmol/L and <11.1 mmol/L during the trial were categorized as suggestive of 'impaired glucose tolerance'. Levels ≥ 11.1 mmol/L were categorized as suggestive of 'diabetes'. These criteria

were based on recommendations of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus according to which random levels ≥ 11.1 mmol/L are diagnostic for diabetes in the presence of clinical symptoms; results of oral glucose tolerance tests 2 hours post-load or fasting plasma glucose levels ≥ 7.8 and < 11.1 mmol/L are diagnostic of impaired glucose tolerance.¹⁶ For research purposes in this summary, these classifications were made without confirmation by observation of clinical symptoms of diabetes, measurement of fasting glucose, or performance of an oral glucose tolerance test. Limits appropriate for fasting samples were applied to glucose data obtained from subjects expected or known to be fasting (patients in RIS-USA-232 and RIS-INT-83, and some patients in trial INT-62): levels < 6.1 mmol/L were considered normal, levels ≥ 6.1 mmol/L but < 7 mmol/L were suggestive of impaired glucose tolerance, and levels ≥ 7 mmol/L were suggestive of diabetes.

The incidence of glucose levels beyond the stated limits among patients with normal baseline levels was examined by trial duration, by age, and by history of diabetes.

3.2.3. Medical History

In the population described in Section 3.1.2.1, a physician reviewed the subjects' available medical histories, including concomitant medications started prior to baseline, to determine the presence of diabetes at baseline. A patient was considered to have prior diabetes if it was clearly stated on the medical history page and/or if prior medications included insulin or other glucose-regulating drugs. For most extension trials, medical history at baseline of the preceding trial was used. Glucose-related adverse events in a preceding trial were not used to determine prior history of diabetes for patients in extension trials.

3.2.4. Weight Gain

Mean change $\pm$ SD in body weight from baseline to study endpoint was analyzed using pooled data from subjects in 76 risperidone clinical studies (Phases 2 through 4). This analysis uses the baseline and last postbaseline weight measurements from subjects in short term (12 weeks or less) or long-term (6 months or longer) studies. Body weight changes were also analyzed by the percentages of subjects with body weight increases at endpoint of $> 7\%$ of baseline weight in short- and long-term trials. A 7% weight gain is the equivalent to a gain of approximately 5 kg in a 70 kg individual, and is a commonly quoted standard for clinically meaningful

weight gain in adults. Since growth and weight gain would be expected in subjects younger than 18 years, any discussion of this age group should take into account the natural weight gain. According to the National Center for Health Statistics (NCHS) percentiles¹⁹, the annual expected weight gain for an 8-year-old male of 34.6 kg is 5.1 kg. Since this normal weight change corresponds to a weight gain of 14.7%, the standard of 7% as the definition for clinically meaningful weight gain is therefore not appropriate for children. It should be noted that the weight gain for risperidone-treated pediatric/adolescent subjects in long-term trials (680 subjects, with the mean age = 9.6 years) was 7.4 kg or 20.4%.

4. RESULTS

4.1. Adverse Events Related to Abnormalities in Glucose Metabolism

4.1.1. Overall Incidence

Table 4 shows the incidence of glucose-related adverse events in short-term trials only. The incidence with risperidone treatment (0.72% of 8458 patients) was very low and comparable to, if not lower than that with placebo or olanzapine treatment (0.88% of 1825 patients and 0.93% of 536 patients respectively). Relative to haloperidol and other neuroleptics (0.33% of 920 patients and 0.34% of 293, respectively) the incidence was higher with both risperidone and placebo. Other neuroleptics included zuclopenthixol (FIN-1), perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

Risperidone: Effects on Glucose Metabolism

Table 4: Incidence (Number of Patients and %) of Adverse Events Related to Abnormalities in Glucose Metabolism in Short-Term Trials

Adverse event preferred term	Placebo N=1825	Risperidone N=8458	Haloperidol N=920	Olanzapine N=536	Other neuroleptics ^a N=293
Any glucose-related adverse event	16 (0.88%)	61 (0.72%)	3 (0.33%)	5 (0.93%)	1 (0.34%)
Acidosis	0	1 (0.01%)	0	0	0
Blood sugar increased	0	2 (0.03%)	0	0	0
Coma diabetic ^b	0	1 (0.01%)	0	0	0
Diabetes mellitus	3 (0.16%)	9 (0.11%)	0	2 (0.37%)	1 (0.34%)
Diabetes mellitus aggravated	0	2 (0.03%)	0	0	0
Glycosuria	1 (0.07%)	6 (0.07%)	0	1 (0.19%)	0
Hyperglycaemia	10 (0.55%)	40 (0.47%)	3 (0.33%)	3 (0.56%)	0
Hypoglycaemia	3 (0.21%)	7 (0.10%)	0	0	0
Ketosis	0	1 (0.01%)	0	0	0
Plasma osmolality increased	0	1 (0.01%)	0	0	0

Trials included: AUT-1, BEL-5, BEL-7, FIN-1, FRA-3, GER-5, INT-10, INT-2, INT-3, INT-5, INT-7, INT-9, INT-39/GBR-28, INT-45, INT-46, KOR-1, SUI-1, USA-1, USA-60, USA-72, USA-102, USA-112, GER-3, INT-1, ITA-1, USA-54, BEL-14, INT-24, USA-63, BEL-11, BEL-24, NED-9, CAN-19, USA-93, BEL-21, BEL-22, AUS-5, INT-32, INT-50, INT-61, USA-121, IND-2, INT-85, USA-239, USA-240, USA-241, INT-69, INT-81, **REDACTED**, USA-232, INT-83

^a Other neuroleptics include: zuclopenthixol (FIN-1), perphenazine (INT-7), remoxipride (INT-9), clozapine (GER-5, SUI-1), methotrimeprazine (FRA-3).

^b Although originally coded as "coma diabetic", this elderly patient (#1204) experienced hyperglycemia with a hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure and died one day later.

Source: Display GAE.1, Display GAE.4, Table GAE.4A GLUCOSE, Table SAF.AE.1 glucose, Table SAF.AE.10 glucose

In long-term trials, there was a comparable incidence of glucose-related adverse events with risperidone treatment (1.49 % of 6590 patients) and with both haloperidol treatment (1.55% of 579 patients) and olanzapine treatment (1.66% of 300 patients) (Table 5). No glucose-related AE's were reported for other neuroleptics (0% of 234 patients). There were no long-term, double-blind trials with placebo.

Table 5: Incidence (Number of Patients and %) of Adverse Events Related to Abnormalities in Glucose Metabolism in Long-Term Trials

Adverse event preferred term	Risperidone N=6590	Haloperidol N=579	Olanzapine N=300	Other neuroleptics ^a N=234
Any glucose-related adverse event	98 (1.49%)	9 (1.55%)	5 (1.66%)	0
Acidosis	1 (0.02%)	0		0
Diabetes mellitus	32 (0.049%)	5 (0.86%)	1 (0.33%)	0
Diabetes mellitus aggravated	2 (0.03%)	0		0
Glycosuria	22 (0.33%)	0		0
Hyperglycaemia	48 (0.73%)	5 (1.66%)	4 (1.33%)	0
Hypoglycaemia	5 (0.11%)	1 (0.17%)		0
Ketosis	1 (0.02%)	0		0

Trials included: INT-6, USA-79, BEL-17, INT-4, INT-8, INT-12, INT-17, INT-47/GBR-29, ISR-1, NED-2, USA-5, USA-6, USA-7, USA-9, INT-23, INT-26, USA-34, USA-64, USA-70, USA-97, CAN-20, INT-41, INT-57, INT-35, INT-70, INT-62, HUN-4, INT-63, REDACTED USA-265, INT-80

^a Conventional neuroleptics, not specified (INT-17)

Source: Display GAE.1, Display GAE.4, Table GAE.4A GLUCOSE, Table SAF.AE.1 glucose, Table SAF.AE.10 glucose

4.1.2. Serious Adverse Events and Discontinuations Due to Adverse Events Related to Abnormalities in Glucose Metabolism

The incidence of serious adverse events related to abnormalities in glucose metabolism with short-term risperidone treatment (0.11% of 8458 patients) was comparable to, if not lower than, short-term placebo (0.22% of 1825 patients) or short-term haloperidol treatment (0% of 920 patients). No serious adverse events with olanzapine or with neuroleptics other than haloperidol were related to abnormalities of glucose metabolism. The incidence of discontinuations due to adverse events related to abnormalities in glucose metabolism with risperidone treatment in short-term trials (0.02%) was lower than for placebo treatment (0.05%). No discontinuations due to adverse events related to abnormalities of glucose metabolism were reported in the groups treated with olanzapine or neuroleptics other than haloperidol in short-term trials (Table 6). However, the number of subjects in these groups was too small to draw any conclusions.

One fatal outcome was reported (#1204 in trial USA-63). It concerned an 85-year-old black man with a history of multiple medical problems, including insulin-dependent diabetes and chronic renal insufficiency. Although the event was originally coded as "coma diabetic", the details indicate that the patient experienced hyperglycemia with a hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure. He discontinued treatment with risperidone after 13 days, when he was

hospitalized for lethargy and somnolence. Evaluation identified a *Proteus* urinary tract infection, hyperglycemia, hypokalemia, and hypocalcemia. The patient progressed to urosepsis complicated by acute renal failure and a nonketotic hyperosmolarity syndrome, and died one day later. The investigator considered the adverse events unrelated to trial medication.

Table 6: Incidence of Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events Related to Abnormalities in Glucose Metabolism in Short-Term Trials

	Placebo N=1825	Risperidone N=8458	Haloperidol N=920
Deaths	0	1 (0.01%) ^{a,b}	0
Serious adverse events	4 (0.22%)	9 (0.11%)	0
Discontinuations due to adverse events	1 (0.05%)	2 (0.02%)	0

^a One patient (#4113 in USA-63) died from non-glucose-related adverse events but did report a glucose-related adverse event during treatment. The narrative is included in Annex 1 but is not included in this summary table.

^b Although originally coded as "coma diabetic", this elderly patient (#1204 in USA-63) experienced hyperglycemia with a hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

No deaths, discontinuations or serious adverse events related to abnormalities of glucose metabolism were reported with olanzapine or other neuroleptic treatment; not shown in the table.

Trials: AUT-1, BEL-5, BEL-7, FIN-1, FRA-3, GER-5, INT-10, INT-2, INT-3, INT-5, INT-7, INT-9, INT-39/GBR-28, INT-45, INT-46, KOR-1, SUI-1, USA-1, USA-60, USA-72, USA-102, USA-112, GER-3, INT-1, ITA-1, USA-54, BEL-14, INT-24, USA-63, BEL-11, BEL-24, NED-9, CAN-19, USA-93, BEL-21, BEL-22 AUS-5, INT-32, INT-61, INT-50, USA-121, IND-2, INT-85, USA-239, USA-240, USA-241, INT-69, INT-81, USA-259, USA-232, INT-83

Source: Table GAE.5A GLUCOSE, Table GAE.5B GLUCOSE, Table GAE.5C GLUCOSE, Table SAF.AE.3 glucose, Table SAF.AE.4 glucose, Table SAF.AE.5 glucose, Table SAF.AE.12 glucose, Table SAF.AE.13 glucose, Table SAF.AE.14 glucose and Clinical Trial Reports

The incidence of serious adverse events with long-term risperidone treatment (0.26% of 6590 patients) was lower than with long-term haloperidol treatment (0.52% of 579 patients). The incidence of discontinuations in long-term trials was lower in patients receiving risperidone (0.05%) than in those receiving haloperidol (0.17%) (Table 7).

Table 7: Incidence of Deaths, Serious Adverse Events and Discontinuations Due to Adverse Events Related to Abnormalities in Glucose Metabolism in Long-Term Trials

	Placebo N=0	Risperidone N=6590	Haloperidol N=579
Deaths	--	0 ^a	0
Serious adverse events	--	17 (0.26%)	3 (0.52%)
Discontinuations due to adverse events	--	3 (0.05%)	1 (0.17%)

^a Two patients (A00367/INT-23 and A30202/INT-63) died from non-glucose-related adverse events but did report a glucose-related adverse event during treatment. The narratives are included in Annex 1 but those patients are not included in this summary table.

No deaths, discontinuations or serious adverse events related to abnormalities of glucose metabolism were reported with other neuroleptic treatment or olanzapine; not shown in the table.

Trials: INT-6, USA-79, BEL-17, INT-4, INT-8, INT-12, INT-17, INT-47/GBR-29, ISR-1, NED-2, USA-5, USA-6, USA-7, USA-9, INT-23, INT-26, USA-34, USA-64, USA-70, USA-97, INT-57, CAN-20, INT-41, INT-70, INT-35, INT-62, HUN-4, INT-63, REDACTED INT-80

Source: Table GAE.5A GLUCOSE, Table GAE.5B GLUCOSE, Table GAE.5C GLUCOSE, Table SAF.AE.3 glucose, Table SAF.AE.4 glucose, Table SAF.AE.5 glucose, Table SAF.AE.12 glucose, Table SAF.AE.13 glucose, Table SAF.AE.14 glucose and Clinical Trial Reports

Glucose-related serious adverse events are listed in Table 8. Among 26 risperidone-treated patients who had a serious adverse event, 11 patients experienced hyperglycemia, 10 patients experienced diabetes mellitus (worsening or new onset), 4 patients experienced hypoglycemia, and 1 had glucosuria. The patient who died had a serious adverse event listed as diabetic coma (described above). Fourteen of the risperidone-treated patients with a serious glucose-related adverse event had a pre-existing glucose-related condition; an additional risperidone-treated patient had history of diabetes documented only in the CIOMS. Among haloperidol-treated patients, serious adverse events included diabetes mellitus, hypoglycemia, and hyperglycemia. Serious adverse events among placebo patients were uncontrolled diabetes, hypoglycemia, and hyperglycemia.

Four of the 7 patients who discontinued due to adverse events related to abnormalities in glucose metabolism were elderly. The one haloperidol patient, the one placebo patient, and 3 of the 5 risperidone-treated patients who discontinued had pre-existing abnormalities in glucose metabolism.

Individual narratives for deaths, other serious adverse events and adverse events leading to discontinuation are provided in Annex 1.

Table 8: Patients Who Died, Had Serious Adverse Events or Discontinued Due to Glucose-Related Adverse Events

Trial no. Patient no.	Treatment group	Adverse event (WHO preferred term)	Discontinued due to AE	Serious adverse event	Death
ADULTS (18-65 years)					
INT-61 (Double-blind short-term)					
A30445 ^a	RIS oral	Hyperglycemia		X	
A30755	RIS oral	Diabetes mellitus		X	
USA-79 (Double-blind long-term)					
0054	RIS	Diabetes mellitus		X	
0601 ^a	RIS	Diabetes mellitus		X	
0084 ^a	HAL	Diabetes mellitus			
		Hypoglycemia		X	
0302	HAL	Diabetes mellitus		X	
0349 ^a	HAL	Hyperglycemia	X	X	
INT-45 (Double-blind short-term)					
A30142 ^a	RIS	Hyperglycemia			
		Hypoglycemia		X	
USA-102 (Double-blind short-term)					
A30030	PLA	Uncontrolled diabetes		X	
USA-6 (Open-label long-term)					
0254	RIS	Hypoglycemia		X ^b	
INT-85 (Open-label short-term)					
30272 ^a	RIS	Hyperglycemia		X	
INT-62 (Open-label long-term)					
30358 ^a	RIS	Hyperglycemia	X	X	
REDACTED					
INT-63 (Open-label long-term)					
30176 ^a	RIS	Diabetes mellitus		X	
30184	RIS	Hyperglycemia		X	
30202	RIS	Hyperglycemia		X	(X ^d)
30468 ^a	RIS	Hyperglycemia		X	
30767 ^a	RIS	Hyperglycemia		X	
30779	RIS	Diabetes mellitus		X	
ELDERLY (>65 years)					
AUS-5 (Double-blind short-term)					
160	PLA	Hypoglycemia		X	

(Continued)

Table 8: Patients Who Died, Had Serious Adverse Events or Discontinued Due to Glucose-Related Adverse Events (Continued)

Trial no. Patient no.	Treatment group	Adverse event (WHO preferred term)	Discontinued due to AE	Serious adverse event	Death
ELDERLY >65 (continued)					
USA-63 (Double-blind short-term)					
0911 ^a	PLA	Hyperglycemia		X	
4113 ^a	PLA	Hyperglycemia	X	X	(X ^d)
0115 ^a	RIS	Hypoglycemia		X	
1204 ^{a,f}	RIS	Diabetic coma	X	X	X
2613 ^a	RIS	Hyperglycemia	X		
4013	RIS	Hyperglycemia		X	
4014 ^a	RIS	Diabetes mellitus		X	
INT-23 (Open-label long-term)					
A00118 ^a	RIS	Diabetes mellitus		X	
A00367	RIS	Hypoglycemia		X	(X ^d)
USA-70 (Open-label long-term)					
2916 ^a	RIS	Diabetes mellitus		X	
4118	RIS	Hyperglycemia	X	X	
4206	RIS	Hyperglycemia		X	
TOTAL			7^c	33	1^e

DC: Discontinuation; SAE: Serious adverse event; PLA: placebo; HAL: haloperidol; RIS: risperidone

A patient narrative is provided in Annex 1 for all patients listed in this table.

^a Patient had a pre-existing condition of diabetes either reported during screening or based on treatment with concomitant medication for the condition before the onset of the glucose-related adverse event; or had a history of endocrine disorder that was unspecified and no concomitant medication suggesting an endocrine disorder other than a glucose-related one; or had elevated glucose levels prior to treatment with risperidone.

^b This patient was not included in the clinical database as having a serious adverse event that was glucose-related although the patient was hospitalized for hypoglycemia.

^c Patient 0076 from trial USA-79 (HAL) was listed in the August 2000 report as having discontinued due to a glucose-related event, but is not included in this table as the discontinuation was due to other reasons. A narrative is provided.

^d This patient died but the cause of death was not due to a glucose-related adverse event. A narrative is provided in Annex 1 for completeness.

^e One patient is indicated because this patient died of a glucose-related adverse event. The additional patients surrounded by parentheses in this column did not die from glucose-related causes but are shown for completeness.

^f Although originally coded as "coma diabetic", this elderly patient (#1204) experienced hyperglycemia with a hyperosmolar non-ketotic state as a complication of urinary sepsis and acute renal failure.

^g History of diabetes documented in CIOMS only.

4.1.3. Subgroup Analysis

4.1.3.1. Age

Overall, the incidence of glucose-related adverse events in all age groups was very low. Incidence of glucose-related adverse events appeared to be age-dependent, with elderly patients having a higher incidence than younger groups regardless of treatment or duration of treatment. This relationship is consistent with epidemiological studies showing a higher incidence of diabetes in elderly as opposed to younger adults in the general population.^{17,18}

In the short-term trials, there were no glucose-related adverse events in the pediatric population. However, glucose levels were not typically measured in pediatric trials so adverse events describing glucose levels (e.g., hyperglycemia) were unlikely to be recorded. In adults, the incidence of glucose-related adverse events was low with risperidone treatment (0.52% of 7169 subjects) and comparable to placebo (0.43% of 935 subjects). Elderly patients treated with risperidone showed a slightly higher incidence of adverse events compared to placebo-treated patients (2.17% of 1105 subjects and 1.70% of 707 subjects, respectively) (Table 9).

In long-term trials, the incidence of glucose-related adverse events was 0.13% of 782 pediatric subjects, 1.51% of 4982 adults, and 2.66% of 826 elderly among risperidone-treated patients. The incidence was 1.58% among 569 haloperidol-treated adults, 1.68% among 297 olanzapine-treated adults and 0% for the 234 adults who received other neuroleptics. There were no comparator groups of elderly or pediatric subjects (10 and 3 subjects only) (Table 9).

Table 9: Incidence (Number of Patients and %) With at Least One Glucose-Related Adverse Event by Age and by Duration of Trial

Trial duration Treatment	Pediatric: <18 yrs		Adult: 18 - 65 years		Elderly: >65 years	
	N	n (%)	N	n (%)	N	n (%)
Short-term trial (≤3 months)						
Placebo	183	0	935	4 (0.43%)	707	12 (1.70%)
Risperidone	184	0	7169	37 (0.52%)	1105	24 (2.17%)
Haloperidol	--	--	802	2 (0.25%)	118	1 (0.85%)
Olanzapine	--	--	458	4 (0.87%)	78	1 (1.28%)
Other Neuroleptic	--	--	293	1 (0.34%)	--	--
Long-term trial (≥6 months)						
Risperidone	782	1 (0.13%)	4982	75 (1.51%)	826	22 (2.66%)
Haloperidol	10	0	569	9 (1.58%)	--	--
Olanzapine	--	--	297	5 (1.68%)	3	0
Other Neuroleptic	--	--	234	0	--	--

Source: Display GAE.5, Table GAE.4A.AGE.GLUCOSE, Table SAF.AE.2 glucose, Table SAF.AE.11 glucose

4.1.3.2. Medical History of Diabetes

In the population described in Section 3.1.2.1, there were 275 distinct patients with pre-existing diabetes and 5023 distinct patients without pre-existing diabetes in the short-term trials. Most glucose-related adverse events occurred in patients with a prior medical history of diabetes. Among those with a prior history of diabetes, glucose-related adverse events occurred in 6.2% (9/145) of the risperidone group and 6.5% (6/93) of the

placebo group in short-term trials. Among patients with no prior history of diabetes, the percentage with glucose-related adverse events was low (0.5%) with risperidone, and similar to groups treated with placebo (0.5%), haloperidol (0.5%) and other neuroleptics (0.4%) in short-term trials. (Table 10).

Table 10: Incidence of Glucose-Related Adverse Events by Medical History in Short-Term Trials

Adverse event preferred term	No pre-existing diabetes				Pre-existing diabetes			
	RIS N=3297	Placebo N=989	Haloperidol N=206	Other N=531	RIS N=145	Placebo N=93	Haloperidol N=2	Other N=35
Any glucose-related adverse event	15 (0.5%)	5 (0.5%)	1 (0.5%)	2 (0.4%)	9 (6.2%)	6 (6.5%)	0	1 (2.9%)
Hyperglycemia	12 (0.4%)	2 (0.2%)	1 (0.5%)	2 (0.4%)	8 (5.5%)	4 (4.3%)	0	0
Glycosuria	4 (0.1%)	1 (0.2%)	0	0 (0%)	1 (0.7%)	1 (1.1%)	0	0
Diabetes mellitus	2 (0.6%)	2 (0.2%)	0	0	0	1 (1.1%)	0	1 (2.9%)
Hypoglycemia	0	1 (0.2%)	0	0	0	1 (1.1%)	0	0

N = Subjects with medical history data.

Source: Table GAE.6A.diab.glucose, Table SAF.AE.6 glucose, Table SAF.AE.15 glucose

In long-term trials, there were 63 distinct patients who had pre-existing diabetes and 2509 distinct patients no history of diabetes. Among patients without prior history of diabetes a higher percentage of patients treated with olanzapine (1.4%) than those treated with risperidone (0.7%) had a glucose-related adverse event. There were few events among those with a positive prior history but the number of patients with data available was too small for any firm conclusions (56 risperidone-treated patients) (Table 11).

Table 11: Incidence of Glucose-Related Adverse Events by Medical History in Long-Term Trials

Adverse event preferred term	No pre-existing diabetes			Pre-existing diabetes		
	RIS N=1840	Olanzapine N=295	Other N=374	RIS N=56	Olanzapine N=5	Other N=2
Any glucose-related adverse event	12 (0.7%)	4 (1.4%)	0	8 (14.3%)	1 (20%)	0
Acidosis	0		0	1 (2.5%)		0
Hyperglycemia	8 (0.4%)	3 (1.0%)	0	6 (10.7%)	1 (20%)	0
Glycosuria	1 (0.1%)	0	0	1 (1.8%)	0	0
Diabetes mellitus	2 (0.1%)	1 (0.3%)	0	1 (2.5%)		0
Hypoglycemia	1 (0.1%)		0	0		0

N = Subjects with medical history data.

Source: Table GAE.6A.diab.glucose, Table SAF.AE.6 glucose, Table SAF.AE.15 glucose

4.1.3.3. Age and Medical History of Diabetes

The subgroups described in Section 4.1.3.2 above were further subdivided by age. Among adults in short-term trials with no prior history of diabetes, glucose-related adverse events occurred at similar rates in risperidone and placebo-treated subjects. Among elderly patients with no prior history of diabetes, glucose-related adverse events occurred in 1.1% of risperidone treated patients and 0.5% of placebo patients. Among patients with a prior history of diabetes, the percentages of patients with glucose-related adverse events were similar in adults and elderly and were no higher with risperidone than with placebo in the elderly. (Table 12)

In long-term trials, among adults with no prior history of diabetes, the percentage of adults with glucose-related adverse events was lower for risperidone-treated patients (0.7%) than for olanzapine-treated patients (1.4%). However the relationship of age with medical history and glucose-related adverse events could not be assessed due to small numbers of patients in the different groups. (Table 13)

Table 12: Incidence of Glucose-Related Adverse Events by Medical History and Age in Short-term Trials

Age	No pre-existing diabetes			Pre-existing diabetes		
	Risperidone	Olanzapine	Placebo	Risperidone	Olanzapine	Placebo
<18	0/8	--	--	--	--	--
18-65	8/2747 (0.3%)	--	3/550 (0.5%)	4/60 (6.7%)	--	0/16
>65	6/531 (1.1%)	--	2/435 (0.5%)	5/85 (5.8%)	--	6/76 (7.9%)

Denominator is the number of subjects with medical history data.

Source: Table GAE.6A.diab.age glucose, Table SAF.AE.6a glucose, Table SAF.AE.16 glucose

Table 13: Incidence of Glucose-Related Adverse Events by Medical History and Age in Long-term Trials

Age	No pre-existing diabetes		Pre-existing diabetes	
	Risperidone	Olanzapine	Risperidone	Olanzapine
<18	0/67	--	--	--
18-65	12/1659 (0.7%)	4/292 (1.4%)	7/45 (15.5%)	1/5 (20%)
>65	0/126	0/3	1/11 (9%)	--

Denominator is the number of subjects with medical history data.

Source: Table GAE.6A.diab.age glucose, Table SAF.AE.6a glucose, Table SAF.AE.16 glucose

4.2. Glucose Levels Suggestive of Disturbances in Glucose Metabolism

4.2.1. Overall Incidence

Glucose levels were available in short-term trials for 7734 patients. In the short-term trials, the percentage of glucose levels suggestive of 'diabetes' (≥ 11.1 mmol/L random samples, ≥ 7 mmol/L fasting) in patients with normal baseline levels (< 7.8 mmol/L random samples, < 6.1 mmol/L fasting) was lower with risperidone (1.6%) than with placebo (3.3%). The percentage with levels suggestive of 'impaired glucose tolerance' (≥ 7.8 and < 11.1 mmol/L random samples, ≥ 6.1 and < 7 mmol/L fasting) was lower with risperidone (5.8%) than placebo treatment (8.7%) (Table 14).

Table 14: Incidence of Elevated Glucose Levels in Short-Term Trials

Glucose levels at any postbaseline time	Risperidone	Placebo	Haloperidol	Other
Suggestive of 'diabetes'	61/3888 (1.6%)	35/1062 (3.3%)	0/161 (0%)	4/611 (0.7%)
Suggestive of 'impaired glucose tolerance'	224/3888 (5.8%)	92/1062 (8.7%)	10/161 (6.2%)	26/611 (4.3%)
Patients with random glucose levels at baseline < 7.8 mmol/L, or fasting glucose levels at baseline < 6.1 mmol/L, and with postbaseline assessments.				

Source: Table SAF.AE.7

Glucose levels were available in long-term trials for 3004 patients. In the long-term trials the percentage of levels suggestive of 'diabetes' was 2.0% for risperidone-treated patients, 2.8% for olanzapine-treated patients, and 3.0% for patients treated with other neuroleptics. The percentage of patients with levels suggestive of 'impaired glucose tolerance' was 10.5% in the risperidone group, 12.6% in the olanzapine group, and 8.7% in the "other" group (Table 15).

Table 15: Incidence of Elevated Glucose Levels in Long-Term Trials

Glucose levels at any postbaseline time	Risperidone	Olanzapine	Other
Suggestive of 'diabetes'	35/1722 (2.0%)	7/247 (2.8%)	7/230 (3.0%)
Suggestive of 'impaired glucose tolerance'	181/1722 (10.5%)	31/247 (12.6%)	20/230 (8.7%)
Patients with random glucose levels at baseline < 7.8 mmol/L, or fasting glucose levels at baseline < 6.1 mmol/L, and with postbaseline assessments.			

Source: Table SAF.AE.7

In trial RIS-INT-62, it was recommended in the protocol that blood samples be taken after fasting and sampling conditions were captured in the database. Of the 106 fasted subjects in the risperidone long-acting injectable group

who had blood glucose values that were normal at baseline, 9 (8.5%) were categorized as having levels 'suggestive of impaired glucose tolerance' at endpoint, and 2 (1.9%) of the subjects were categorized as having fasting blood glucose values 'suggestive of diabetes' at endpoint. Of the 136 fasted subjects in the olanzapine treatment group that had blood glucose levels that were normal at baseline, 13 (9.6%) subjects were categorized as having levels 'suggestive of impaired glucose tolerance' at endpoint, and 4 (2.9%) of the subjects were categorized as having a fasting blood glucose values 'suggestive of diabetes' at endpoint. Although there was a numerical trend for a greater occurrence of glucose metabolism abnormalities in subjects in the olanzapine treatment group, this difference was not statistically significant. It should be noted that the study was not powered to evaluate differences between these treatment groups (Table SAF.LAB.6/INT-62).

4.2.2. Subgroup Analysis

4.2.2.1. Age

Because incidence of diabetes in the general population increases with age, the data were also examined by age group. In addition to the expected age relationship, there appeared to be a higher incidence of glucose levels suggestive of impaired glucose tolerance, but not of levels suggestive of diabetes, among elderly patients treated with risperidone than those treated with placebo or other neuroleptics in short-term trials. In contrast, among non-elderly adults the percentages for risperidone were similar to, if not lower than, those for other treatments (Table 16). In long-term trials, the percentage of glucose abnormalities was lower among adult patients receiving risperidone than those receiving olanzapine or other treatment; there were only 2 subjects in the comparator group (olanzapine) for elderly patients in long-term trials (Table 17).

Table 16: Incidence of Elevated Glucose Levels in Short-Term Trials by Age

Age Group Glucose levels at any postbaseline time	Risperidone	Placebo	Haloperidol	Other
Adults (18-65)				
Suggestive of 'diabetes'	13/3131 (0.4%)	3/598 (0.5%)	0/158 (0%)	1/464 (0.2%)
Suggestive of 'impaired glucose tolerance'	97/3131 (3.1%)	38/598 (6.4%)	9/158 (5.7%)	13/464 (2.8%)
Elderly (>65)				
Suggestive of 'diabetes'	48/743 (6.5%)	32/464 (6.9%)	0/3 (0%)	3/142 (2.1%)
Suggestive of 'impaired glucose tolerance'	116/743 (15.6%)	50/464 (10.8%)	0/3 (0%)	12/142 (8.5%)

Patients with random glucose levels at baseline <7.8 mmol/L, or fasting glucose levels at baseline <6.1 mmol/L, and with postbaseline assessments.

Age was missing for 6 patients treated with risperidone, none of whom had abnormal glucose levels, and 2 in the other treatment group, one of whom had levels suggestive of 'impaired glucose tolerance'.

Source: Table SAF.AE.8

Table 17: Incidence of Elevated Glucose Levels in Long-Term Trials by Age

Age Glucose levels at any postbaseline time	Risperidone	Olanzapine	Other
Adults (18-65)			
Suggestive of 'diabetes'	23/1424 (1.6%)	6/245 (2.4%)	7/230 (3.0%)
Suggestive of 'impaired glucose tolerance'	104/1424 (7.3%)	31/245 (12.7%)	19/230 (8.3%)
Elderly (>65)			
Suggestive of 'diabetes'	12/292 (4.1%)	1/2 (50.0%)	--
Suggestive of 'impaired glucose tolerance'	73/292 (25.0%)	0/2 (0%)	--

Patients with random glucose levels at baseline <7.8 mmol/L, or fasting glucose levels at baseline <6.1 mmol/L, and postbaseline assessments.

Age was missing for 2 risperidone-treated patients, neither of whom had elevated glucose levels.

Source: Table SAF.AE.8

4.2.2.2. Medical History of Diabetes

Of the subjects with medical history assessed for diabetes (See Section 3.2.3), 3854 in the short-term trials and 1281 in the long-term trials had normal glucose levels at baseline. The majority had no prior history of diabetes. Elevations of glucose levels were observed in a higher

percentage of patients with a history of diabetes than in those without such history (Table 18 and Table 19).

Table 18: Incidence of Elevated Glucose Levels in Short-Term Trials by Medical History

Glucose levels at any postbaseline time	No pre-existing diabetes				Pre-existing diabetes		
	RIS	Placebo	Haloperidol	Other	RIS	Placebo	Other
Suggestive of 'diabetes'	34/2488 (1.4%)	22/712 (3.1%)	0/161 (0%)	0/382 (0%)	8/56 (14.3%)	8/39 (20.5%)	3/16 (18.8%)
Suggestive of 'impaired glucose tolerance'	108/2488 (4.3%)	61/712 (8.6%)	10/161 (6.2%)	12/382 (3.1%)	11/56 (19.6%)	6/39 (15.4%)	3/16 (18.8%)

Patients with random glucose levels at baseline <7.8 mmol/L, or fasting glucose levels at baseline <6.1 mmol/L, and with postbaseline assessments.

Source: Table SAF.AE.9 glucose

Table 19: Incidence of Elevated Glucose Levels in Long-Term Trials by Medical History

Glucose levels at any postbaseline time	No pre-existing diabetes			Pre-existing diabetes		
	Risperidone	Olanzapine	Other	Risperidone	Olanzapine	Other
Suggestive of 'diabetes'	8/943 (0.8%)	7/246 (2.8%)	0/79 (0%)	1/10 (10.0%)	0/1 (0%)	0/2 (0%)
Suggestive of 'impaired glucose tolerance'	47/943 (5.0%)	31/246 (12.6%)	0/79 (0%)	4/10 (40.0%)	0/1 (0%)	2/2 (100%)

Patients with random glucose levels at baseline <7.8 mmol/L, or fasting glucose levels at baseline <6.1 mmol/L, and with postbaseline assessments.

Source: Table SAF.AE.9 glucose

4.3. Weight Gain

Weight gain is associated with antipsychotic treatment. A widely referenced study on antipsychotic-induced weight gain (Allison et al) categorizes olanzapine and clozapine as being associated with the highest weight gain among the antipsychotics, risperidone as associated with moderate weight gain and haloperidol as associated with low weight gain.¹ Since weight gain and changes in body composition are associated with glucose-related metabolic disorders²⁰, the J&JPRD clinical database was explored to assess if the rank order of antipsychotic-induced weight gain reported by Allison was confirmed by the J&JPRD clinical database. In addition, weight gain data for both elderly and pediatric populations were examined.

Table 20 summarizes the mean weight changes in short- and long-term trials in pediatric/adolescent (less than 18 years of age), adult (18 to 65 years), and elderly (>65 years) subjects. The mean weight gain ($\pm$ SD) in adults in short-term trials was greater in the risperidone group (1.2 ± 3.64 kg) than in

the placebo group (-0.1 ± 3.38 kg). In comparison, mean weight change at endpoint was 0.4 ± 3.66 kg in the haloperidol, and 0.7 ± 3.19 kg treatment group in the other neuroleptics treatment group. In contrast, weight gain was 3.2 ± 4.53 kg in the olanzapine group. In general, weight increases were lower in elderly subjects in all treatment groups in short-term trials, but the trends in weight gain with treatment type were the same as those for adult subjects. Mean weight change was lowest in elderly subjects receiving placebo or haloperidol (-0.6 ± 3.07 kg and -1.3 ± 3.62 kg, respectively), was slightly higher for risperidone (0.3 ± 3.16 kg), and highest with olanzapine treatment (1.5 ± 3.73 kg).

In long-term trials, the incidence of weight increase in adults taking risperidone or haloperidol was similar (2.3 ± 6.86 kg or 2.9 ± 8.46 kg, respectively), and was greater in those taking olanzapine (4.0 ± 6.59 kg). Insufficient data are available for treatments other than risperidone in elderly subjects in long-term trials. The incidence of weight change observed for risperidone in the elderly in long-term trials (0.2 ± 4.61 kg) is consistent, however, with that observed for risperidone in elderly subjects in short-term trials (0.3 ± 3.16 kg).

Table 20: Mean $\pm$ SD Weight Change (kg) From Baseline to Endpoint by Age Group

Trial duration						
Treatment	N	<18 years	N	18-65 years	N	>65 years
Short term trials						
Placebo	142	0.6 ± 1.67	833	-0.1 ± 3.38	602	-0.6 ± 3.07
Risperidone	139	2.2 ± 1.78	4874	1.2 ± 3.64	964	0.3 ± 3.16
Haloperidol	-	-	651	0.4 ± 3.66	90	-1.3 ± 3.62
Olanzapine	-	-	412	3.2 ± 4.53	72	1.5 ± 3.73
Other neuroleptics ^a	-	-	256	0.7 ± 3.19	-	-
Long-term trials						
Risperidone	680	7.4 ± 5.8	3914	2.3 ± 6.86	660	0.2 ± 4.61
Haloperidol	-	-	484	2.9 ± 8.46	-	-
Olanzapine	-	-	294	4.0 ± 6.59	-	-

^a Other neuroleptics included zuclopenthixol, perphenazine, remoxipride, clozapine, thioridazine, levomepromazine, divalproex.

Trials: AUS-5, AUT-001, BEL-005, BEL-007, BEL-14, BEL-21, BEL-22, BEL-24, CAN-19, CAN-20, FIN-001, FRA-003, GER-003, GER-005, IND-2, INT-002, INT-003, INT-004, INT-005, INT-006, INT-007, INT-008, INT-009, INT-010, INT-12, INT-23, INT-24, INT-26, INT-35, INT-41, INT-45, INT-46, INT-50, INT-57, INT-61, INT-62, INT-63, INT-69, INT-70, INT-80, INT-81, INT-83, INT-85, ISR-001, HUN-004, KOR-001, NED-9, RIS-INT-39/GBR-28, RIS-INT-47/GBR-29, SUI-001, USA-001, USA-005, USA-006, USA-009, USA-007, USA-060, USA-102, USA-112, USA-121, **REDACTED** USA-232, USA-239, USA-240, USA-241, USA-259, USA-265, USA-34, USA-63, USA-64, USA-70, USA-72, USA-79, USA-93, USA-97

Source: Table aSAF.WEIGHT.1.

Table 21 summarizes the percentages of subjects with clinically significant weight gain (>7%) in short- and long-term trials in adults and elderly populations only. The standard of 7% as the definition for clinically meaningful weight gain is not appropriate for children (Section 3.2.4). It should be noted that the average weight gain for risperidone-treated pediatric/adolescent subjects in long-term trials (680 subjects, with the mean age = 9.6 years) is 7.4 kg or 20.4%. In short-term trials, incidence of weight gain >7% was greater in the risperidone group (11.9%) than in the placebo group (5.4%), but similar to that in the haloperidol (10.4%) and other neuroleptics (11.3%) treatment groups. In contrast, the incidence of clinically significant weight gain with olanzapine treatment was greater than 2-fold higher (26.9%) than that with risperidone.

In long-term trials, the incidence of clinically significant weight increase was 24.1% for adult subjects in the risperidone treatment group, and slightly higher (28.1%) in the haloperidol treatment group. The percentage of adult subjects with body weight increases at endpoint of >7% of baseline weight was highest in the olanzapine treatment group (35.7%).

In placebo- and risperidone-treated elderly subjects, results were similar (4.7% and 9.9% of subjects gaining >7% baseline body weight, respectively) to those in short-term trials. Weight data from long-term trials was not available for other neuroleptics.

Table 21: Incidence of Body Weight Increase >7% in Subjects >18 Years

Trial duration Treatment	% subjects with increase of >7% of baseline weight			
	N	18-65 years	N	>65 years
Short-term trials				
Placebo	833	5.4%	602	4.7%
Risperidone	4874	11.9%	964	9.9%
Haloperidol	651	10.4%	90	4.4%
Olanzapine	412	26.9%	72	13.9%
Other neuroleptics ^a	256	11.3%	-	-
Long-term trials				
Risperidone	3914	24.1%	660	16.4%
Haloperidol	484	28.1%	-	-
Olanzapine	294	35.7%	-	-

^a Other neuroleptics included zuclopenthixol, perphenazine, remoxipride, clozapine, thioridazine, levomepromazine, divalproex.

Source: Table aSAF.Weight.2.

Descriptive statistics for subjects with weight change >7% of baseline weight is presented by age group for long- and short-term trials in Table aSAF.WEIGHT.3.

Risperidone: Effects on Glucose Metabolism

The J&JPRD clinical database reflects the rank-order of antipsychotic weight gain reported by Allison in the American Journal of Psychiatry.¹ That is, in the J&JPRD database, olanzapine was associated with the highest weight gain, risperidone with moderate weight gain, and haloperidol with low weight gain. This rank order (olanzapine>risperidone>haloperidol) was generally true in each analysis of weight gain including short-term and long-term trials, elderly population, pediatric population, and in the percentage of patients gaining a clinically significant amount of weight.

5. CONCLUSION

The information derived from a large number of clinical trials reporting on more than 12,000 subjects in short-term trials and over 7500 subjects in long-term trials supports the conclusion that disturbances of glucose metabolism during risperidone treatment are not very common. Overall, the incidence of glucose-related adverse events was lower with risperidone than with placebo or olanzapine. Serious glucose-related adverse events were rare and were not more frequent with risperidone than with placebo. One fatal case resulted from urosepsis. In the pediatric and adult populations, risperidone was similar to, if not lower than, placebo, and lower than olanzapine in terms of percentage of individuals with abnormalities in glucose metabolism. Elderly patients showed a higher incidence of some abnormalities in glucose metabolism with risperidone compared to placebo in short-term trials. Most observations were hyperglycemia and poorly controlled glucose levels in patients with a history of diabetes; new-onset diabetes and blood levels suggestive of diabetes were infrequent among subjects with no prior history of diabetes.

6. REFERENCES

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7. SUPPORTING DATA

7.1. Displays

Risperidone: Effects on Glucose Metabolism
 Display GAE.1: Number of Glucose Related AE's by WHO Preferred Term and Treatment

Display GAE.1 Number of glucose related AEs by WHO preferred term and treatment.

August, 2000

	TRIAL DURATION											
	LONG-TERM			SHORT-TERM					Short + Long Term			
	Treatment			Treatment					Treatment			
	Haloperidol	Risperidone	Other	Haloperidol	Olanzapine	Neuroleptic	Placebo	Risperidone	Haloperidol	Olanzapine	Neuroleptic	Placebo
	n	n	n	n	n	n	n	n	n	n	n	n
ADVERSE EVENT PREFERRED TERM												
ACIDOSIS	-	1	-	-	-	-	-	-	-	-	-	1
BLOOD SUGAR INCREASED	-	-	-	-	-	-	-	2	-	-	-	2
CONA DIABETIC	-	-	-	-	-	-	-	1	-	-	-	1
DIABETES MELLITUS	5	11	-	1	1	1	4	5	1	1	1	5
DIABETES MELLITUS AGGRAVATED	-	-	-	-	-	-	-	2	-	-	-	2
GLYCOSURIA	-	2	-	-	-	-	-	-	1	-	-	1
HYPERGLYCAEMIA	5	23	2	3	-	5	20	7	3	-	5	43
HYPOGLYCAEMIA	1	2	-	-	-	1	7	1	-	-	1	2
KEOTOSIS	-	1	-	-	-	-	1	-	-	-	-	1
PLASMA CARNITINE INCREASED	-	-	-	-	-	-	-	1	-	-	-	1

Risperidone: Effects on Glucose Metabolism
Display GAE.2: List of Trials and Number of Patients by Treatment

Display GAE.2 List of trials and number of patients by treatment

August 2002

AGE GROUP	TRIAL BLIND- ING DESIGN	TRIAL DURATION TERM	TRIAL ID	Treatment						Total
				Ris- perid- ol	Olans- zap- ine	Other Medi- cations	Place- bo	Rispi- done		
				n	n	n	n	n	n	
18 - 65										
		LONG- TERM	INT-6	99	-	-	-	51	190	
			USA-79	203	-	-	-	152	395	
		SHORT- TERM	AUT-1	-	-	32	-	24	67	
			BEL-5	22	-	-	-	22	44	
			DEL-7	32	-	-	-	28	60	
			FIN-1	-	-	50	-	48	98	
			FRA-3	20	-	21	-	21	62	
			GBR-26	-	-	-	13	10	23	
			GER-5	-	-	20	-	29	59	
			INT-10	-	-	-	-	211	211	
			INT-2	225	-	-	-	1136	1362	
			INT-3	87	-	-	88	348	523	
			INT-39	-	-	-	25	29	54	
			INT-45	-	24	-	-	247	490	
			INT-46	-	-	-	75	75	150	
			INT-5	84	-	-	-	99	183	
			INT-7	-	-	52	-	53	107	
			INT-9	-	-	74	-	75	149	
			KOR-1	20	-	-	-	39	39	
			SUI-1	-	-	43	-	43	86	
			USA-1	53	-	-	54	53	160	
			USA-102	53	-	-	52	52	156	
			USA-112	-	205	-	-	202	407	
			USA-60	-	-	-	-	441	441	
			USA-72	-	-	-	83	163	246	
	OPWA- LABEL	LONG- TERM	BEL-17	-	-	-	-	116	116	

Risperidone: Effects on Glucose Metabolism
Display GAE.2: List of Trials and Number of Patients by Treatment

(CONTINUED)
Display GAE.2 List of trials and number of patients by treatment

				Treatment						
				Haloperidol	Olanzapine	Other Neuroleptics	Placebo	Risperidone	Total	
				n	n	n	n	n	n	
AGE GROUP	TRIAL BLINDING BY DESIGN	TRIAL DURATION	TRIAL ID							
18 - 65	OPEN-LANE	LONG-TERM	GDR-29	-	-	-	-	19	19	
			INT-12	-	-	-	-	483	483	
			INT-17	-	-	234	-	258	492	
			INT-4	-	-	-	-	386	386	
			INT-47	-	-	-	-	39	39	
			INT-8	-	-	-	-	109	109	
			ISK-1	-	-	-	-	135	135	
			WRN-2	-	-	-	-	40	40	
			USA-5	-	-	-	-	4	4	
			USA-5/USA-7	-	-	-	-	3	3	
			USA-6	-	-	-	-	194	194	
			USA-6/USA-7	-	-	-	-	71	71	
			USA-9	-	-	-	-	76	76	
			USA-9/USA-7	-	-	-	-	31	31	
		SHORT-TERM	GER-3	-	-	-	-	13	13	
			INT-1	-	-	-	-	121	121	
			ITA-1	-	-	-	-	31	31	
			USA-054	-	-	-	-	93	93	
			Total	899	448	327	389	6797	4063	
			< 18	TRIAL BLINDING BY DESIGN	TRIAL DURATION	TRIAL ID				
DOUBLE-BLIND	SHORT-TERM	BEL-11	-	-	-	37	37	74		
		BEL-24	-	-	-	7	6	13		
		CAN-19	-	-	-	37	53	110		
		MDU-9	-	-	-	19	19	38		

Risperidone: Effects on Glucose Metabolism
 Display GAE.2: List of Trials and Number of Patients by Treatment

(CONTINUED)
 Display GAE.2 List of trials and number of patients by treatment

				Treatment						
				Haloperidol	Olanzapine	Neuroleptics	Placebo	Risperidone	Total	
				n	n	n	n	n	n	
AGE GROUP	TRIAL BLINDING	TRIAL DURATION	TRIAL ID							
< 18	DESIGN									
		DOUBLED-BLIND	SHORT-TERM	USA-93	-	-	-	63	25	118
		OPEN-LABEL	LONG-TERM	USA-97	-	-	-	-	107	107
			SHORT-TERM	BEL-21	-	-	-	-	6	6
				BEL-22	-	-	-	-	7	7
		Total			-	-	-	183	290	473
> 65	TRIAL BLINDING BY DESIGN									
		DOUBLED-BLIND	SHORT-TERM	BEL-14	-	-	-	19	20	39
				INT-24	115	-	-	114	115	344
				USA-063	-	-	-	163	462	625
	OPEN-LABEL	LONG-TERM	INT-23	-	-	-	-	180	180	
			INT-26	-	-	-	-	63	63	
			USA-34	-	-	-	-	22	22	
			USA-64	-	-	-	-	103	103	
			USA-70	-	-	-	-	330	330	
			Total			115	-	-	296	1315
Total				1014	448	527	868	8402	11259	

Risperidone: Effects on Glucose Metabolism
 Display GAE.4: Number of Patients With/Without Glucose Related AE's by Treatment and Trial Duration

Display GAE.4 Number of patients with/without glucose related AEs by treatment and trial duration August 2000

	TRIAL DURATION																					
	LONG-TERM										SHORT-TERM										Short + Long Term	
	Treatment					Treatment					Treatment					Treatment						
	Haloperidol	Other Neuroleptics	Risperidone	Haloperidol	Olanzapine	Other Neuroleptics	Placebo	Risperidone	Haloperidol	Olanzapine	Other Neuroleptics	Placebo	Risperidone	Haloperidol	Olanzapine	Other Neuroleptics	Placebo	Risperidone	Haloperidol	Olanzapine	Other Neuroleptics	Placebo
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Glucose related AE																						
NO	293	97.02	234	100.0	3032	98.70	710	99.72	444	99.11	292	99.66	261	99.19	5297	99.38	1003	98.92	444	99.11	526	99.81
YES	9	2.98	-	-	40	1.30	2	0.28	4	0.89	1	0.34	7	0.81	33	0.62	11	1.08	4	0.89	1	0.19
Total	302	100.0	234	100.0	3072	100.0	712	100.0	448	100.0	293	100.0	268	100.0	5330	100.0	1014	100.0	448	100.0	527	100.0

(CONTINUED)

	Short + Long Term		
	Treatment		
	Risperidone	Total	
	n	%	n
Glucose related AE			
NO	8329	99.14	11163
YES	73	0.87	96
Total	8402	100.0	11259

Risperidone: Effects on Glucose Metabolism
 Display GAE.5: Number of Patients With/Without Glucose Related AE's by Demographics

Display GAE.5 Number of patients with/without glucose related AEs by demographics

August 2000

			AGE GROUP							
			18 - 65		< 18		> 65		Total	
			n	%	n	%	n	%	n	%
Glucose related AE	TRIAL DURATION	Treatment								
NO	LONG-TERM	Haloperidol	293	97.02	-	-	-	-	293	
		Other Neuroleptics	234	100.0	-	-	-	-	234	
		Risperidone	2230	99.24	106	99.07	656	95.94	3032	
		All treatments	2757	99.07	106	99.07	656	95.94	3559	
	SHORT-TERM	Haloperidol	595	99.83	-	-	114	99.13	720	
		Clanzapine	444	99.11	-	-	-	-	444	
		Other Neuroleptics	292	99.66	-	-	-	-	292	
		Placebo	387	99.45	183	100.0	251	98.31	861	
		Risperidone	4532	99.60	183	100.0	582	97.49	5297	
		All treatments	6251	99.55	366	100.0	987	97.92	7604	
	Short + Long Term	Haloperidol	889	99.85	-	-	114	99.13	1003	
		Clanzapine	444	99.11	-	-	-	-	444	
		Other Neuroleptics	526	99.81	-	-	-	-	526	
		Placebo	387	99.45	183	100.0	251	98.31	861	
		Risperidone	6762	99.49	289	99.56	1278	97.19	8329	
		All treatments	9008	99.43	472	99.79	1683	97.51	11163	
YES	LONG-TERM	Haloperidol	9	2.98	-	-	-	-	9	
		Risperidone	17	3.76	1	0.93	22	3.06	40	
		All treatments	26	3.92	1	0.93	22	3.06	49	
	SHORT-TERM	Haloperidol	1	0.17	-	-	1	0.87	2	
		Clanzapine	4	0.89	-	-	-	-	4	

Risperidone: Effects on Glucose Metabolism
Display GAE.5: Number of Patients With/Without Glucose Related AE's by Demographics

(CONTINUED)
Display GAE.5 Number of patients with/without glucose related AEs by demographics

			AGE GROUP								Total	
			18 - 45		< 18		> 65					
			n	%	n	%	n	%				
Glucose related AE	TRIAL DURATION	Treatment										
YES	SHORT-TERM	Other Neuroleptics	1	0.34	-	-	-	-	-	-	1	
		Placebo	2	0.51	-	-	5	1.69	-	-	7	
		Risperidone	18	0.40	-	-	15	2.51	-	-	33	
		All treatments	25	0.41	-	-	21	2.09	-	-	47	
	Short + Long Term	Treatment										
		Haloperidol	30	1.11	-	-	1	0.87	-	-	31	
		Olanzapine	4	0.89	-	-	-	-	-	-	4	
		Other Neuroleptics	1	0.19	-	-	-	-	-	-	1	
		Placebo	2	0.51	-	-	5	1.69	-	-	7	
		Risperidone	35	0.51	1	0.34	57	2.81	-	-	73	
		All treatments	52	0.57	1	0.21	43	2.49	-	-	96	
Total	LONG-TERM	Haloperidol	302	100.0	-	-	-	-	-	-	302	
		Other Neuroleptics	234	100.0	-	-	-	-	-	-	234	
		Risperidone	2247	100.0	107	100.0	718	100.0	-	-	3072	
		All treatments	2783	100.0	107	100.0	718	100.0	-	-	3608	
	SHORT-TERM	Treatment										
		Haloperidol	597	100.0	-	-	115	100.0	-	-	712	
		Olanzapine	448	100.0	-	-	-	-	-	-	448	
		Other Neuroleptics	293	100.0	-	-	-	-	-	-	293	
		Placebo	389	100.0	183	100.0	256	100.0	-	-	868	
		Risperidone	4550	100.0	183	100.0	557	100.0	-	-	5330	
		All treatments	6277	100.0	366	100.0	1068	100.0	-	-	7651	

Risperidone: Effects on Glucose Metabolism
 Display GAE.5: Number of Patients With/Without Glucose Related AE's by Demographics

(CONTINUED)
 Display GAE.5 Number of patients with/without glucose related AEs by demographics

			AGE GROUP								Total
			18 - 65		< 18		> 65				
			n	%	n	%	n	%	n	%	
Total	Short + Long Term	Treatment									
		Risperidone	899	100.0	-	-	115	100.0	-	-	1014
		Glaxapline	448	100.0	-	-	-	-	-	-	448
		Other Neuroleptics	527	100.0	-	-	-	-	-	-	527
		Placebo	369	100.0	183	100.0	256	100.0	-	-	868
		Risperidone	6797	100.0	290	100.0	1315	100.0	-	-	8402
		All treatments	9060	100.0	473	100.0	1726	100.0	-	-	11259

Risperidone: Effects on Glucose Metabolism
 Display GAE.5: Number of Patients With/Without Glucose Related AE's by Demographics

(CONT-NUM2)
 Display GAE.5 Number of patients with/without glucose related AEs by demographics

			SEX							
			FEMALE				MALE			
			n	%	n	%	n	%	n	Total
Glucose related AE	TRIAL DURATION	Treatment								
NO	LONG-TERM	Haloperidol	-	-	103	96.26	150	97.44	253	
		Other Neuroleptics	1	100.0	75	100.0	158	100.0	234	
		Risperidone	2	100.0	1192	98.43	1838	98.87	3032	
		All treatments	3	100.0	1370	98.35	2186	98.82	3559	
	SHORT-TERM	Haloperidol	-	-	246	99.50	464	99.78	710	
		Clazapine	-	-	131	99.24	313	99.05	444	
		Other Neuroleptics	-	-	106	100.0	186	99.47	292	
		Placebo	-	-	363	99.45	498	99.01	861	
		Risperidone	6	100.0	1970	99.19	3321	99.49	5297	
		All treatments	6	100.0	2816	99.29	4782	99.44	7604	
	Short + Long Term	Haloperidol	-	-	349	98.59	654	99.09	1003	
		Clazapine	-	-	131	99.24	313	99.05	444	
		Other Neuroleptics	1	100.0	181	100.0	344	99.71	526	
		Placebo	-	-	363	99.45	498	99.01	861	
		Risperidone	8	100.0	3162	98.91	5159	99.27	8329	
		All treatments	9	100.0	4186	98.98	6968	99.25	11163	
YES	LONG-TERM	Haloperidol	-	-	4	3.74	5	2.56	9	
		Risperidone	-	-	19	1.57	21	1.13	40	
		All treatments	-	-	23	1.85	26	1.18	49	
	SHORT-TERM	Haloperidol	-	-	1	0.40	1	0.22	2	
		Clazapine	-	-	1	0.76	3	0.95	4	

Risperidone: Effects on Glucose Metabolism
 Display GAE.5: Number of Patients With/Without Glucose Related AE's by Demographics

(CONTINUED)
 Display GAE.5 Number of patients with/without glucose related AEs by demographics

			SEX								
							FEMALE		MALE		Total
			n	%	n	%	n	%	n		
Glucose related AE	TRIAL DURATION	Treatment									
YFS	SHORT-TERM	Other Neuroleptics	-	-	-	-	1	0.53	1		
		Placebo	-	-	2	0.55	5	0.99	7		
		Risperidone	-	-	16	0.82	17	0.51	33		
		All treatments	-	-	20	0.72	27	0.56	47		
	Short + Long Term	Treatment									
		Haloperidol	-	-	5	1.42	6	0.91	11		
		Olanzapine	-	-	1	0.76	3	0.95	4		
		Other Neuroleptics	-	-	-	-	1	0.29	1		
		Placebo	-	-	2	0.55	5	0.99	7		
		Risperidone	-	-	35	1.09	38	0.73	73		
		All treatments	-	-	43	1.02	53	0.75	96		
Total	LONG-TERM	Haloperidol	-	-	107	100.0	195	100.0	302		
		Other Neuroleptics	1	100.0	75	100.0	158	100.0	234		
		Risperidone	2	100.0	1211	100.0	1859	100.0	2072		
		All treatments	3	100.0	1393	100.0	2212	100.0	2608		
	SHORT-TERM	Treatment									
		Haloperidol	-	-	247	100.0	465	100.0	712		
		Olanzapine	-	-	132	100.0	316	100.0	448		
		Other Neuroleptics	-	-	106	100.0	187	100.0	293		
		Placebo	-	-	365	100.0	563	100.0	868		
		Risperidone	5	100.0	1986	100.0	3338	100.0	5330		
		All treatments	5	100.0	2836	100.0	4869	100.0	7651		

Risperidone: Effects on Glucose Metabolism
 Display GAE.5: Number of Patients With/Without Glucose Related AE's by Demographics

(CONT.NUED)
 Display GAE.5 Number of patients with/without glucose related AEs by demographics

			SEX								
			FEMALE				MALE				Total
			n	%	n	%	n	%	n	%	
Total	Short + Long Term	Treatment									
		Risperidone	-	-	354	100.0	660	100.0	1014		
		Olanzapine	-	-	132	100.0	316	100.0	448		
		Other Neuroleptics	1	100.0	181	100.0	345	100.0	527		
		Placebo	-	-	365	100.0	563	100.0	928		
		Risperidone	8	100.0	3197	100.0	5197	100.0	8402		
		All treatments	9	100.0	4229	100.0	7021	100.0	11259		

Risperidone: Effects on Glucose Metabolism
 Display GAE.5: Number of Patients With/Without Glucose Related AE's by Demographics

(CONT. NUSU)
 Display GAE.5 Number of patients with/without glucose related AEs by demographics

Glucose related AE	TRIAL DURATION	Treatment	RACE									
			Other		Black		White		Total		n	
			n	%	n	%	n	%	n	%		
NO	LONG-TERM	Haloperidol	-	-	31	98.57	72	97.30	190	98.45	293	
		Other Neuroleptics	2	100.0	20	100.0	-	-	22	100.0	234	
		Risperidone	254	100.0	267	98.57	237	95.34	2277	98.83	3032	
		All Treatments	256	100.0	315	97.52	309	95.56	2679	98.89	3559	
	SHORT-TERM	Treatment										
		Haloperidol	56	100.0	101	100.0	63	98.44	490	99.80	710	
		Clazapine	-	-	41	97.62	74	97.37	329	99.70	444	
		Other Neuroleptics	72	100.0	7	100.0	8	100.0	205	99.51	292	
		Placebo	75	100.0	58	98.37	116	100.0	622	99.03	861	
		Risperidone	377	100.0	530	99.62	707	98.19	2683	99.51	5297	
		All Treatments	580	100.0	737	99.46	968	98.37	5399	99.49	7604	
	Short + Long Term	Treatment										
		Haloperidol	56	100.0	132	97.06	135	97.83	680	99.42	1003	
		Clazapine	-	-	41	97.52	74	97.37	329	99.70	444	
		Other Neuroleptics	74	100.0	27	100.0	8	100.0	472	99.76	576	
		Placebo	75	100.0	58	98.37	116	100.0	622	99.03	861	
		Risperidone	631	100.0	794	99.25	944	97.72	5960	99.25	8329	
		All Treatments	836	100.0	1052	98.87	1277	97.93	7998	99.29	11153	
YES	LONG-TERM	Treatment										
		Haloperidol	-	-	4	11.43	2	2.70	3	1.55	9	
		Risperidone	-	-	4	1.49	9	3.66	27	1.17	40	
		All Treatments	-	-	8	2.48	11	3.44	30	1.11	49	
	SHORT-TERM	Treatment										
		Haloperidol	-	-	-	-	1	1.56	1	0.20	2	
		Clazapine	-	-	1	2.38	2	2.63	1	0.30	4	

Risperidone: Effects on Glucose Metabolism
 Display GAE.5: Number of Patients With/Without Glucose Related AE's by Demographics

(CONT. NUMB)
 Display GAE.5 Number of patients with/without glucose related AEs by demographics

			RACE										Total n
			Other		Black		White						
			n	%	n	%	n	%					
Glucose related AE	TRIAL DURATION	Treatment											
YES	SHORT-TERM	Other Neuroleptics	-	-	-	-	-	-	1	0.49	1		
		Placebo	-	-	1	1.59	-	-	6	0.97	7		
		Risperidone	-	-	2	0.38	13	1.81	18	0.49	33		
		All treatments	-	-	4	0.54	16	1.63	27	0.51	47		
	Short + Long Term	Treatment											
		Haloperidol	-	-	4	2.94	3	2.17	4	0.58	11		
		Olanzapine	-	-	1	2.38	2	2.63	1	0.30	4		
		Other Neuroleptics	-	-	-	-	-	-	1	0.24	1		
		Placebo	-	-	1	1.59	-	-	6	0.97	7		
		Risperidone	-	-	6	0.75	22	2.28	43	0.75	73		
		All treatments	-	-	12	1.13	27	2.07	57	0.71	96		
	Total	Treatment											
		LONG-TERM											
		Haloperidol	-	-	35	100.0	74	100.0	193	100.0	302		
		Other Neuroleptics	2	100.0	20	100.0	-	-	2	100.0	234		
		Risperidone	254	100.0	268	100.0	246	100.0	2304	100.0	3072		
		All treatments	256	100.0	323	100.0	320	100.0	2709	100.0	3608		
		SHORT-TERM											
		Treatment											
		Haloperidol	55	100.0	101	100.0	64	100.0	491	100.0	712		
		Olanzapine	-	-	42	100.0	76	100.0	330	100.0	448		
		Other Neuroleptics	72	100.0	7	100.0	8	100.0	206	100.0	293		
		Placebo	75	100.0	59	100.0	116	100.0	6	100.0	858		
		Risperidone	377	100.0	532	100.0	720	100.0	3701	100.0	5330		
		All treatments	580	100.0	741	100.0	964	100.0	5346	100.0	7651		

Risperidone: Effects on Glucose Metabolism
 Display GAE.5: Number of Patients With/Without Glucose Related AE's by Demographics

(CONT-NUM2)
 Display GAE.5 Number of patients with/without glucose related AEs by demographics

		RACE										Total
		Other		Black		White						
		n	%	n	%	n	%	n	%	n	%	
Total	Short + Long Term	Treatment										
		Haloperidol	56	100.0	136	100.0	158	100.0	684	100.0		1014
		Olanzapine	-	-	42	100.0	76	100.0	330	100.0		448
		Other Neuroleptics	74	100.0	27	100.0	8	100.0	418	100.0		527
		Placebo	75	100.0	59	100.0	116	100.0	618	100.0		868
		Risperidone	631	100.0	800	100.0	966	100.0	6005	100.0		8402
		All treatments	835	100.0	1064	100.0	1304	100.0	8055	100.0		11259

Risperidone: Effects on Glucose Metabolism
Table GAE.4A Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration

PAGE 1 OF 3

28HCV2001 09:07
SYSTEM USED: ARROW2.1 (11) /arwin

GLUCOSE RELATED ANALYSES

TABLE GAE.4A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION

POPULATION: ALL SUBJECTS
DURATION: SHORT TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	1519	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	4 (1.4)	14 (0.9)	1 (1.1)
METABOLIC AND NUTRITIONAL DISORDERS	4 (1.4)	14 (0.9)	1 (1.1)
HYPERGLYCAEMIA	2 (0.7)	8 (0.5)	0 (0.0)
DIABETES MELLITUS	3 (0.0)	3 (0.2)	1 (1.1)
GLYCOBURIA	3 (0.0)	2 (0.1)	0 (0.0)
ACIDOSIS	3 (0.0)	1 (0.1)	0 (0.0)
HYPERGLYCAEMIA	2 (0.7)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-32, INT-61, INT-50, USA-121
LONG TERM : CAN-20, INT-41, INT-57

Risperidone: Effects on Glucose Metabolism
Table GAE.4A Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration

PAGE 2 OF 3

28MCV2001 09:07
SYSTEM USED: ARROW2.1 (D) / aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM

--- RISPERIDONE ---	
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)

TOTAL NUMBER OF SUBJECTS	1343
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	5 (0.4)
METABOLIC AND NUTRITIONAL DISORDERS	5 (0.4)
GLYCCSURIA	3 (0.2)
HYPERGLYCAEMIA	2 (0.1)
DIABETES MELLITUS	1 (0.1)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.4A Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration

PAGE 3 OF 3

28HCV2001 09:07
SYSTEM USED: ARROW2.1 (D)/aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	2862	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	4 (1.4)	19 (0.7)	1 (1.1)
METABOLIC AND NUTRITIONAL DISORDERS	4 (1.4)	19 (0.7)	1 (1.1)
HYPERGLYCAEMIA	2 (0.7)	10 (0.3)	0 (0.0)
GLYCCSURIA	0 (0.0)	5 (0.2)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	4 (0.1)	1 (1.1)
ACIDOSIS	0 (0.0)	1 (0.0)	0 (0.0)
HYPOGLYCAEMIA	2 (0.7)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.5A Glucose : Incidence of All Glucose Related AE's With Action Taken Perm Stop of Trial Medication

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28MAY2001 09:07
SYSTEM USED: ARROW2.1 (1) /aetna

GLUCOSE RELATED ANALYSIS

TABLE GAE.5A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION

POPULATION: ALL SUBJECTS
DURATION: SHORT TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	1519	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-32, INT-61, INT-5C, USA-121
LONG TERM : CAN-20, INT-41, INT-57

Risperidone: Effects on Glucose Metabolism
Table GAE.5A Glucose : Incidence of All Glucose Related AE's With Action Taken Perm Stop of Trial Medication

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28MCV2001 09:07
SYSTEM USED: ARROW2.1 (11) / aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.5A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS	--- RISPERIDONE --- NO. ADVERSE EVENT PREFERRED TERM SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1343
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.5A Glucose : Incidence of All Glucose Related AE's With Action Taken Perm Stop of Trial Medication

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28HCV2001 09:07
SYSTEM USED: ARROW2.1 (R) /aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.5A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	2862	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.5B Glucose : Incidence of All Glucose Related Serious AE's

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SYSTEM USED: ARROW2.1 (D) /aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.5B GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S

POPULATION: ALL SUBJECTS

DURATION: SHORT TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	1519	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.4)	2 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.4)	2 (0.1)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	1 (0.1)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	1 (0.4)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-32, INT-61, INT-5C, USA-121
LONG TERM : CAN-20, INT-11, INT-37

Risperidone: Effects on Glucose Metabolism
Table GAE.5B Glucose : Incidence of All Glucose Related Serious AE's

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SYSTEM USED: ARROW2.1 (D) / aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.5B GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM

--- RISPERIDONE ---	
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1343
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.5B Glucose : Incidence of All Glucose Related Serious AE's

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28MCV2001 09:07
SYSTEM USED: ARROW2.1 (N) /aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.5B GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	2862	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.4)	2 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.4)	2 (0.1)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	1 (0.0)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	1 (0.0)	0 (0.0)
HYPOGLYCAEMIA	1 (0.4)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.5C Glucose : Incidence of All Glucose Related Serious AE's With Outcome Death

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28MAY2001 09:07
SYSTEM USED: ARROW2.1 (11) /aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.5C GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH

POPULATION: ALL SUBJECTS
DURATION: SHORT TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	1519	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-32, INT-61, INT-5C, USA-121
LONG TERM : CAN-20, INT-41, INT-37

Risperidone: Effects on Glucose Metabolism
Table GAE.5C Glucose : Incidence of All Glucose Related Serious AE's With Outcome Death

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SYSTEM USED: ARRCW2.1 (11) /aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.5C GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS	---	RISPERIDONE	---
ADVERSE EVENT PREFERRED TERM		NO.	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS		1343	
TOTAL NO. SUBJECTS WITH ADVERSE EVENT		0 (0.0)	

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.5C Glucose : Incidence of All Glucose Related Serious AE's With Outcome Death

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SYSTEM USED: ARROW2.1 (R) /aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.5C GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	277	2862	88
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.4A.AGE Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (D)/aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS

POPULATION: ALL SUBJECTS
DURATION: SHORT TERM
AGE CLASS: <18 years

--- RISPERIDONE ---	
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)

TOTAL NUMBER OF SUBJECTS	1
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-32, INT-61, INT-5C, USA-121
LONG TERM : CAN-20, INT-41, INT-57

Risperidone: Effects on Glucose Metabolism
Table GAE.4A.AGE Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (1) / aerin

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS

DURATION: SHORT TERM

AGE CLASS: 18-65 years

	----- PLACEBO -----	--- RISPERIDONE ---	--- OLANZAPINE ---
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.	NO.	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)	SUBJECTS (%)	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	112	1285	10
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.9)	8 (0.6)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.9)	8 (0.6)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	3 (0.2)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	3 (0.2)	0 (0.0)
ACIDOSIS	0 (0.0)	1 (0.1)	0 (0.0)
GLYCCOSURIA	0 (0.0)	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	1 (0.9)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.4A.AGE Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (P) / asun

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS

DURATION: SHORT TERM

AGE CLASS: >65 years

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	--- OLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	165	233	78
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (1.8)	6 (2.6)	1 (1.3)
METABOLIC AND NUTRITIONAL DISORDERS	3 (1.8)	6 (2.6)	1 (1.3)
HYPERGLYCAEMIA	2 (1.2)	5 (2.1)	0 (0.0)
GLYCCSURIA	0 (0.0)	1 (0.4)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	0 (0.0)	1 (1.3)
HYPOGLYCAEMIA	1 (0.6)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.4A.AGE Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (II) /aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM
AGE CLASS: <18 years

	--- RISPERIDONE ---
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	561
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.4A.AGE Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (D) /aerun

GLUCOSE RELATED ANALYSES

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM
AGE CLASS: 18-65 years

--- RISPERIDONE ---	
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)

TOTAL NUMBER OF SUBJECTS	711
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	5 (0.7)
METABOLIC AND NUTRITIONAL DISORDERS	5 (0.7)
GLYCCSURIA	3 (0.4)
HYPERGLYCAEMIA	2 (0.3)
DIABETES MELLITUS	1 (0.1)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.4A.AGE Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (D) /aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG TERM
AGE CLASS: >65 years

	--- RISPERIDONE ---
ADVERSE EVENT SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	51
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.4A.AGE Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (D) /aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM
AGE CLASS: <18 years

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE --- NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	582
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.4A.AGE Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARRCN2.1 (0) / aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM
AGE CLASS: 18-65 years

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO ----- NO. SUBJECTS (%)	--- RISPERIDONE --- NO. SUBJECTS (%)	--- OLANZAPINE --- NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	112	1996	10
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.9)	13 (0.7)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.9)	13 (0.7)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	5 (0.3)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	4 (0.2)	0 (0.0)
GLYCUSSURIA	0 (0.0)	4 (0.2)	0 (0.0)
ACIDOSIS	0 (0.0)	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	1 (0.9)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.4A.AGE Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (II) / aerun

GLUCOSE RELATED ANALYSIS

TABLE GAE.4A.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM
AGE CLASS: >65 years

ADVERSE EVENT SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	---- OLANZAPINE ----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	165	284	78
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (1.8)	6 (2.1)	1 (1.3)
METABOLIC AND NUTRITIONAL DISORDERS	3 (1.8)	6 (2.1)	1 (1.3)
HYPERGLYCAEMIA	2 (1.2)	5 (1.8)	0 (0.0)
GLYCCSURIA	0 (0.0)	1 (0.4)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	0 (0.0)	1 (1.3)
HYPOGLYCAEMIA	1 (0.6)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB Glucose : Incidence of All Glucose Related AE's by Trial Duration and Diabetics for Subj. With Med. Hist. Info.

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SYSTEM USED: ARRCN2.1(U)/aerun_aq-

GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND DIABETICS FOR SUBJ. WITH MED. HIST. INFO

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: SHORT TERM
DIABETIC SUBJECT: YES

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO ----- NO. SUBJECTS (%)	--- RISPERIDONE --- NO. SUBJECTS (%)	----- OTHER ----- NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	31	50	35
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (9.7)	4 (8.0)	1 (2.9)
METABOLIC AND NUTRITIONAL DISORDERS	3 (9.7)	4 (8.0)	1 (2.9)
HYPERGLYCAEMIA	2 (6.5)	4 (8.0)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	0 (0.0)	1 (2.9)
HYPOGLYCAEMIA	1 (3.2)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-2, INT-24, INT-46, INT-5, INT-50, USA-02
LONG TERM : INT6, INT12, INT-23, INT-26

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB Glucose : Incidence of All Glucose Related AE's by Trial Duration and Diabetics for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(0)/aerun_aq-

GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND DIABETICS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: SHORT TERM

DIABETIC SUBJECT: NO

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	----- OTHER -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	379	1793	531
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (0.8)	5 (0.3)	2 (0.4)
METABOLIC AND NUTRITIONAL DISORDERS	3 (0.8)	5 (0.3)	2 (0.4)
HYPERGLYCAEMIA	1 (0.3)	4 (0.2)	2 (0.4)
GLYCCSURIA	0 (0.0)	1 (0.1)	0 (0.0)
DIABETES MELLITUS	1 (0.3)	0 (0.0)	0 (0.0)
HYPOGLYCAEMIA	1 (0.3)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.6A.DIAB Glucose : Incidence of All Glucose Related AE's by Trial Duration and Diabetics for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(0)/aerun_eq.

GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND DIABETICS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: LONG TERM
DIABETIC SUBJECT: YES

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	----- OTHER -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	38	2
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (7.9)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	3 (7.9)	0 (0.0)
ACIDOSIS	1 (2.6)	0 (0.0)
DIABETES MELLITUS	1 (2.6)	0 (0.0)
HYPERGLYCAEMIA	1 (2.6)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB Glucose : Incidence of All Glucose Related AE's by Trial Duration and Diabetics for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(0)/aerun_aq-

GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND DIABETICS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: LONG TERM

DIABETIC SUBJECT: NO

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	----- OTHER -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	799	97
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	1 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(U)/aerun_ag.

GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: SHORT TERM

DIABETIC SUBJECT: YES

AGE CLASS: 18-65 years

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	----- OTHER -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	11	9
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : AUS-5, INT-2, INT-24, INT-46, INT-5, INT-50, USA-102
LONG TERM : INT6, INT12, INT-23, INT-28

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: SHORT TERM

DIABETIC SUBJECT: YES

AGE CLASS: >65 years

	----- PLACEBO -----	--- RISPERIDONE ---	----- OTHER -----
AE SYSTEM ORGAN CLASS	NO.	NO.	NO.
ADVERSE EVENT- PREFERRED TERM	SUBJECTS (%)	SUBJECTS (%)	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	31	39	25
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (9.7)	4 (10.3)	1 (4.0)
METABOLIC AND NUTRITIONAL DISORDERS	3 (9.7)	4 (10.3)	1 (4.0)
HYPERGLYCAEMIA	2 (6.5)	4 (10.3)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	0 (0.0)	1 (4.0)
HYPOGLYCAEMIA	1 (3.2)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: SHORT TERM

DIABETIC SUBJECT: YES

AGE CLASS: MISSING

AE SYSTEM OR CAN CLASS	----- OTHER ----- NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: SHORT TERM

DIABETIC SUBJECT: NO

AGE CLASS: <18 years

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	----- OTHER -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	8	3
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(U)/aerun_aq.

GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: SHORT TERM

DIABETIC SUBJECT: NO

AGE CLASS: 18-65 years

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACERO -----	--- RISPERIDONE ---	----- OTHER -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	132	1462	360
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	2 (1.5)	1 (0.1)	1 (0.3)
METABOLIC AND NUTRITIONAL DISORDERS	2 (1.5)	1 (0.1)	1 (0.3)
HYPERGLYCAEMIA	1 (0.8)	1 (0.1)	1 (0.3)
DIABETES MELLITUS	1 (0.8)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: SHORT TERM

DIABETIC SUBJECT: NO

AGE CLASS: >65 years

	----- PLACERO -----	--- RISPERIDONE ---	----- OTHER -----
AE SYSTEM ORGAN CLASS	NO.	NO.	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)	SUBJECTS (%)	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	247	312	167
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.4)	4 (1.3)	1 (0.6)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.4)	4 (1.3)	1 (0.6)
HYPERGLYCAEMIA	0 (0.0)	3 (1.0)	1 (0.6)
GLYCCSURIA	0 (0.0)	1 (0.3)	0 (0.0)
HYPOGLYCAEMIA	1 (0.4)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: SHORT TERM

DIABETIC SUBJECT: NO

AGE CLASS: MISSING

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	----- OTHER -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	11	1
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: LONG TERM

DIABETIC SUBJECT: YES

AGE CLASS: 18-65 years

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- OTHER ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	21	2
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	2 (7.4)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	2 (7.4)	0 (0.0)
ACIDOSIS	1 (3.7)	0 (0.0)
DIABETES MELLITUS	1 (3.7)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: LONG TERM

DIABETIC SUBJECT: YES

AGE CLASS: >65 years

--- RISPERIDONE ---	
AE SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	11
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (9.1)
METABOLIC AND NUTRITIONAL DISORDERS	1 (9.1)
HYPERGLYCAEMIA	1 (9.1)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: LONG TERM

DIABETIC SUBJECT: NO

AGE CLASS: <18 years

AE SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
--- RISPERIDONE ---	
TOTAL NUMBER OF SUBJECTS	8
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(U)/aerun_aq.

GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: LONG TERM

DIABETIC SUBJECT: NO

AGE CLASS: 18-65 years

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	OTHER
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	699	97
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.1)	0 (0.0)
HYPOGLYCAEMIA	1 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: LONG TERM
DIABETIC SUBJECT: NO
AGE CLASS: >65 years

--- RISPERIDONE ---	
AE SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	90
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table GAE.6A.DIAB.AGE Glucose : Incidence of All Glucose Related AE's by Trial Duration, Diabetics and Age for Subj. With Med. Hist. Info.

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GLUCOSE RELATED ANALYSIS

TABLE GAE.6A.DIAB.AGE GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION, DIABETICS AND AGE FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: LONG TERM
DIABETIC SUBJECT: NO
AGE CLASS: MISSING

--- RISPERIDONE ---	
AE SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	2
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.1 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration

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SYSTEM USED: ARROW2.1(U)/www.in

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.1 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION

POPULATION: ALL SUBJECTS
DURATION: SHORT

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	294	477
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.3)	8 (1.7)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.3)	8 (1.7)
HYPERGLYCAEMIA	0 (0.0)	7 (1.5)
GLYCOSURIA	1 (0.3)	2 (0.4)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 8 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-85, INT-2, USA-239, USA-240, USA-241
LONG TERM : INT-35, INT-70

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.1 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration

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SYSTEM USED: ARROW2.1(U)/awr.un

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.1 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	-- RISPERIDONE -- NO. SUBJECTS (%)	-- HALOPERIDOL -- NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	326	277
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.3)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.3)	0 (0.0)
HYPERGLYCAEMIA	1 (0.3)	0 (0.0)

883 FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.2 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.2 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS

POPULATION: ALL SUBJECTS
DURATION: SHORT
AGE CATEGORY: 19-65 YEARS

AE SYSTEM ORGAN CLASS OR PREFERRED TERM	PLACEBO	RISPERIDONE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	292	464
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.3)	8 (1.7)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.3)	8 (1.7)
HYPERGLYCAEMIA	0 (0.0)	7 (1.5)
GLYCOURIA	1 (0.3)	2 (0.4)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-65, INT-2, USA-239, USA-240, USA-241
LONG TERM : INT-35, INT-70

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Risperidone: Effects on Glucose Metabolism
Table SAF.AE.2 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (U)/sef.jn

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.2 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT
AGE CATEGORY: >65 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	2	13
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.2 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.2 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG
AGE CATEGORY: <18 YEARS

AE SYSTEM ORGAN CLASS OR PREFERRED TERM	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	59	10
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.2 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.2 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG
AGE CATEGORY: 18-65 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	267	267
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.4)	0 (0.0)
MYOARTIC AND NUTRITIONAL DISORDERS	1 (0.4)	0 (0.0)
HYPERGLYCAEMIA	1 (0.4)	0 (0.0)

803 FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.2 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1 (U) / awr.jn

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.2 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM
AGE CATEGORY: <18 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	59	10
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.2 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.2 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM
AGE CATEGORY: 18-65 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	PLACERO	RISPERIDONE	HALOPERIDOL
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	292	731	267
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.3)	9 (1.2)	0 (0.0)
MYOARGOLIC AND METRITICAT. DISORDERS	1 (0.3)	9 (1.2)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	0 (0.0)	0 (0.0)
GLYCOGURCA	1 (0.3)	2 (0.3)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.2 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.2 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM
AGE CATEGORY: >65 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACENO -----	--- RISPERIDONE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	2	13
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.3 Glucose : Incidence of All Glucose Related AE's With Action Taken Perm Stop of Trial Medication

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SYSTEM USED: ARROW2.1 (U)/AME.JE

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.3 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION

POPULATION: ALL SUBJECTS
DURATION: SHORT

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACEBO -----	RISPERIDONE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	294	477
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-65, INT-2, USA-239, USA-240, USA-241
LCTO TERM : INT-35, INT-70

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.3 Glucose : Incidence of All Glucose Related AE's With Action Taken Perm Stop of Trial Medication

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17DEC2002 13:49
SYSTEM USED: ARROW2.1(U)/AVE.JH

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.3 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG

AN SYSTEM ORGAN CLASS AK PREFERRED TERM	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	326	277
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.3 Glucose : Incidence of All Glucose Related AE's With Action Taken Perm Stop of Trial Medication

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SYSTEM USED: ARROW2.1(U)/AME.JR

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.3 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	294	003	277
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.4 Glucose : Incidence of All Glucose Related Serious AE's

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SYSTEM USED: ARROW2.1(U)/msl.jl

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.4 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S

POPULATION: ALL SUBJECTS
DURATION: SHORT

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	PLACEBO	RISPERIDONE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	294	477
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	1 (0.2)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	1 (0.2)
HYPERGLYCAEMIA	0 (0.0)	1 (0.2)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-65, IND-2, USA-239, USA-240, USA-241
LONG TERM : INT-35, INT-70

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R. 6802

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.4 Glucose : Incidence of All Glucose Related Serious AE's

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SYSTEM USED: ARROW2.1(U)/dwr.ln

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.4 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	326	277
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.4 Glucose : Incidence of All Glucose Related Serious AE's

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SYSTEM USED: ARROW2.1(U)/wslju

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.4 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	294	303	277
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	1 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	1 (0.1)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	1 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.5 Glucose : Incidence of All Glucose Related Serious AE's With Outcome Death

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SYSTEM USED: ARROW2.1(U)/mwrjn

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.5 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH

POPULATION: ALL SUBJECTS
DURATION: SHORT

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	PLACEBO	RISPERIDONE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	294	477
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-85, INT-2, USA-239, USA-240, USA-241
LONG TERM : INT-35, INT-70

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.5 Glucose : Incidence of All Glucose Related Serious AE's With Outcome Death

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SYSTEM USED: ARROW2.1 (U)/www.jn

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.5 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	326	277
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.5 Glucose : Incidence of All Glucose Related Serious AE's With Outcome Death

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SYSTEM USED: ARROW2.1(U)/msl.jn

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.5 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT + LONG TERM

	----- PLACEBO -----	--- RISPERIDONE ---	--- HALOPERIDOL ---
AE SYSTEM ORGAN CLASS	NO.	NO.	NO.
AE PREFERRED TERM	SUBJECTS (%)	SUBJECTS (%)	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	294	003	277
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.6 Glucose : Incidence of All Glucose Related AE's by Trial Duration for Subj. With Med. Hist. Info.

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SYSTEM USED: A3ROW2.1 (U) / aewrun_ah

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO

POPULATION: ALL SUBJECTS

DURATION: SHORT

ALL SUBJECTS WITH MED.HIST.INFO: YES

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACEBO -----	----- RISPERIDONE -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	14	24
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	2 (8.3)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	2 (8.3)
HYPERGLYCAEMIA	0 (0.0)	2 (8.3)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATION.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-65, INT-2, USA-239, USA-240, USA-241
LONG TERM : INT-35, INT-70

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Risperidone: Effects on Glucose Metabolism
Table SAF.AE.6 Glucose : Incidence of All Glucose Related AE's by Trial Duration for Subj. With Med. Hist. Info.

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SYSTEM USED: ASROW2.1(U)/asrun_mh

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT
ALL SUBJECTS WITH MED.HIST.INFO: NO

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	280	453
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.4)	6 (1.3)
MYOCLONIC AND NEUTRONIC DISORDERS	1 (0.4)	6 (1.3)
HYPERGLYCAEMIA	0 (0.0)	5 (1.1)
GLYCOBURIA	1 (0.4)	2 (0.4)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.6 Glucose : Incidence of All Glucose Related AE's by Trial Duration for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1 (U) / RUCUB_ah

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG
ALL SUBJECTS WITH MED.HIST.INFO: YES

--- RISPERIDONE ---	
AE SYSTEM ORGAN CLASS	NO.
AE PREFERRED TERM	SUBJECTS (%)

TOTAL NUMBER OF SUBJECTS	2
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (50.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (50.0)
HYPERGLYCAEMIA	1 (50.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.6 Glucose : Incidence of All Glucose Related AE's by Trial Duration for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1 (U)/sacun_sh

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURATION: LONG

ALL SUBJECTS WITH MED.HIST.INFO: NO

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	324	277
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.6A Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info

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16OCT2003 14:57
SYSTEM 038D: ARROW2.1(U)/aerun_mh

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO

POPULATION: ALL SUBJECTS

DURATION: SHORT

ALL SUBJECTS WITH MED.HIST.INFO: YES

AGE CATEGORY: 18-65 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	14	23
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	2 (8.7)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	2 (8.7)
HYPERGLYCAEMIA	0 (0.0)	2 (8.7)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-05, IND-2, USA-239, USA-240, USA-241
LONG TERM : INT-35, INT-70

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.6A Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info

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SYSTEM USED: ARROW2.1(0)/aerun_mh

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURATION: SHORT

ALL SUBJECTS WITH MED.HIST.INFO: YES

AGE CATEGORY: >65 YEARS

AE SYSTEM ORGAN CLASS	---	RISPERIDONE	---
AE PREFERRED TERM	NO.		
	SUBJECTS (%)		
TOTAL NUMBER OF SUBJECTS	1		
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)		

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.6A Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info

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SYSTEM USED: ARROW2.1(0)/aerun_mh

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: SHORT
ALL SUBJECTS WITH MED.HIST.INFO: NO
AGE CATEGORY: 18-65 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---
	NC. SUBJECTS (%)	NC. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	276	441
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.4)	6 (1.4)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.4)	6 (1.4)
HYPERGLYCAEMIA	0 (0.0)	5 (1.1)
GLYCOSURIA	1 (0.4)	2 (0.5)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.6A Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info

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SYSTEM USED: ARROW2.1(0)/aerun_mh

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURATION: SHORT

ALL SUBJECTS WITH MED.HIST.INFO: NO

AGE CATEGORY: >65 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	PLACEBO	RISPERIDONE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	2	12
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.6A Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info

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SYSTEM USED: ARROW2.1(0)/aerun_mh

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURATION: LONG

ALL SUBJECTS WITH MED.HIST.INFO: YES

AGE CATEGORY: 18-65 YEARS

AE SYSTEM ORGANS CLASS AE PREFERRED TERM	--- RISPERIDONE ---	
	NO.	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	2	
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1	(50.0)
METABOLIC AND NUTRITIONAL DISORDERS	1	(50.0)
HYPERGLYCAEMIA	1	(50.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.6A Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info

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SYSTEM USED: ARROW2.1(0)/aerun_mh

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS
DURATION: LONG
ALL SUBJECTS WITH MED.HIST.INFO: NO
AGE CATEGORY: <18 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	59	10
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.6A GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS
 DURATION: LONG
 ALL SUBJECTS WITH MED.HIST.INFO: NO
 AGE CATEGORY: 18-65 YEARS

AE SYSTEM ORGAN CLASS AE PREFERRED TERM	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	265	267
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.7: Abnormal Glucose Levels by Duration

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SYSTEM USED: EFST903(-)/glucrun2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.7: ABNORMAL GLUCOSE LEVELS BY DURATION

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT

LAB. TEST	----- PLACEBO -----	----- RISPERIDONE -----	----- HALOPERIDOL -----	----- OTHER -----
	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --
GLUCOSE				
IMPAIRED GLUCOSE TOLERANCE	92/1062 (8.7)	224/3088 (7.3)	10/161 (6.2)	28/611 (4.6)
DIABETES	35/1062 (3.3)	61/3088 (1.9)	0/161 (0.0)	4/611 (0.7)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (<7.0 mmol/l (RANDOM) OR <6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (>=7.0 mmol/l (RANDOM) OR >=6.1 mmol/l (FASTED)) SOMEWHERE DURING TREATMENT
- DIABETES (>=11.1 mmol/l (RANDOM) OR >=7 mmol/l (FASTED)) SOMEWHERE DURING TREATMENT

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.7: Abnormal Glucose Levels by Duration

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SYSTEM USED: EPST903(-)/GLUCR01J2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.7: ABNORMAL GLUCOSE LEVELS BY DURATION (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG

LAB. TEST	---- RISPERIDONE ----	---- CLONAZAPINE ----	---- OTHER ----
	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --
GLUCOSE			
IMPAIRED GLUCOSE TOLERANCE	181/1722 (10.5)	31/247 (12.6)	20/230 (8.7)
DIABETES	35/1722 (2.0)	7/247 (2.8)	7/230 (3.0)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (≤ 7.0 mmol/L (RANDOM) or ≤ 6.1 mmol/L (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (≥ 7.8 mmol/L (RANDOM) or ≥ 6.1 mmol/L (FASTED) SOMEWHERE DURING TREATMENT)
- DIABETES (≥ 11.1 mmol/L (RANDOM) or ≥ 7 mmol/L (FASTED) SOMEWHERE DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.8: Glucose : Abnormal Glucose Levels by Duration and Age Class

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SYSTEM USED: EPST903 (71)/glucoseu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.8: GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT
AGE CATEGORY: <18 YEARS

LAB. TEST	----- RISPERIDONE -----	----- OTHER -----
	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --
GLUCOSE		
IMPAIRED GLUCOSE TOLERANCE	0/8 (0.0)	0/3 (0.0)
DIABETES	0/8 (0.0)	0/3 (0.0)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (<7.0 mmol/l (RANDOM) OR <6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (>=7.8 mmol/l (RANDOM) OR >=6.1 mmol/l (FASTED) SOMETIME DURING TREATMENT)
- DIABETES (>=11.1 mmol/l (RANDOM) OR >=7.0 mmol/l (FASTED) SOMETIME DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.8: Glucose : Abnormal Glucose Levels by Duration and Age Class

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SYSTEM USED: EPST903(7)/GLUCR002

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.8: GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT
AGE CATEGORY: 18-65 YEARS

LAB. TEST	----- PLACEBO ----- -- * INCIDENCE (%) --	----- RISPERIDONE ----- -- * INCIDENCE (%) --	----- HALOPERIDOL ----- -- * INCIDENCE (%) --	----- OTHER ----- -- * INCIDENCE (%) --
GLUCOSE				
IMPAIRED GLUCOSE TOLERANCE	38/598 (6.4)	97/3131 (3.1)	9/158 (5.7)	13/464 (2.8)
DIABETES	3/598 (0.5)	13/3131 (0.4)	0/158 (0.0)	1/464 (0.2)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (≤ 7.0 mmol/l (RANDOM) or ≤ 6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (≥ 7.8 mmol/l (RANDOM); or ≥ 6.1 mmol/l (FASTED; SOMEBODY DURING TREATMENT))
- DIABETES (≥ 11.1 mmol/l (RANDOM); or ≥ 7 mmol/l (FASTED) SOMEBODY DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.8: Glucose : Abnormal Glucose Levels by Duration and Age Class

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16DEC2003 14:09
SYSTEM USED: EFSY903(=)/glucuronJ2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.8: GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT
AGE CATEGORY: >55 YEARS

LAB. TEST	----- PLACEBO ----- -- * INCIDENCE (%) --	--- RISPERIDONE --- -- * INCIDENCE (%) --	--- HALOPERIDOL --- -- * INCIDENCE (%) --	----- OTHER ----- -- * INCIDENCE (%) --
GLUCOSE				
IMPAIRED GLUCOSE TOLERANCE	50/464 (10.8)	115/743 (15.5)	3/3 (0.0)	12/42 (28.6)
DIABETES	32/464 (6.9)	49/743 (6.6)	3/3 (0.0)	3/42 (7.1)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (<7.0 mmol/l (RANDOM) OR <6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (>=7.0 mmol/l (RANDOM) OR >=6.1 mmol/l (FASTED) SOMETIME DURING TREATMENT)
- DIABETES (>=11.1 mmol/l (RANDOM) OR >=7.0 mmol/l (FASTED) SOMETIME DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.8: Glucose : Abnormal Glucose Levels by Duration and Age Class

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16DEC2003 14:39
SYSTEM USED: EFST903(=)/glucrun2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.8: GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: SHORT
AGE CATEGORY: MISSING AGE

LAB. TEST	RISPERIDONE	OTHER
	* INCIDENCE (%)	* INCIDENCE (%)
GLUCOSE		
IMPAIRED GLUCOSE TOLERANCE	0/6 (0.0)	1/2 (50.0)
DIABETES	0/6 (0.0)	0/2 (0.0)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (≤ 7.0 mmol/L (RANDOM) or ≤ 6.1 mmol/L (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (≥ 7.0 mmol/L (RANDOM) or ≥ 6.1 mmol/L (FASTED) SOMETIME DURING TREATMENT)
- DIABETES (≥ 11.1 mmol/L (RANDOM) or ≥ 7.0 mmol/L (FASTED) SOMETIME DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.8: Glucose : Abnormal Glucose Levels by Duration and Age Class

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16DEC2003 14:39
SYSTEM USED: EPST903(-1)/GLUCETM02

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.8: GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG
AGE CATEGORY: <18 YEARS

LAB. TEST	----- RISPERIDONE ----- -- % INCIDENCE (%) --
GLUCOSE	
IMPAIRED GLUCOSE TOLERANCE	0/4 (C.O)
DIABETES	0/4 (C.O)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (<7.0 mmol/l (RANDOM) OR <6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (>=7.8 mmol/l (RANDOM) OR >=6.1 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)
- DIABETES (>=11.1 mmol/l (RANDOM) OR >=7.0 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.8: Glucose : Abnormal Glucose Levels by Duration and Age Class

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16DEC2003 14:39
SYSTEM USED: EPST503(1)/glucrun2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.8: GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG
AGE CATEGORY: 19-65 YEARS

LAB. TEST	RISPERIDONE	OLANZAPINE	OTHER
	* INCIDENCE (%)	* INCIDENCE (%)	* INCIDENCE (%)
GLUCOSE			
IMPAIRED GLUCOSE TOLERANCE	104/1424 (7.3)	31/245 (12.7)	19/230 (8.3)
DIABETES	23/1424 (1.6)	5/245 (2.4)	7/230 (3.0)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (≤ 7.8 mmol/l (RANDOM) or ≤ 6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (≥ 7.8 mmol/l (RANDOM) or ≥ 6.1 mmol/l (FASTED) SOMETIME DURING TREATMENT)
- DIABETES (≥ 11.1 mmol/l (RANDOM) or ≥ 7 mmol/l (FASTED) SOMETIME DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.8: Glucose : Abnormal Glucose Levels by Duration and Age Class

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16DEC2003 14:39
SYSTEM USED: EFST903 (7)/Glucose.m2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.8: GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG
AGE CATEGORY: >55 YEARS

LAB. TEST	----- RISPERIDONE -----		----- OLANZAPINE -----	
	-- * INCIDENCE (%) --		-- * INCIDENCE (%) --	

GLUCOSE				

IMPAIRED GLUCOSE TOLERANCE	73/292	(25.0)	0/2	(0.0)
DIABETES	12/292	(4.1)	1/2	(50.0)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (<7.8 mmol/l (RANDOM) or <6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (>=7.8 mmol/l (RANDOM) or >=6.1 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)
- DIABETES (>=11.1 mmol/l (RANDOM) or >=7 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.8: Glucose : Abnormal Glucose Levels by Duration and Age Class

PAGE 9 (LAST PAGE)

16DEC2003 14:39
SYSTEM USED: EPST903(-)/glucrunj2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.8: GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
TRIAL DURATION: LONG
AGE CATEGORY: MISSING AGE

LAB. TEST	----- RISPERIDONE ----- -- * INCIDENCE (%) --
GLUCOSE	
IMPAIRED GLUCOSE TOLERANCE	0/2 (0.0)
DIABETES	0/2 (0.0)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (≤ 7.0 mmol/L (RANDOM) or ≤ 6.1 mmol/L (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (≥ 7.8 mmol/L (RANDOM) or ≥ 6.1 mmol/L (FASTED) SOMEWHERE DURING TREATMENT)
- DIABETES (≥ 11.1 mmol/L (RANDOM) or ≥ 7.0 mmol/L (FASTED) SOMEWHERE DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.9 Glucose : Abnormal Glucose Levels by Duration for Subj. With Med. Hist. Info.

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16DEC2003 14:11
SYSTEM USED: RFSY603 (U) /glucsum_rh22

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.9 GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION FOR SUBJ. WITH MED. HIST. INFO

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: SHORT

ALL SUBJECTS WITH MED.HIST.INFO: YES

LAB. TEST	----- PLACEBO -----	----- RISPERIDONE -----	----- OTHER -----
	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --	-- * INCIDENCE (%) --
GLUCOSE			
IMPAIRED GLUCOSE TOLERANCE	6/39 (15.4)	11/56 (19.6)	3/16 (18.8)
DIABETES	6/39 (20.5)	8/56 (14.3)	3/16 (18.8)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (<7.0 mmol/l (RANDOM) or <6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (≥ 7.0 mmol/l (RANDOM) or ≥ 6.1 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)
- DIABETES (≥ 11.1 mmol/l (RANDOM) or ≥ 7 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.9 Glucose : Abnormal Glucose Levels by Duration for Subj. With Med. Hist. Info.

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16DEC2003 14:11
SYSTEM USED: RFSYS03(U)/glucose_rh12

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.9 GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: SHORT
ALL SUBJECTS WITH MED.HIST.INFO: NO

LAB. TEST	----- PLACEBO ----- -- * INCIDENCE (%) --	----- RISPERIDONE ----- -- * INCIDENCE (%) --	----- HALOPERIDOL ----- -- * INCIDENCE (%) --	----- OTHER ----- -- * INCIDENCE (%) --
GLUCOSE				
IMPAIRED GLUCOSE TOLERANCE	61/712 (8.6)	108/2488 (4.3)	10/161 (6.2)	12/382 (3.1)
DIABETES	22/712 (3.1)	34/2488 (1.4)	0/161 (0.0)	0/382 (0.0)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (≤ 7.0 mmol/l (RANDOM) or ≤ 6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (≥ 7.8 mmol/l (RANDOM) or ≥ 6.1 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)
- DIABETES (≥ 11.1 mmol/l (RANDOM) or ≥ 7 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.9 Glucose : Abnormal Glucose Levels by Duration for Subj. With Med. Hist. Info.

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16DEC2003 14:11
SYSTEM USED: RFSYS03 (U)/glucose_rh2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.9 GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO
TRIAL DURATION: LONG
ALL SUBJECTS WITH MED.HIST.INFO: YES

LAB. TEST	---- RISPERIDONE ---- -- * INCIDENCE (%) --	---- OLANZAPINE ---- -- * INCIDENCE (%) --	---- OTHER ---- -- * INCIDENCE (%) --
GLUCOSE*			
IMPAIRED GLUCOSE TOLERANCE	4/20 (40.0)	0/1 (0.0)	2/2 (100)
DIABETES	1/20 (10.0)	0/1 (0.0)	0/2 (0.0)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (≤ 7.0 mmol/L (RANDOM) OR ≤ 6.1 mmol/L (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (≥ 7.8 mmol/L (RANDOM) OR ≥ 6.1 mmol/L (FASTED) SOMEWHERE DURING TREATMENT)
- DIABETES (≥ 11.1 mmol/L (RANDOM) OR ≥ 7.0 mmol/L (FASTED) SOMEWHERE DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism
Table SAF.AE.9 Glucose : Abnormal Glucose Levels by Duration for Subj. With Med. Hist. Info.

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16DEC2003 14:11
SYSTEM USED: EFSY603 (U)/glucrm_rh02

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.9 GLUCOSE : ABNORMAL GLUCOSE LEVELS BY DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS WITH MED. HIST. INFO

TRIAL DURATION: LONG

ALL SUBJECTS WITH MED.HIST.INFO: NO

LAB. TEST	--- RISPERIDONE --- -- * INCIDENCE (%) --	--- OLANZAPINE --- -- * INCIDENCE (%) --	--- OTHER --- -- * INCIDENCE (%) --
GLUCOSE			
IMPAIRED GLUCOSE TOLERANCE	47/943 (5.0)	31/246 (12.6)	0/79 (0.0)
DIABETES	8/943 (0.8)	7/246 (2.9)	0/79 (0.0)

* NUMBER AND % OF SUBJECTS WITH NORMAL GLUCOSE LEVELS (≤ 7.0 mmol/l (RANDOM) or ≤ 6.1 mmol/l (FASTED)) AT BASELINE AND POST-BASELINE ASSESSMENT INDICATING:
- IMPAIRED GLUCOSE TOLERANCE (≥ 7.8 mmol/l (RANDOM); or ≥ 6.1 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)
- DIABETES (≥ 11.1 mmol/l (RANDOM); or ≥ 7 mmol/l (FASTED) SOMEWHERE DURING TREATMENT)

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.10 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration

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01OCT2003 13:52
SYSTEM USED: ARROW2.1(U)/acrum2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.10 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION

POPULATION: ALL SUBJECTS

DURAT: SHORT

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	HALOPERIDOL
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	386	1132	208
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	4 (1.0)	6 (0.5)	1 (0.5)
METABOLIC AND NUTRITIONAL DISORDERS	4 (1.0)	6 (0.5)	1 (0.5)
HYPERGLYCAEMIA	3 (0.8)	5 (0.4)	1 (0.5)
DIABETES MELLITUS	2 (0.5)	2 (0.2)	0 (0.0)
GLYCOSURIA	0 (0.0)	2 (0.2)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-69, INT-81, USA-259, USA-232, INT-83
LONG TERM : INT-62, HUN-4, INT-63, USA-196, USA-265, INT-80

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.10 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: LONG

AE SYSTEM ORG CLASS ADVERSE EVENT PREFERRED TERM	-- RISPERIDONE -- NO. SUBJECTS (%)	--- OLANZAPINE --- NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1849	300
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	52 (2.8)	5 (1.7)
METABOLIC AND NUTRITIONAL DISORDERS	52 (2.8)	5 (1.7)
HYPERGLYCAEMIA	22 (1.2)	4 (1.3)
DIABETES MELLITUS	20 (1.1)	1 (0.3)
GLYCOSURIA	17 (0.9)	0 (0.0)
DIABETES MELLITUS AGGRAVATED	2 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.11 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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01OCT2003 13:52
SYSTEM USED: ARROW2.1(U)/acrumu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.11 GLUCOSE : INCIDENCY OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS

POPULATION: ALL SUBJECTS
DURAT: SHORT
AGE CATEGORY: 18-65 YEARS

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	142	870	205
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	3 (0.3)	1 (0.5)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	3 (0.3)	1 (0.5)
GLYCOSURIA	0 (0.0)	2 (0.2)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	2 (0.2)	1 (0.5)
DIABETES MELLITUS	0 (0.0)	1 (0.1)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-69, INT-81, USA-259, USA-232, INT-83
LONG TERM : INT-62, HUN-4, INT-63, USA-196, USA-265, INT-80

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.11 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: SHORT
AGE CATEGORY: >65 YEARS

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	244	262	3
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	4 (1.6)	3 (1.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	4 (1.6)	3 (1.1)	0 (0.0)
HYPERGLYCAEMIA	3 (1.2)	3 (1.1)	0 (0.0)
DIABETES MELLITUS	2 (0.8)	1 (0.4)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.11 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1(U)/serimu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.11 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

AGE CATEGORY: <18 YEARS

--- RISPERIDONE ---	
AE SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	35
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.11 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: LONG
AGE CATEGORY: 18-65 YEARS

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- OLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1757	297
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	52 (3.0)	5 (1.7)
METABOLIC AND NUTRITIONAL DISORDERS	52 (3.0)	5 (1.7)
HYPERGLYCAEMIA	22 (1.3)	4 (1.3)
DIABETES MELLITUS	20 (1.1)	1 (0.3)
GLYCOSURIA	17 (1.0)	0 (0.0)
DIABETES MELLITUS AGGRAVATED	2 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.11 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1(U)/acrumu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.11 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

AGE CATEGORY: >65 YEARS

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- OLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	57	3
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.11 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: SHORT + LONG TERM
AGE CATEGORY: <18 YEARS

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE --- NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	35
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.11 Glucose : Incidence of All Glucose Related AE's by Treatment and Trial Duration and Age Class

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SYSTEM USED: ARROW2.1(U)/aerumu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.11 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: SHORT + LONG TERM
AGE CATEGORY: 18-65 YEARS

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO NO. SUBJECTS (%)	RISPERIDONE NO. SUBJECTS (%)	HALOPERIDOL NO. SUBJECTS (%)	OLANZAPINE NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	142	2627	205	297
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	55 (2.1)	1 (0.5)	5 (1.7)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	55 (2.1)	1 (0.5)	5 (1.7)
HYPERGLYCAEMIA	0 (0.0)	24 (0.9)	1 (0.5)	4 (1.3)
DIABETES MELLITUS	0 (0.0)	21 (0.8)	0 (0.0)	1 (0.3)
GLYCOSURIA	0 (0.0)	19 (0.7)	0 (0.0)	0 (0.0)
DIABETES MELLITUS AGGRAVATED	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.11 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TREATMENT AND TRIAL DURATION AND AGE CLASS (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: SHORT + LONG TERM
AGE CATEGORY: >65 YEARS

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO ----- NO. SUBJECTS (%)	--- RISPERIDONE --- NO. SUBJECTS (%)	--- HALOPERIDOL --- NO. SUBJECTS (%)	----- OLANZAPINE ----- NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	244	319	3	3
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	4 (1.6)	3 (0.9)	0 (0.0)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	4 (1.6)	3 (0.9)	0 (0.0)	0 (0.0)
HYPERGLYCAEMIA	3 (1.2)	3 (0.9)	0 (0.0)	0 (0.0)
DIABETES MELLITUS	2 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.12 Glucose : Incidence of All Glucose Related AE's With Action Taken Perm Stop of Trial Medication

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SYSTEM USED: ARROW2.1(U)/aerumu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.12 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION

POPULATION: ALL SUBJECTS
DURAT: SHORT

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	386	1132	208
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-69, INT-81, USA-259, USA-232, INT-83
LONG TERM : INT-62, HCN-4, INT-63, USA-196, USA-265, INT-80

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.12 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: LONG

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- OLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1849	300
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	2 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	2 (0.1)	0 (0.0)
HYPERGLYCAEMIA	2 (0.1)	0 (0.0)
GLYCOSURIA	1 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.12 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S WITH ACTION TAKEN PERM STOP OF TRIAL MEDICATION (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: SHORT + LONG TERM

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO NO. SUBJECTS (%)	RISPERIDONE NO. SUBJECTS (%)	HALOPERIDOL NO. SUBJECTS (%)	OLANZAPINE NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	385	2981	208	300
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
GLYCOSURIA	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.13 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S

POPULATION: ALL SUBJECTS
DURAT: SHORT

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	HALOPERIDOL
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	386	1132	208
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	1 (0.1)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	1 (0.1)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	1 (0.1)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-69, INT-81, USA-259, USA-232, INT-83
LONG TERM : INT-62, HON-4, INT-63, USA-196, USA-265, INT-80

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.13 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: LONG

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- OLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1849	300
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	9 (0.5)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	9 (0.5)	0 (0.0)
HYPERGLYCAEMIA	6 (0.3)	0 (0.0)
DIABETES MELLITUS	3 (0.2)	0 (0.0)
GLYCOSURIA	1 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.13 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: SHORT + LONG TERM

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	HALOPERIDOL	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	386	2981	208	300
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	10 (0.3)	0 (0.0)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	10 (0.3)	0 (0.0)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	6 (0.2)	0 (0.0)	0 (0.0)
DIABETES MELLITUS	0 (0.0)	4 (0.1)	0 (0.0)	0 (0.0)
GLYCOSURIA	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.14 Glucose : Incidence of All Glucose Related Serious AE's With Outcome Death

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SYSTEM USED: ARROW2.1(U)/acrumu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.14 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH

POPULATION: ALL SUBJECTS

DURAT: SHORT

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	386	1132	208
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN 4 DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-69, INT-81, USA-259, USA-232, INT-83
LONG TERM : INT-62, HON-4, INT-61, USA-196, USA-265, INT-80

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.14 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: LONG

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- OLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	1849	300
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAP.AE.14 Glucose : Incidence of All Glucose Related Serious AE's With Outcome Death

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SYSTEM USED: ARROW2.1(U) /aerumu2

GLUCOSE RELATED ANALYSIS

TABLE SAP.AE.14 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED SERIOUS AE'S WITH OUTCOME DEATH (CONTINUED)

POPULATION: ALL SUBJECTS
DURAT: SHORT + LONG TERM

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	HALOPERIDOL	OLANZAPINE
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	386	2981	208	300
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.15 Glucose : Incidence of All Glucose Related AE's by Trial Duration for Subj. With Med. Hist. Info.

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SYSTEM USBD: ARROW2.1(0)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.15 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO

POPULATION: ALL SUBJECTS

DURAT: SHORT

ALL SUBJECTS WITH MED.HIST.INFO: YES

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---	--- HALOPERIDOL ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	48	71	2
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (6.3)	3 (4.2)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	3 (6.3)	3 (4.2)	0 (0.0)
HYPERGLYCAEMIA	2 (4.2)	2 (2.8)	0 (0.0)
GLYCOSURIA	0 (0.0)	1 (1.4)	0 (0.0)
DIABETES MELLITUS	1 (2.1)	0 (0.0)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-69, INT-81, USA-259, USA-232, INT-83
LONG TERM : INT-62, INT-63, INT-80, HUN-4, USA-196, USA-265

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.15 Glucose : Incidence of All Glucose Related AE's by Trial Duration for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(U)/aerun_nhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.15 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: SHORT

ALL SUBJECTS WITH MED.HIST.INFO: NO

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACEBO	RISPERIDONE	HALOPERIDOL
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	330	1051	206
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.3)	3 (0.3)	1 (0.5)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.3)	3 (0.3)	1 (0.5)
HYPERGLYCAEMIA	1 (0.3)	3 (0.3)	1 (0.5)
DIABETES MELLITUS	1 (0.3)	2 (0.2)	0 (0.0)
GLYCOSURIA	0 (0.0)	1 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.15 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: SHORT

ALL SUBJECTS WITH MED.HIST.INFO: MISSING

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	8	10
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAP.AE.15 Glucose : Incidence of All Glucose Related AE's by Trial Duration for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(U)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAP.AE.15 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

ALL SUBJECTS WITH MED.HIST.INFO: YES

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- OLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	16	5
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	4 (25.0)	1 (20.0)
METABOLIC AND NUTRITIONAL DISORDERS	4 (25.0)	1 (20.0)
HYPERGLYCAEMIA	4 (25.0)	1 (20.0)
GLYCOSURIA	1 (6.3)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.15 Glucose : Incidence of All Glucose Related AE's by Trial Duration for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1 (U) / aerun_rhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.15 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

ALL SUBJECTS WITH MED.HIST.INFO: NO

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- OLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	717	295
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	11 (1.5)	4 (1.4)
METABOLIC AND NUTRITIONAL DISORDERS	11 (1.5)	4 (1.4)
HYPERGLYCAEMIA	8 (1.1)	3 (1.0)
DIABETES MELLITUS	2 (0.3)	1 (0.3)
GLYCOEURIA	1 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.15 Glucose : Incidence of All Glucose Related AE's by Trial Duration for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(U)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.15 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

ALL SUBJECTS WITH MED.HIST.INFO: MISSING

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	
	NO.	SUBJECTS (%)

TOTAL NUMBER OF SUBJECTS	1116	
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	37 (3.3)	
METABOLIC AND NUTRITIONAL DISORDERS	37 (3.3)	
DIABETES MELLITUS	18 (1.6)	
GLYCOSURIA	15 (1.3)	
HYPERGLYCAEMIA	10 (0.9)	
DIABETES MELLITUS AGGRAVATED	2 (0.2)	

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.16 Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1 (U)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO

POPULATION: ALL SUBJECTS

DURAT: SHORT

AGE CATEGORY: 18-65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: YES

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	----- RISPERIDONE -----	----- HALOPERIDOL -----
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	2	26	2
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	2 (7.7)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	2 (7.7)	0 (0.0)
GLYCOSURIA	0 (0.0)	1 (3.8)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	1 (3.8)	0 (0.0)

NOTE: THE PERCENTAGES FOR EACH GROUP ARE CALCULATED BY USING THE TOTAL NUMBER OF SUBJECTS AS DENOMINATOR.
NOTE: ADVERSE EVENT REPORTED ANY TIME DURING TREATMENT OR WITHIN DAYS OF END OF TREATMENT ARE INCLUDED.
NOTE: INCIDENCE IS BASED ON THE NUMBER OF SUBJECTS, NOT THE NUMBER OF EVENTS.
TRIALS INCLUDED : SHORT TERM : INT-69, INT-81, USA-259, USA-232, INT-83
LONG TERM : INT-62, INT-63, INT-80, HUN-4, USA-196, USA-265

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.16 Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(U)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: SHORT

AGE CATEGORY: 18-65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: NO

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACBO	RISPERIDONE	HALOPERIDOL
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	140	844	203
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	1 (0.1)	1 (0.5)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.0)	1 (0.1)	1 (0.5)
DIABETES MELLITUS	0 (0.0)	1 (0.1)	0 (0.0)
GLYCOSURIA	0 (0.0)	1 (0.1)	0 (0.0)
HYPERGLYCAEMIA	0 (0.0)	1 (0.1)	1 (0.5)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: SHORT

AGE CATEGORY: >65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: YES

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	46	45
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	3 (6.5)	1 (2.2)
METABOLIC AND NUTRITIONAL DISORDERS	3 (6.5)	1 (2.2)
HYPERGLYCAEMIA	2 (4.3)	1 (2.2)
DIABETES MELLITUS	1 (2.2)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.16 Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(U)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: SHORT

AGE CATEGORY: >65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: NO

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	PLACBO	RISPERIDONE	HALOPERIDOL
	NO. SUBJECTS (%)	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	190	207	1
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	1 (0.5)	2 (1.0)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.5)	2 (1.0)	0 (0.0)
HYPERGLYCAEMIA	1 (0.5)	2 (1.0)	0 (0.0)
DIABETES MELLITUS	1 (0.5)	1 (0.5)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.16 Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1(U)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: SHORT

AGE CATEGORY: >65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: MISSING

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	----- PLACEBO -----	--- RISPERIDONE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	8	10
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.16 Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1 (U)/aerun_nhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

AGE CATEGORY: <18 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: MISSING

	---	RISPERIDONE	---
AE SYSTEM ORGAN CLASS		NO.	
ADVERSE EVENT PREFERRED TERM		SUBJECTS (%)	
TOTAL NUMBER OF SUBJECTS		35	
TOTAL NO. SUBJECTS WITH ADVERSE EVENT		0 (0.0)	

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.16 Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info.

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SYSTEM USBD: ARROW2.1 (0) / aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

AGE CATEGORY: 18-65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: YES

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- CLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	16	5
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	4 (25.0)	1 (20.0)
METABOLIC AND NUTRITIONAL DISORDERS	4 (25.0)	1 (20.0)
HYPERGLYCAEMIA	4 (25.0)	1 (20.0)
GLYCOSURIA	1 (6.3)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.16 Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1 (U)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

AGE CATEGORY: 18-65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: NO

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- CLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	695	292
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	11 (1.6)	4 (1.4)
METABOLIC AND NUTRITIONAL DISORDERS	11 (1.6)	4 (1.4)
HYPERGLYCAEMIA	8 (1.2)	3 (1.0)
DIABETES MELLITUS	2 (0.3)	1 (0.3)
GLYCOSURIA	1 (0.1)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.16 Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info.

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SYSTEM USED: ARROW2.1 (U)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

AGE CATEGORY: 18-65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: MISSING

--- RISPERIDONE ---	
AE SYSTEM ORGAN CLASS	NO.
ADVERSE EVENT PREFERRED TERM	SUBJECTS (%)

TOTAL NUMBER OF SUBJECTS	1046
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	37 (3.5)
METABOLIC AND NUTRITIONAL DISORDERS	37 (3.5)
DIABETES MELLITUS	18 (1.7)
GLYCOSURIA	15 (1.4)
HYPERGLYCAEMIA	10 (1.0)
DIABETES MELLITUS AGGRAVATED	2 (0.2)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism

Table SAF.AE.16 Glucose : Incidence of All Glucose Related AE's by Trial Duration and Age Class for Subj. With Med. Hist. Info.

PAGE 10 OF 11

16OCT2003 14:19

SYSTEM USED: ARROW2.1(U)/aerun_mhu2

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

AGE CATEGORY: >65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: NO

AE SYSTEM ORGAN CLASS ADVERSE EVENT PREFERRED TERM	--- RISPERIDONE ---	--- OLANZAPINE ---
	NO. SUBJECTS (%)	NO. SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	22	3
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0 (0.0)	0 (0.0)

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

GLUCOSE RELATED ANALYSIS

TABLE SAF.AE.16 GLUCOSE : INCIDENCE OF ALL GLUCOSE RELATED AE'S BY TRIAL DURATION AND AGE CLASS FOR SUBJ. WITH MED. HIST. INFO (CONTINUED)

POPULATION: ALL SUBJECTS

DURAT: LONG

AGE CATEGORY: >65 YEARS

ALL SUBJECTS WITH MED.HIST.INFO: MISSING

AE SYSTEM ORGAN CLASS	---	RISPERIDONE	---
ADVERSE EVENT PREFERRED TERM	NO.		SUBJECTS (%)
TOTAL NUMBER OF SUBJECTS	35		
TOTAL NO. SUBJECTS WITH ADVERSE EVENT	0	(0.0)	

SEE FOOTNOTES ON THE FIRST PAGE OF THIS DISPLAY.

Risperidone: Effects on Glucose Metabolism
Table SAF.LAB.6: Laboratory Results - Shifts in Fasting Glucose Categories - All Subjects: OLA - RIS 25/50mg Depot

Page 1 of 2

12JUN2003 11:07
System Used: Arrow3.1(7)/librun_sgl

TRIAL RIS-INT-62

Table SAF.LAB.6: Laboratory results - shifts in fasting glucose categories - All Subjects: ola - ris 25/50mg depot

Analysis Set: All Subjects: Ola - Ris 25/50mg Depot (Restricted to Subjects with Visit Baseline Data Only)

Diabetes: Yes

EVALUATION: normal=0, impaired glucose tolerance=1, suggestive of diabetes=2.

	Treatment Group and Evaluation of Baseline:			
	----- OLANZAPINE -----			
	normal	impaired	sugge	Total
Glucose				
Overall				
End point				
Normal	0	0	1	1
Impaired glucose	0	0	0	0
Suggestive of di	0	0	2	2
Total	0	0	3	3

Note: a subject may be in more than one category

Risperidone: Effects on Glucose Metabolism
Table SAF.LAB.6: Laboratory Results - Shifts in Fasting Glucose Categories - All Subjects: OLA - RIS 25/50mg Depot

Page 2 of 2

123732603 11:37
System Used: Arrow3.1.1(1)/librun_wgl

TRIAL RIS-INT-62

Table SAF.LAB.6: Laboratory results - shifts in fasting glucose categories - All Subjects: ola - ris 25/50mg depot (continued)

Analysis Set: All Subjects: Ola - Ris 25/50mg Depot (Restricted to Subjects with Visit Baseline Data Only)

Diabetes: No

EVALUATION: normal=0; impaired glucose tolerance=1; suggestive of diabetes=2.

	Treatment Group and Evaluation of Baseline:							
	OLANZAPINE		RIS DEPOT					
	norma	impai	sugge	Total	norma	impai	sugge	Total
Glucose								
Overall								
End point								
Normal	114	7	1	122	95	6	1	102
Impaired glucose	13	1	0	14	9	3	1	13
Suggestive of di	4	0	1	5	2	1	0	3
Total	136	8	2	146	106	10	2	118

See footnotes on the first page of the table.

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JJRPrev 00481905
D919.414

R. 6870

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint

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17FEB2004 12:56
System Daid: A2003.1/weight.disp

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: SHORT TERM

ACE3 CATEGORY: missing

	N	Mean	SE	SD	Med	Min	Max	Base Mean	Change from Overall Baseline				Med	Min	Max
									N	Mean	SE	SE			
Weight, kg															
RISPERIDONE															
OVERALL	13	64.6	3.53	12.71	63.0	50	92								
BASELINE	11	65.0	4.22	14.61	62.0	47	90	65.1	11	-0.1	0.39	1.95	0.0	-3	3
END POINT															
HALOPERIDOL															
OVERALL	3	67.0	2.89	5.00	67.0	62	72								
BASELINE	3	67.4	2.47	4.28	66.0	64	72	67.0	3	0.4	0.97	1.51	0.2	-1	2
END POINT															
OTHER NEURO															
OVERALL	1	75.0			75.0	75	75								
BASELINE	1	75.0			75.0	75	75	75.0	1	0.0			0.0	0	0
END POINT															

Short term: less than or equal to 12 weeks

Long term: greater than or equal to 6 months

Other neuroleptics included zuclopentixol, perphenazine, risperidone, clozapine, thioridazine, levomepromazine and divalproex

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JURPrep 00481906
D919.415

R. 6871

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint

Page 2 of 8

17FEB2004 12:56
System Used: Arrow3.1/weight.dsp

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint (continued)

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: SHORT TERM

ACS CATEGORY: <18

	N	Mean	SE	SD	Med	Min	Max	Base Mean	N	Mean	SE	SD	Med	Min	Max
Weight, kg															
PLACEBO															
OVERALL	144	35.2	1.15	13.77	31.9	16	73								
BASLINE	143	35.8	1.17	13.97	33.4	16	74	35.3	142	0.6	0.14	1.67	0.4	-10	7
END POINT															
RISPERIDONE															
OVERALL	155	38.1	1.49	18.44	33.1	15	119								
BASLINE	141	41.2	1.61	19.08	35.4	13	112	39.3	139	2.2	0.15	1.79	2.0	-3	8
END POINT															
HA OPERING															
OVERALL	4	58.3	2.70	7.40	57.7	50	68								
BASLINE	4	59.3	3.28	6.55	58.1	53	68	58.3	4	1.0	1.28	2.56	1.5	-2	3
END POINT															
OLANZAPINE															
OVERALL	2	50.5	1.50	2.12	50.5	57	50								
BASLINE	2	60.0	2.00	2.83	60.0	58	62	58.5	2	1.5	0.50	0.71	1.5	1	2
END POINT															
OTHER NEURO															
OVERALL	2	74.0	9.00	12.73	74.0	65	83								
BASLINE	2	74.5	6.50	12.62	74.5	66	93	74.0	2	0.5	0.50	0.71	0.5	0	1
END POINT															

See footnotes on the first page of the table.

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint

Page 3 of 8

17FEB2004 12:56
System Used: Arrow3.1/weight.dmp

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint (continued)

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: SHORT TERM

AGE CATEGORY: 18-65

	N	Mean	SE	SD	Med	Min	Max	Change from Overall Baseline							
								Base Mean	N	Mean	SE	SD	Med	Min	Max
Weight, kg															
PLACEBO															
OVERALL	907	74.4	0.68	20.55	72.0	30	172								
BASELINE	936	74.3	0.71	20.63	72.0	30	172	74.3	833	-0.1	0.12	3.39	0.0	-27	14
END POINT															
RISPERIDONE															
OVERALL	5439	75.9	0.25	18.79	73.9	30	230								
BASELINE	4911	77.0	0.27	18.71	74.8	30	235	75.8	4874	1.2	0.35	3.64	1.0	-41	28
END POINT															
HALOPERIDOL															
OVERALL	715	71.4	0.61	16.23	69.5	30	136								
BASELINE	659	71.4	0.61	15.85	69.8	32	125	71.0	651	0.4	0.14	3.65	0.0	-19	20
END POINT															
OLANZAPINE															
OVERALL	450	80.4	0.09	10.94	70.3	40	159								
BASELINE	418	83.7	0.25	12.25	81.8	40	159	80.6	412	3.2	0.22	4.53	3.0	23	20
END POINT															
OTHER NEURO															
OVERALL	297	75.4	0.88	15.15	74.9	43	131								
BASELINE	258	76.0	0.90	14.52	75.3	40	127	75.3	256	0.7	0.20	3.13	0.5	-11	13
END POINT															

See footnotes on the first page of the table.

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint

Page 4 of 8

17FEB2004 12:56
System Used: Arrow3.1/weightdisp

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint (continued)

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: SHORT TERM

AGE CATEGORY: >65

	N	Mean	SE	SD	Med	Min	Max	Base Mean	N	Mean	SE	SE	Med	Min	Max
Weight, kg															
PLACEBO															
OVERALL															
BASELINE	582	60.3	0.50	13.13	59.0	33	114								
END POINT	508	59.8	0.53	12.97	56.4	34	114	60.4	602	-0.5	0.12	3.07	0.0	-15	14
RISPERIDONE															
OVERALL															
BASELINE	1076	60.5	0.41	13.50	59.0	30	122								
END POINT	970	60.9	0.44	13.65	59.4	30	124	60.6	964	0.3	0.10	3.15	0.0	-20	15
HA OPRINDOL															
OVERALL															
BASELINE	109	62.7	1.22	12.70	60.0	40	90								
END POINT	96	62.5	1.18	11.46	61.0	40	90	63.9	90	-1.3	0.38	3.62	-1.0	-10	7
OLANZAPINE															
OVERALL															
BASELINE	70	71.3	1.72	15.23	73.5	37	105								
END POINT	72	72.7	1.63	15.56	73.0	30	107	71.2	72	1.5	0.44	3.73	1.0	0	16
OTHER NEURO															
OVERALL															
BASELINE	1	80.0			80.0	80	80								
END POINT	1	80.0			80.0	80	90	80.0	1	0.0			0.0	0	0

See footnotes on the first page of the table.

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint

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17FEB2004 12:56
System Used: Arrow3.1/weight.dsp

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint (continued)

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: LONG TERM

AGE CATEGORY: missing

								Change from Overall Baseline							
	N	Mean	SE	SD	Med	Min	Max	Base Mean	N	Post	SE	SD	Med	Min	Max
Weight, kg															
RISPERIDONE															
OVERALL	12	71.6	2.45	8.50	70.3	62	90								
BASELINE	12	71.6	1.89	6.53	69.5	65	93	71.6	12	-0.1	0.97	3.03	-0.1	-8	3
END POINT															

See footnotes on the first page of the table.

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint

Page 5 of 8

17FEB2004 12:56
System Used: Arrow3.1/weight.dsp

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint (continued)

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: LONG TERM

AC3 CATEGORY: 418

	N	Mean	SE	SD	Med	Min	Max	Base Mean	N	Post	SE	SD	Med	Min	Max
Weight, kg															
RISPERIDONE															
OVERALL	701	36.4	0.53	13.59	33.4	14	98								
BASLINE	587	43.6	0.63	16.62	40.4	17	130	36.3	660	7.4	0.22	5.83	6.0	-5	48
END POINT															
HALOPERIDOL															
OVERALL	10	58.3	2.29	7.25	58.0	48	69								
BASLINE	7	67.5	4.62	11.69	66.0	58	91	58.9	7	8.6	3.33	8.81	9.0	-5	23
END POINT															

See footnotes on the first page of the table.

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint

Page 7 of 8

17FEB2004 12:56
System Used: Arrow3.1/weight.dsp

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint (continued)

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: LONG TERM

AGE CATEGORY: 19-65

	N	Mean	SE	SD	Med	Min	Max	Change from Overall Baseline							
								Base Mean	N	Mean	SE	SD	Med	Min	Max
Weight, kg															
RISPERIDONE															
OVERALL	4868	78.8	0.26	17.81	76.6	37	157								
BASLINE	3370	81.3	0.29	17.98	79.0	40	177	79.0	3914	2.2	0.11	6.85	1.4	-35	97
END POINT															
HALOPERIDOL															
OVERALL	565	75.7	0.76	18.14	73.0	34	159								
BASLINE	487	78.8	0.85	18.69	75.3	38	176	75.9	484	2.5	0.38	8.45	1.0	-23	50
END POINT															
OLANZAPINE															
OVERALL	296	76.6	0.88	15.11	76.0	40	128								
BASLINE	295	80.6	0.94	16.06	79.0	41	128	76.6	294	4.0	0.38	6.59	3.0	-14	29
END POINT															

See footnotes on the first page of the table.

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint

Page 9 of 8

17FEB2004 12:56
System Used: A2row3.1/weight.disp

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.1 : Mean +/-SD Weight Change (kg) From Baseline to Endpoint (continued)

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: LONG TERM

AGE CATEGORY: >65

	N	Mean	SE	SD	Med	Min	Max	Change from Overall Baseline							
								Base Mean	N	Mean	SE	SD	Med	Min	Max
Weight, kg															
RISPERIDONE															
OVERALL															
BASELINE	766	63.7	0.51	14.18	63.0	35	126								
END POINT	588	63.4	0.52	13.72	62.6	34	116	63.3	660	0.2	0.18	4.61	0.0	-17	17
OLANZAPINE															
OVERALL															
BASELINE	3	77.7	12.91	22.37	73.0	58	102								
END POINT	3	79.0	15.72	27.22	68.0	59	110	77.7	3	1.3	3.76	6.51	1.0	-5	8

See footnotes on the first page of the table.

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.2: Incidence of Body Weight Percent change From Baseline in Subjects >18 Years

Page 1 of 4

17FEB2004 12:36
Sys.em Data: Arrow3.1/aSAF.WEIGHT.1

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.2: Incidence of Body Weight Percent change from Baseline in Subjects >18 Years

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: SHORT TERM

ACE CATEGORY: 13-65

	--- PLACEBO ---			-- RISPERIDONE --			-- HALOPERIDOL --			-- OLANZAPINE --			-- OTHER NEURO --		
	n	%	Cum.%	n	%	Cum.%	n	%	Cum.%	n	%	Cum.%	n	%	Cum.%
WEIGHT PERCENT CHANGE															
OVERALL															
END POINT															
<-7%	36	4.3	4.3	127	2.6	2.6	31	4.0	4.0	6	1.5	1.5	7	2.7	2.7
[-7%,+7%]	272	32.7	37.0	120	26.3	28.9	222	34.1	28.9	60	14.6	16.0	72	28.1	30.9
[0%,+7%]	480	57.6	94.6	289	59.2	89.1	320	50.7	89.6	235	57.0	73.1	148	57.8	88.7
>+7%	45	5.4	100.0	579	11.9	100.0	68	10.4	100.0	111	26.9	100.0	29	11.3	100.0
Total	833			4874			651			412			256		

Short term: less than or equal to 12 weeks
Long term: greater than or equal to 12 months
other neuroleptics included zuclopentixol, perphenazine, meroxipride, clozapine, thioridazine, levomepromazine and divalproex

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.2: Incidence of Body Weight Percent change From Baseline in Subjects >18 Years

Page 2 of 4

17FEB2004 12:56
System Used: Arrow3.1/aSAF.WEIGHT.1

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.2: Incidence of Body Weight Percent change from Baseline in Subjects >18 Years (continued)

ANALYSIS SET: ALL SUBJECTS
TRIAL TYPE: SHORT TERM
AGE CATEGORY: >65

	--- PLACEBO ---			-- RISPERIDONE --			-- HALOPERIDOL --			-- OLANZAPINE --			-- OTHER NEURO --		
	n	%	Cum.%	n	%	Cum.%	n	%	Cum.%	n	%	Cum.%	n	%	Cum.%
WEIGHT PERCENT CHANGE															
OVERALL															
END POINT															
<-7%	56	9.3	9.3	53	5.5	5.5	13	14.4	14.4	2	2.0	2.0	0	0.0	0.0
[-7%,0%]	220	33.0	47.3	210	22.2	37.7	29	43.3	59.8	12	15.7	10.4	0	0.0	0.0
[0%,+7%]	289	49.0	95.3	506	52.5	90.1	34	37.9	95.6	48	66.7	86.1	1	100.0	100.0
>+7%	28	4.7	100.0	95	9.9	100.0	4	4.4	100.0	10	13.9	100.0	0	0.0	100.0
Total	602			964			90			72					

See footnotes on the first page of the table.

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JJRPrev 00481915
D919.424

R. 6880

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.2: Incidence of Body Weight Percent change From Baseline in Subjects >18 Years

Page 3 of 4

17FEB2004 12:56
System Used: ATROW3.1/aSAF.WEIGHT.1

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.2: Incidence of Body Weight Percent change From Baseline in Subjects >18 Years (continued)

ANALYSIS SET: ALL SUBJECTS
TRIAL TYPE: LONG TERM
ACC CATEGORY: 13-65

	-- RISPERIDONE --			-- HALOPERIDOL --			-- CLANZAPINE --		
	n	%	Cum.%	n	%	Cum.%	n	%	Cum.%
WEIGHT PERCENT CHANGE									
OVERALL									
END POINT									
<-7%	269	5.9	6.9	43	0.9	0.9	19	6.5	6.5
[-7%,+7%]	940	24.0	30.9	131	27.1	36.0	39	13.3	19.7
[0%,+7%]	1762	53.0	75.9	174	36.0	72.9	131	44.6	64.3
>+7%	943	24.1	100.0	136	28.1	100.0	165	33.7	100.0
Total	3914			484			254		

See footnotes on the first page of the table.

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.2: Incidence of Body Weight Percent change From Baseline in Subjects >18 Years

Page 4 of 4

L7FEB2004 12:56
System Used: Arrow3.1/aSAF.WEIGHT.1

RIS-POOLED WEIGHT ANALYSIS

aSAF.WEIGHT.2: Incidence of Body Weight Percent change from Baseline in subjects >18 Years (continued)

ANALYSIS SET: ALL SUBJECTS
TRIAL TYPE: LONG TERM
AGE CATEGORY: >55

	-- RISPERIDONE --			-- OLANZAPINE --		
	n	%	Cum.%	n	%	Cum.%
WEIGHT PERCENT CHANGE						
OVERALL						
<-7%	06	13.0	13.0	0	0.0	0.0
[-7%,+7%]	184	27.0	40.0	33	33.3	33.3
[0%,+7%]	282	42.7	82.6	33	33.3	66.7
>+7%	108	16.4	100.0	33	33.3	100.0
Total	660			33		

See footnotes on the first page of the table.

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JJRPprev 00481917
Confidential/Produced in Litigation Pursuant to Protective Order
D919.426

R. 6882

Risperidone: Effects on Glucose Metabolism
Table aSAF.WEIGHT.3 : Descriptive Statistics of Body Weight Increase >7% in Subjects >18 Years

Page 1 of 4

17FEB2004 12:56
System Used: Arrow3.1/aSAF.WEIGHT.2

RIS-POOLED WEIGHT ANALYSE

aSAF.WEIGHT.3 : Descriptive statistics of Body Weight Increase >7% in Subjects >18 Years

ANALYSIS SET: ALL SUBJECTS

TRIAL TYPE: SHORT TERM

AGE CATEGORY: 18-65

	N	Mean	SE	SD	Med	Min	Max	Base Mean	Change from Overall Baseline						
									N	Mean	SE	SD	Med	Min	Max
Weight, kg															
PLACEBO															
OVERALL															
BASLINE	45	64.5	2.59	17.39	63.5	36	121								
END POINT	45	71.2	2.85	19.10	68.0	40	135	64.5	45	6.6	0.39	2.62	5.8	3	14
RISPERIDONE															
OVERALL															
BASLINE	579	66.4	0.66	15.97	65.0	33	146								
END POINT	579	73.8	0.72	17.33	72.0	36	161	66.4	579	7.3	0.12	2.97	6.8	3	28
HALOPERIDOL															
OVERALL															
BASLINE	68	63.6	1.70	14.74	61.6	34	134								
END POINT	68	70.8	1.95	16.09	68.0	43	113	63.6	68	7.2	0.41	3.34	6.5	3	20
OLANZAPINE															
OVERALL															
BASLINE	111	74.0	1.52	15.57	71.7	44	121								
END POINT	111	82.4	1.62	17.77	79.8	47	135	74.0	111	8.2	0.34	3.55	7.0	3	20
OTHER NEURO															
OVERALL															
BASLINE	29	68.7	2.08	11.22	70.0	43	90								
END POINT	29	75.5	2.20	11.85	76.5	48	100	68.7	29	6.5	0.35	1.90	6.6	4	15

Short term: less than or equal to 12 weeks

Long term: greater than or equal to 6 months

Other neuroleptics included zuclopentixol, perphenazine, risperidone, clozapine, thioridazine, levomepromazine and divalproex