Zyprexa Presentation Overview
GPLC 15MAY02

Zyprexa Presentation Overview - GPLC Meeting
May 15, 2002

Introduction:

As a result of the Zyprexa label change in Japan, the question posed by GPLC is as follows: Is a change to the olanzapine Core Data Sheet warranted?

To date, extensive data has been generated by Lilly on olanzapine and glucose dysregulation, including data from spontaneous post-marketing adverse events, clinical trials, epidemiological analyses of two large prescription/health care provider databases, and a hyperglycemic clamp study investigating insulin secretion in healthy volunteers administered olanzapine or risperidone. Based upon the data that has been generated to date on olanzapine and glucose dysregulation (described below in this document), the Zyprexa Product Team and the Pharmacovigilance Department do not agree with the changes recently made to the Zyprexa Japan label and do not recommend a change to the olanzapine Core Data Sheet.

The purpose of the remainder of this document is to provide an overview of the analyses that have been completed and that are in process to examine the issues involving olanzapine and glucose dysregulation. In addition, a brief overview is provided of Regulatory reports that have been recently prepared for submission as requested. Documents providing additional information, including several in-press manuscripts that describe completed analyses, are provided as attachments in the accompanying email.

Analyses and documents that have been completed (May 2002):

1. Spontaneous Post-Marketing Adverse Event Reports
   - **Hyperglycemia, Weight Gain, and Olanzapine** (Submitted to the FDA and CPMP, summer 2000)
     - A large, 3-volume document prepared in response to requests from the FDA and CPMP in the spring of 2000 (due to length not attached)
     - Included analyses of spontaneous post-marketing adverse event reports thru April 2000
     - Also included extensive analyses of clinical trial data

2. Clinical Trial Data
   - **Analyses of Random Blood Glucose Concentrations in Patients with Schizophrenia Treated with Typical and Atypical Antipsychotic Agents** (Initially submitted to Canadian HPB, April 2002)
     - A series of analyses conducted using the olanzapine integrated clinical trial database of direct-comparator trials for schizophrenia-spectrum patients (report section "clinical trial analysis – April 2002" attached)

3. Epidemiological Studies
   - **Pharmacoepidemiological Study of Diabetes Mellitus and Antipsychotic Treatment in the United States Using the AdvancePCS Prescription Claim Database**
     - Prescription claims for diabetes medications used to identify subjects with diabetes. (manuscript attached)

   Diabetes Mellitus and Antipsychotic Treatment in the United Kingdom
     - Patients with recorded diagnosis of diabetes or prescribed any antidiabetic medication were considered to have diabetes. (manuscript attached)

4. Clinical Pharmacology Study
   - **Hyperglycemic Clamp Assessment of Insulin Secretory Responses in Normal Subjects Treated with Olanzapine, Risperidone, or Placebo**
     - Changes (baseline to endpoint) in insulin levels were studied using a hyperglycemic clamp in healthy subjects treated with olanzapine, risperidone, or placebo. (manuscript attached)

5. Educational Tools/Documents Created for Customer Health Care Professionals
   - Global Response Documents (from Global Medical Information)
     - **Blood Glucose Changes and Olanzapine** (attached)
     - **Acute Complications or Presentations of Diabetes – DKA & HHNS** (attached)
   - US Medical Letter: **Natural History, Diagnosis and Management of Diabetes** (from US Medical Information; intended for a Psychiatrist audience - attached)

Ongoing analyses and documents in ongoing development:

1. Spontaneous Post-Marketing Adverse Event Reports
   - **Glucose Dysregulation Adverse Events (Spontaneous) and Commercially Marketed Olanzapine**. This document will contain: Analyses of all post-marketing reports of glucose dysregulation thru 30 Sep 2001, including detailed narratives for selected serious cases.

2. Clinical Trial Analysis
   - **Treatment-Emergent Diabetes Clinical Trial Analysis:** A large non-diabetic cohort receiving olanzapine, risperidone, haloperidol, clozapine, or placebo (n=5013) was retrospectively identified from 24 clinical trials and examined for evidence of treatment-emergent diabetes. The relationship between pre-existing risk factors for diabetes (entry glucose levels, age, BMI, ethnicity, hypertension, or evidence of impaired glucose tolerance), treatment-emergent weight gain, and therapy assignment on the risk of TED are assessed. (See the attached abstract)

3. Clinical Pharmacology Study
   - **S013 Study Report**: F1D-MC-S013 seeks to determine the effect of antipsychotic therapy on insulin receptor sensitivity in healthy lean and obese subjects. The primary objective of this study is to assess whether olanzapine 10 mg/day and risperidone 4 mg/day for 2 weeks, compared to placebo, have adverse effects on glucose metabolic parameters in healthy, lean and obese, non-diabetic subjects as measured by changes in the glucose infusion rate during a euglycemic, hyperinsulinemic clamp. This study is completed and analysis is ongoing. The final study report is targeted for completion in Q3 2002.

Documents recently prepared for global affiliates for the basis of their responses to local regulatory authorities (provided on an as needed basis):

1. **Glucose Regulatory Response Document** (Sent to several affiliates for submission to local regulatory agencies)
   - The purpose of this document is to address issues raised by global regulatory authorities regarding the recent label change in Japan.
   - The document is an executive summary of completed and ongoing analyses individualized (sections included or excluded) according to the nature of the regulatory request.

2. **Glucose Dysregulation Adverse Event Reports (Spontaneous) and Commercially Marketed Olanzapine in Japan** (Submitted to the FDA 25 Apr 2002)
   - This report provides narrative summaries for the 13 Japanese adverse event reports that were the basis of the label change in Japan.

3. **Glucose Dysregulation Adverse Event Reports (Spontaneous) with Outcome of Death and Commercially Marketed Olanzapine** (Prepared in case needed for a regulatory response)
   - This document provides narrative summaries of the 36 adverse event reports with an outcome of death for reports received thru 30 Sep 2001. Also includes a summary data from the 36 spontaneous reports.
   - This is a subset of the spontaneous post-marketing document that is in preparation.

Listing of Olanzapine Attachments
For GPLC on 15MAY2002

1. Zyprexa Presentation Overview – GPLC Meeting May 15, 2002
2. Glucose Olanzapine Labeling Comparison
3. Analyses of Random Blood Glucose Concentrations in Patients with Schizophrenia Treated with Typical and Atypical Antipsychotic Agents
4. Pharmacoepidemiological Study of Diabetes Mellitus and Antipsychotic Treatment in the United States Using the AdvancePCS Prescription Claim Database
5. Diabetes Mellitus and Antipsychotic Treatment in the United Kingdom
6. Hyperglycemic Clamp Assessment of Insulin Secretory Responses in Normal Subjects Treated with Olanzapine, Risperidone, or Placebo
7. Global Response Document – Blood Glucose Changes and Olanzapine
8. Global Response Document – Acute Complications or Presentations of Diabetes – DKA & HHNS
9. US Medical Letter – Natural History, Diagnosis, and Management of Diabetes
10. Treatment-Emergent Diabetes Clinical Trial Analysis

Glucose Olanzapine Labeling Comparison

GLUCOSE RELATED STATEMENTS IN OLANZAPINE LABELING

CDS	USPI	EU SmPC	Japan
			CONTRAINDICATIONS
			Patients with diabetes mellitus and those who have a history of diabetes mellitus.
		4.4 Special warnings and special precautions for use	**WARNINGS**
		Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predispos ing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.	1. From marked increase in blood glucose, serious adverse reactions such as diabetic ketoacidosis, diabetic coma, etc. may appear leading potentially to death. Observe sufficiently with such as measurement of blood glucose during the olanzapine administration. 2. Upon administration, explain sufficiently in advance to the patient and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately, if such symptoms appear. (See the section on "Important Precautions")

CDS	USPI	EU SmPC	Japan
			PRECAUTIONS
			1. Careful Administration 6. Patients with risk factors for diabetes mellitus such as family history of diabetes mellitus, hyperglycemia, obesity, etc. (See the section on "Important Precautions"). **2. Important Precautions** 1. By administration of this drug, marked increase in blood glucose may appear leading to fatal clinical course such as diabetic ketoacidosis, diabetic coma, etc. Observe sufficiently with such as measurement of blood glucose (appearance of) thirst, polydipsia, polyurea, and frequent urination during the olanzapine administration. In particular, patients with risk factors for diabetes mellitus such as hyperglycemia, obesity, etc., blood glucose may increase, leading to acute worsening of metabolic state. 2. Upon administration, explain sufficiently in advance to patients and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately, if such symptoms appear.

CDS	USPI	EU SmPC	Japan
Section C.8 Undesirable Effects	**Adverse Reactions**	**4.8 Undesirable effects**	**4. Adverse Reactions**
Random plasma glucose levels ≥200mg/dL (suggestive of potential diabetes){ **XE "37141" }** as well as random levels ≥160mg/dL but <200mg/dL (suggestive of potential hyperglycemia){ **XE "37142" }** in patients with baseline random glucose levels ≤140mg/dL have been seen occasionally in clinical trials. The following glucose related terms are documented with their appropriate frequencies in the adverse event tables: • Diabetic coma • Diabetic ketoacidosis • Hyperglycemia • Random glucose ≥160 mg/dL <200 mg/dL (suggestive of potential hyperglycemia) • Random glucose ≥200 mg/dL (suggestive of potential diabetes)	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. **Endocrine System**--*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis **Metabolic and Nutritional Disorders** --*Infrequent*: hyperglycemia, hypoglycemia; *Rare:* ketosis *Postintroduction Reports*--Adverse events reported since market introduction which were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: diabetic coma	The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials. **Metabolism and nutrition disorders** *Common (1-10%):* Elevated glucose levels (see note 1 below). *[1] In clinical trials with olanzapine in over 5000 patients with baseline non-fasting glucose levels ≤ 7.8 mmol/l, the incidence of non-fasting plasma glucose levels ≥ 11 mmol/l (suggestive of diabetes) was 1.0%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels ≥ 8.9 mmol/l but < 11 mmol/l (suggestive of hyperglycaemia) was 2.0%, compared to 1.6% with placebo. Hyperglycaemia is also reported as a Very Rare (<0.01%) spontaneous event.* The following table of undesirable effects is based on post-marketing spontaneous reports. **Metabolism and nutrition disorders** *Very rare (<0.01%):* Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases (see also	**(1) Clinically significant adverse reactions** 1. Hyperglycemia, Diabetic ketoacidosis, Diabetic coma: Hyperglycemia may develop leading to fatal clinical course, such as diabetic ketoacidosis and diabetic coma leading to death. Thus, make a close observation, with such as blood glucose measurement, (appearance of) thirst, polydipsia, polyurea, and frequent urination. If any abnormalities are noted, discontinue administration and take an appropriate measure(s) including administration of insulin. The following terms are identified in a table titled, "Japanese clinical studies and postmarketing reports:" • Sugar urinary • Diabetes The following terms are identified in a table titled, "Foreign clinical studies and postmarketing spontaneous reports:" • Hyperglycemia (Casual blood glucose: Not less than 160 mg/dL) • Coma diabetic • Diabetic ketoacidosis

CDS	USPI	EU SmPC	Japan
		Note 1 above and Section 4.4, Special warnings and special precautions for use).	

Analyses of Random Blood Glucose Concentrations in Patients with Schizophrenia Treated with Typical and Atypical Antipsychotic Agents

Note:

A report was prepared in April 2002 for the Canadian HPB covering stroke, hypotension, weight gain, and hyperglycemia. This is the section from the report that provides an analysis of the clinical trial data for hyperglycemia.

4.3.2.Clinical Trials

4.3.2.1. Methodology

It has been documented in the literature that patients with schizophrenia have an increased risk for the development of diabetes (Dixon 2000). A relatively homogenous psychiatric population known to be at greater risk for glucose abnormalities, the analyses were conducted using the olanzapine schizophrenia clinical trial database.

Hyperglycemia adverse events were evaluated in the integrated olanzapine clinical trial database. The integrated olanzapine clinical trial database was divided into five sections by comparator (placebo, haloperidol, clozapine, and risperidone) and an olanzapine overall integrated database.

Treatment-emergent events of hyperglycemia were defined as RANDOM glucose measurements ≥140mg/dL (≥7.8mmol/L) (random measurement suggestive of glucose intolerance [ADA 2001]) and ≥200mg/dL (≥11.1mmol/L) (random glucose measurement suggestive of diabetes [ADA 2001; Meltzer et al. 1998]) at any time during the treatment period. No FASTING glucose measurements were collected in any of the trials included in the analysis. Glucose measurements are reported utilizing the Traditional Units of mg/dL. To convert to the Système International Units of mmol/L, a conversion factor of 0.05551 may be utilized (Anonymous 1995).

The incidence of hyperglycemic events was calculated for each comparison (olanzapine versus placebo, olanzapine versus haloperidol, olanzapine versus clozapine, and olanzapine versus risperidone). The annualized incidence was also calculated to adjust for differences in duration of exposure between olanzapine and each comparator (placebo, haloperidol, clozapine, and risperidone). Comparative incidence analyses were also conducted across age groups and dose ranges. Since the majority of these studies were flexible dose trials, the mean *modal* dose was used in all analyses involving dose.

The comparator integrated databases and the olanzapine overall integrated database are described in greater detail below *(Note: *Rapid acting intramuscular (RAIM) studies; **RAIM studies with <10 days of oral therapy after IM)*:

- The placebo-controlled olanzapine integrated database includes pooled data from the following studies: HGAD, HGAO, HGAP, HGBH, HGEH, HGEU, HGFV, HGGP, HGGU, HGGW, HGGY, HGHB**, HGHV*, HGHW*, and HGHX*.

- The haloperidol-controlled olanzapine integrated database includes pooled data from the following studies: E003, HGAD, HGAJ, HGBQ, HGCJ, HGCR, HGCU, HGDD, HGDH, HGEC, HGFH, HGGN, HGHB**, HGHD, HGHO, HGHV*, and P022.
- The clozapine-controlled olanzapine integrated database includes pooled data from the following studies: HGBF, HGBO, HGCF, HGCK, and HGCP.
- The risperidone-controlled olanzapine integrated database includes pooled data from the following studies: HGBG, HGBO, HGBS, HGBU, HGDG, HGEC, HGGN, HGGU, HGHG, and P022.
- The olanzapine overall integrated database includes pooled data from the following studies: E003, HGAD, HGAJ, HGAO, HGAP, HGBA, HGBB, HGBF, HGBG, HGBH, HGBI, HGBJ, HGBK, HGBL, HGBM, HGBO, HGBQ, HGBR, HGBS, HGBT, HGBU, HGBX, HGCA, HGCF, HGCG, HGCH, HGCJ, HGCK, HGCL, HGCM, HGCO, HGCP, HGCQ, HGCR, HGCS, HGCU, HGCV, HGCX, HGCY, HGCZ, HGDD, HGDG, HGDH, HGDM, HGDQ, HGDT, HGDU, HGDV, HGDY, HGDZ, HGEB, HGEC, HGEF, HGEH, HGEJ, HGEP, HGER, HGES, HGET, HGEU, HGEZ, HGFH, HGFM, HGFR, HGFT, HGFV, HGFW, HGGC, HGGI, HGGN, HGGP, HGGU, HGGV, HGGW, HGGY, HGHB**, HGHD, HGHG, HGHO, HGHQ, HGHV*, HGHW*, HGHX*, HGJA*, LOAR**, LOAT**, and P022.

The cases identified are included in Appendix II (Olanzapine Master Table).

4.3.2.2. Results – Incidence of Treatment-Emergent Hyperglycemia (≥140mg/dL)

The following tables include patients with treatment-emergent hyperglycemia defined as treatment-emergent random glucose elevation of ≥140mg/dL. Table 4.20 below includes the results from studies comparing olanzapine and placebo.

Table 4.20. Incidence of Treatment-Emergent Hyperglycemia (≥140mg/dL)
Olanzapine versus Placebo Integrated Database

Therapy	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence %	P-Value* (CI)	Incidence per 1000 Pat Yr	P-Value** (IR)
1) Olz	0.12	1623	188	11.6	.065	984.0	.243
2) Placebo	0.08	952	88	9.2		1153.9	

N - Number of patients at risk (< 140 mg/dl at baseline).
n - Number of events (>= 140 mg/dl anytime postbaseline).
% - (crude) incidence.

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* - P-value testing (crude) incidence between therapy groups using Fisher's exact test.
**- P-value testing incidence rate between therapy groups using
    normal approximation.
Studies included:
  HGAD HGAO HGAP HGBH HGEH HGEU HGFV HGGP HGGU HGGW HGGY HGHB HGHV HGHW HGHX.
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Table 4.20 shows that there was no statistically significant difference between olanzapine and placebo groups in the incidence of treatment-emergent hyperglycemia, defined as random glucose elevation of ≥140mg/dL anytime during the treatment period, with or without adjustment for differences in duration of drug exposure. As indicated by the annualized incidence analysis, the lack of difference was even more robust once differences in duration of exposure were accounted for.

Table 4.21 below includes the results from studies comparing olanzapine and haloperidol.

Table 4.21. Incidence of Treatment-Emergent Hyperglycemia (≥140mg/dL) Olanzapine versus Haloperidol Integrated Database

Therapy	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value* (CI)	Incidence per 1000 Pat Yr	P-Value** (IR)
1) Olz	0.37	2480	280	11.3	.080	304.5	.035
2) Hal	0.25	1357	128	9.4		383.5	

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N - Number of patients at risk (< 140 mg/dl at baseline).
n - Number of events (>= 140 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-value testing (crude) incidence between therapy groups using Fisher's exact test.
**- P-value testing incidence rate between therapy groups using
    normal approximation.
Studies included:
  E003 HGAD HGAJ HGBQ HGCJ HGCU HGDD HGDH HGEC HGFH HGGN HGHB HGHD HGHO HGHV P022.
RMP.F1DSCRT2.SASPGM(ISSK09CN) 69997 02APR02
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Table 4.21 shows that there was no statistically significant difference in the incidence of treatment-emergent random glucose elevations ≥140mg/dL in patients treated with olanzapine compared to patients treated with haloperidol. However, a statistically significant difference between olanzapine and haloperidol was observed after controlling for differences in duration of exposure.

Table 4.22 below includes the results from studies comparing olanzapine and clozapine.

Table 4.22. Incidence of Treatment-Emergent Hyperglycemia (≥140mg/dL) Olanzapine versus Clozapine Integrated Database

Therapy	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value* (CI)	Incidence per 1000 Pat Yr	P-Value** (IR)

1) Olz	0.28	230	41	17.8	.032	634.2	<.001
2) Czp	0.20	186	50	26.9		1341.4	

N - Number of patients at risk (< 140 mg/dl at baseline).
n - Number of events (>= 140 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-value testing (crude) incidence between therapy groups using Fisher's exact test.
**- P-value testing incidence rate between therapy groups using
normal approximation.
Studies included:
HGBF HGBO HGCF HGCK HGCP.
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Table 4.22 shows that there was a statistically significant difference between the olanzapine and clozapine groups in the incidence of treatment-emergent hyperglycemia, defined as random glucose elevation of ≥140mg/dL anytime during the treatment period, with a higher incidence observed in the clozapine group regardless of adjustment for differences in duration of drug exposure.

Table 4.23 below includes the results from studies comparing olanzapine and risperidone.

Table 4.23. Incidence of Treatment-Emergent Hyperglycemia (≥140mg/dL) Olanzapine versus Risperidone Integrated Database

Therapy	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value* (CI)	Incidence per 1000 Pat Yr	P-Value** (IR)
1) Olz	0.41	559	100	17.9	.134	432.4	.305
2) Risp	0.39	508	73	14.4		364.9	

N - Number of patients at risk (< 140 mg/dl at baseline).
n - Number of events (>= 140 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-value testing (crude) incidence between therapy groups using Fisher's exact test.
**- P-value testing incidence rate between therapy groups using
normal approximation.
Studies included:
HGBG HGBO HGBS HGBU HGDG HGEC HGGN HGGU HGHG P022.
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Table 4.23 shows that there was no statistically significant difference between the olanzapine and risperidone groups in the incidence of treatment-emergent hyperglycemia, defined as random glucose elevation of ≥140mg/dL anytime during the treatment period, with or without adjustment for differences in duration of drug exposure.

Table 4.24 below includes the overall results regarding olanzapine.

Table 4.24. Incidence of Treatment-Emergent Hyperglycemia (≥140mg/dL) Olanzapine Overall Integrated Database

Duration of

Therapy	Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	Incidence per 1000 Pat Yr
1) Olz	0.42	5699	786	13.8	328.2

N - Number of patients at risk (< 140 mg/dl at baseline).
n - Number of events (>= 140 mg/dl anytime postbaseline).
% - (crude) incidence.
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Table 4.24 shows that 13.8% of olanzapine group experienced treatment-emergent hyperglycemia, defined as random glucose elevation of ≥140mg/dL anytime during the treatment period.

Table 4.25 below contains comparative incidence data across age groups for the olanzapine overall integrated database.

Table 4.25. Incidence Comparison of Treatment-Emergent Hyperglycemia (≥140mg/dL) Across Age Groups Olanzapine Overall Integrated Database

Age	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value*	Incidence per 1000 Pat Yr	P-Value**
<=45	0.47	3916	445	11.4	<.001	244.0	<.001
45-65	0.38	1153	195	16.9		447.9	
>65	0.22	630	146	23.2		1059.2	

N - Number of patients at risk (< 140 mg/dl at baseline).
n - Number of events (>= 140 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-Value testing linear association between TE hyperglycemia and Age groups using CMH statistic.
**- P-Values testing effects of Age from logit model: Model = Duration of exposure and Age groups.
RMP.F1DSCRT2.SASPGM(ISSK09CN) 69997 02APR02

Table 4.25 shows that there was a statistically significant linear association between age groups and the incidence of treatment-emergent hyperglycemia, indicating the older group was more likely to develop hyperglycemia, defined as random glucose elevation of ≥140mg/dL anytime during the treatment period, with or without adjustment for differences in duration of drug exposure. This finding is consistent with advancing age being a well-established risk factor for glucose intolerance and diabetes in the general population (ADA 2001).

Table 4.26 below contains comparative incidence data across dose groups for the olanzapine overall integrated database.

Table 4.26. Incidence Comparison of Treatment-Emergent Hyperglycemia (≥140mg/dL) Across Dose Groups Olanzapine Overall Integrated Database

Modal Dose	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value*	Incidence per 1000 Pat Yr	P-Value**
<=7.5	0.26	1504	236	15.7	.039	605.7	.382
7.5-12.5	0.37	1709	204	11.9		322.1	
>12.5	0.56	2461	321	13.0		234.3	

N - Number of patients at risk (< 140 mg/dl at baseline).
n - Number of events (>= 140 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-Value testing linear association between TE hyperglycemia and Dose groups using CMH statistic.
**- P-Values testing effects of Dose from logit model: Model = Duration of exposure and Dose groups.
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Table 4.26 shows that there was a statistically significant linear association between dose groups and incidence of treatment-emergent hyperglycemia, defined as random glucose elevation of ≥140mg/dL anytime during the treatment period. However, once we adjusted for differences in duration of drug exposure across dose ranges, a statistically significant linear association between incidence of random glucose elevation of ≥140mg/dL was no longer observed.

4.3.2.3. Results – Incidence of Treatment-Emergent Hyperglycemia (≥200mg/dL)

The following tables include patients with treatment-emergent hyperglycemia defined as treatment-emergent random glucose elevation of ≥200mg/dL. Table 4.27 below includes the results from studies comparing olanzapine and placebo.

Table 4.27. Incidence of Treatment-Emergent Hyperglycemia (≥200mg/dL) Olanzapine versus Placebo Integrated Database

Therapy	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value* (CI)	Incidence per 1000 Pat Yr	P-Value** (IR)
1) Olz	0.14	1772	42	2.4	.421	171.6	.557
2) Placebo	0.09	1042	19	1.8		210.0	

N - Number of patients at risk (< 200 mg/dl at baseline).
n - Number of events (>= 200 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-value testing (crude) incidence between therapy groups using Fisher's exact test.
**- P-value testing incidence rate between therapy groups using normal approximation.
Studies included:
HGAD HGAO HGAP HGBH HGEH HGEU HGFV HGGP HGGU HGGW HGGY HGHB HGHV HGHW HGHX.
RMP.F1DSCRT2.SASPGM(ISSK09CN) 69997 02APR02

Table 4.27 shows that there was no statistically significant difference between the olanzapine and placebo groups in the incidence of treatment-emergent hyperglycemia, defined as random glucose elevation of ≥200mg/dL anytime during the treatment period, with or without adjustment for differences in duration of drug exposure.

Table 4.28 below includes results from studies comparing olanzapine and haloperidol.

Table 4.28. Incidence of Treatment-Emergent Hyperglycemia (≥200mg/dL) Olanzapine versus Haloperidol Integrated Database

Therapy	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value* (CI)	Incidence per 1000 Pat Yr	P-Value** (IR)
1) Olz	0.41	2640	72	2.7	.001	66.6	.148
2) Hal	0.27	1441	17	1.2		43.8	

N - Number of patients at risk (< 200 mg/dl at baseline).
n - Number of events (>= 200 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-value testing (crude) incidence between therapy groups using Fisher's exact test.
**- P-value testing incidence rate between therapy groups using
normal approximation.
Studies included:
E003 HGAD HGAJ HGBQ HGCJ HGCU HGDD HGDH HGEC HGFH HGGN HGHB HGHD HGHO HGHV P022.
RMP.F1DSCRT2.SASPGM(ISSK09CN) 69997 02APR02

Table 4.28 shows that there were statistically significant differences between the olanzapine and haloperidol groups in the incidence of treatment-emergent hyperglycemia, defined as random glucose elevation ≥200mg/dL at any time during the treatment period, with a higher incidence observed in the olanzapine group. However, the duration of exposure to olanzapine was considerably longer than the duration of exposure to haloperidol. As indicated by the annualized incidence results, the difference in incidence of random glucose elevation ≥200mg/dL between olanzapine and haloperidol was no longer statistically significant after controlling for differences in duration of drug exposure.

Table 4.29 below includes the results from studies comparing olanzapine and clozapine.

Table 4.29. Incidence of Treatment-Emergent Hyperglycemia (≥200mg/dL) Olanzapine versus Clozapine Integrated Database

Therapy	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value* (CI)	Incidence per 1000 Pat Yr	P-Value** (IR)
1) Olz	0.33	244	4	1.6	.240	49.0	.105
2) Czp	0.25	211	8	3.8		150.9	

N - Number of patients at risk (< 200 mg/dl at baseline).
n - Number of events (>= 200 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-value testing (crude) incidence between therapy groups using Fisher's exact test.
**- P-value testing incidence rate between therapy groups using
exact binomial calculation.
Studies included:
HGBF HGBO HGCF HGCK HGCP.
RMP.F1DSCRT2.SASPGM(ISSK09CN) 69997 02APR02

Table 4.29 shows that there were no statistically significant differences between the olanzapine and clozapine groups in the incidence of treatment-emergent hyperglycemia, defined as random glucose elevation of ≥200mg/dL anytime during the treatment period, with or without adjustment for differences in duration of drug exposure.

Table 4.30 below includes the results from studies comparing olanzapine and risperidone.

Table 4.30. Incidence of Treatment-Emergent Hyperglycemia (≥200mg/dL) Olanzapine versus Risperidone Integrated Database

Therapy	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value* (CI)	Incidence per 1000 Pat Yr	P-Value** (IR)
1) Olz	0.47	601	23	3.8	.520	82.0	.783
2) Risp	0.42	567	17	3.0		71.3	

N - Number of patients at risk (< 200 mg/dl at baseline).
n - Number of events (>= 200 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-value testing (crude) incidence between therapy groups using Fisher's exact test.
**- P-value testing incidence rate between therapy groups using normal approximation.
Studies included:
HGBG HGBO HGBS HGBU HGDG HGEC HGGN HGGU HGHG P022.
RMP.F1DSCRT2.SASPGM(ISSK09CN) 69997 02APR02

Table 4.30 shows that there were no statistically significant differences between the olanzapine and risperidone groups in the incidence of treatment-emergent hyperglycemia, defined as random glucose elevation of ≥200mg/dL anytime during the treatment period, with or without adjustment for differences in duration of drug exposure.

Table 4.31 below includes the results for the olanzapine overall integrated database.

Table 4.31. Incidence of Treatment-Emergent Hyperglycemia (≥200mg/dL) Olanzapine Overall Integrated Database

Therapy	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	Incidence per 1000 Pat Yr
1) Olz	0.48	6102	177	2.9	60.4

N - Number of patients at risk (< 200 mg/dl at baseline).
n - Number of events (>= 200 mg/dl anytime postbaseline).
% - (crude) incidence.
RMP.F1DSCRT2.SASPGM(ISSK09CN) 69997 02APR02

Table 4.31 shows that 2.9% of the olanzapine group experienced treatment-emergent hyperglycemia, defined as random glucose elevation of at least 200mg/dL anytime during the treatment period.

Table 4.32 below contains comparative incidence data across age groups for the olanzapine overall integrated database.

Table 4.32. Incidence Comparison of Treatment-Emergent Hyperglycemia (≥200mg/dL) Across Age Groups Olanzapine Overall Integrated Database

Age	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value*	Incidence per 1000 Pat Yr	P-Value**
<=45	0.52	4093	79	1.9	<.001	36.8	<.001
45-65	0.46	1269	57	4.5		96.7	
>65	0.27	740	41	5.5		207.8	

N - Number of patients at risk (< 200 mg/dl at baseline).
n - Number of events (>= 200 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-Value testing linear association between TE hyperglycemia and Age groups using CMH statistic.
**- P-Values testing effects of Age from logit model: Model = Duration of exposure and Age groups.
RMP.F1DSCRT2.SASPGM(ISSK09CN) 69997 02APR02

Table 4.32 shows that there was a statistically significant linear association between age groups and the incidence of treatment-emergent hyperglycemia, indicating the older group was more likely to develop hyperglycemia, defined as random glucose elevation of ≥200mg/dL anytime during the treatment period, with or without adjustment for differences in duration of drug exposure. This finding is consistent with advancing age being a well-established risk factor for glucose intolerance and diabetes in the general population (ADA 2001).

Table 4.33 below contains comparative incidence data across dose groups for the olanzapine overall integrated database.

Table 4.33. Incidence Comparison of Treatment-Emergent Hyperglycemia (≥200mg/dL) Across Dose Groups Olanzapine Overall Integrated Database

Modal Dose	Duration of Exposure (Yr/Pat)	N	Incidence n	Incidence (%)	P-Value*	Incidence per 1000 Pat Yr	P-Value**
<=7.5	0.31	1591	57	3.6	.051	116.3	.121
7.5-12.5	0.41	1799	48	2.7		64.7	
>12.5	0.63	2708	68	2.5		40.0	

N - Number of patients at risk (< 200 mg/dl at baseline).
n - Number of events (>= 200 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-Value testing linear association between TE hyperglycemia and Dose groups using CMH statistic.
**- P-Values testing effects of Dose from logit model: Model = Duration of exposure and Dose groups.
RMP.F1DSCRT2.SASPGM(ISSK09CN) 69997 02APR02

Table 4.33 shows that there was a trend towards a statistically significant linear association between dose groups and the incidence of glucose elevation of ≥200mg/dL, with numerically higher incidences observed at relatively **lower** doses. However, with adjustment for differences in duration of drug exposure, a statistically significant linear association between dose groups and incidence of glucose elevation of ≥200mg/dL was not observed.

Table 4.34 below reports on the incidence of hyperglycemia, defined as random glucose elevation ≥200mg/dL at any time during the treatment period, according to the presence or absence of treatment-emergent weight gain >1.8kg.

Table 4.34. Incidence of Treatment-Emergent Hyperglycemia (≥200mg/dL) by Weight Gain >1.8kg Olanzapine Overall Integrated Database

Variable	Group	N	Incidence n	Incidence (%)	P-Value*
Weight Gain	<=1.8 kg	2491	77	3.1	.937
	> 1.8 kg	2999	91	3.0	

N - Total number of patients (< 200 mg/dl at baseline).
n - Number of events of hyperglycemia (>=200 mg/dl anytime postbaseline).
% - (crude) incidence.
* - P-values refer to comparison of (crude) incidence using Fisher's exact test.
RMP.F1DSCRT2.SASPGM(ISSK08CN) 69997 03APR02

Table 4.34 shows that the presence of treatment-emergent weight gain >1.8kg was not associated with a greater incidence of hyperglycemic events, defined as random glucose elevation ≥200mg/dL at anytime during the treatment period.

4.3.2.4. Summary of Clinical Trial Results of Treatment-Emergent Hyperglycemic Events

There were no statistically significant differences in incidence of treatment-emergent random glucose elevations =140mg/dL (suggestive of glucose intolerance [ADA 2001]) in patients treated with olanzapine compared to patients treated with placebo or risperidone. There was also no statistically significant difference in the incidence of treatment-emergent random glucose elevations =140mg/dL in patients treated with olanzapine compared to patients treated with haloperidol, although a statistically significant difference between olanzapine and haloperidol was observed after controlling for differences in duration of exposure. The incidence of treatment-emergent glucose =140mg/dL observed in olanzapine-treated patients was statistically significantly lower than the incidence observed in clozapine-treated patients. The overall incidence of treatment-emergent glucose =140mg/dL in olanzapine-treated patients was 13.8%.

The incidence of treatment-emergent random glucose elevations =200mg/dL (suggestive of diabetes [ADA 2001; Meltzer et al. 1998]) was statistically significantly greater in patients treated with olanzapine compared to haloperidol. However, the difference was not statistically significant after controlling for the fact that the mean duration of exposure in the olanzapine group was longer than the duration of exposure in the haloperidol group. There were no statistically significant differences in the incidence of treatment-emergent glucose =200mg/dL in patients treated with olanzapine compared to placebo, risperidone, or clozapine.

In analyses of the overall integrated olanzapine database, no association between dose and incidence of treatment-emergent glucose elevations =140mg/dL or =200mg/dL was observed, once differences in duration of exposure were controlled for. Greater incidences of treatment-emergent glucose =140mg/dL and =200mg/dL were observed in older patients. This finding is consistent with advancing age being a well-established risk factor for diabetes (ADA 2001).

In analyses of the overall integrated olanzapine database, treatment-emergent weight gain >1.8kg was not associated with a greater incidence of treatment-emergent glucose elevations =200mg/dL at anytime during the treatment period.

4.3.2.5. Conclusions on Clinical Trial Results of Treatment-Emergent Hyperglycemic Events

Results from clinical trial analyses are consistent with the known safety profile of olanzapine, and data provided to the TPD as part of the Notifiable Change (Control No. 073735 and 073737) we filed September 26, 2001.

Pharmcoepidemiological Study of Diabetes Mellitus and Antipsychotic Treatment in the United States Using the AdvancePCS Prescription Claim Database

A Retrospective Cohort Study of Diabetes Mellitus and Antipsychotic Treatment in the United States

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ABSTRACT

Background: Treatment-emergent DM has been described for conventional and atypical antipsychotics.

Method: Antipsychotic prescription claims from AdvancePCS' database were used to identify patients starting antipsychotic monotherapy. The relative risk of developing DM was determined using prescription claims for anti-diabetic agents in the following cohorts: AdvancePCS general patient population, combined conventional antipsychotics, haloperidol, thioridazine, combined atypical antipsychotics, olanzapine, risperidone, quetiapine, and clozapine. 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.

Results: Hazard ratios for developing DM in the combined conventional, combined atypical as well as individual conventional and atypical antipsychotic treatment cohorts were also greater than the AdvancePCS general patient population cohort.

Conclusions: An increased risk of developing diabetes compared to the AdvancePCS general patient population was observed during treatment with either conventional or atypical antipsychotics.

Running headline: Antipsychotic Treatment and Diabetes

Key words: antipsychotics, diabetes, epidemiological study

INTRODUCTION

Studies over several decades have suggested that diabetes mellitus (DM), impaired glucose tolerance (IGT), and insulin resistance were more common in patients with psychiatric disorders, including major mood disorders and schizophrenia, than in the general population [1-6]. Further, literature reports have associated treatment-emergent glucose intolerance with both 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 development of DM has not been supported by all investigations [26, 27] as higher than expected rates of insulin resistance and impaired glucose tolerance had been reported in patients with schizophrenia prior to 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 primarily consisted of small case series and prevalence studies in relatively small population samples [33-36]. These studies have been marked by significant methodological limitations, and the results have been largely inconclusive. Ultimately, questions regarding the frequency of DM in patients treated with antipsychotics are most effectively answered in epidemiological studies. Due to their large sample size and less rigorous exclusion criteria than prospective clinical trials, epidemiological 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 pharmacoepidemiology of antispychotics and DM. Mahmoud et al. [37] examined prescription claims data from two large mixed indemnity and managed health care plans in the United States (US) and determined the hazard ratios for developing DM during exposure to antipsychotic medications. They identified treatment emergent diabetes by prescription claims and ICD-CM-9 diagnostic criteria over a two-year period with 4 and 8 month prescreening periods prior to initiation of antipsychotic therapy. They reported an increased risk of developing DM in patients exposed to both high and low potency conventional antipsychotics, clozapine and olanzapine. Another recent epidemiological study by Caro et al. retrospectively examined treatment emergent diabetes during exposure to either risperidone or olanzapine from prescription claims and physician diagnoses from the Réige de l' Assurance Maladie de Québec (RAMQ) [38]. The results of this study showed a numerically greater incidence of DM for the olanzapine cohort (1.7%) as compared to the risperidone (1.5%) cohort. On the basis of a crude relative risk of 1.08 (95% CI: 0.89-1.31) and hazard ratio 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 those who had been treated with risperidone. Both 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 epidemiological study evaluating the potential association of diabetes with antipsychotic treatment has been published to date.

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 to each other, and to the general AdvancePCS general patient population.

METHODS

This is a retrospective cohort study that determined the risk of developing DM during antipsychotic treatment using prescription claim data from AdvancePCS (Scottsdale, AZ). AdvancePCS processes over 300 million prescription claims per year for the over 50 million members covered by the over 2,000 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 only 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. Further, the > 65 group represents over 24% of AdvancePCS's patient population, as a greater proportion of elderly individuals receive prescriptions, compared to the younger, generally healthier members. As of 1997, 42% of the patients starting an antipsychotic prescription were on Social Assistance, covered by Medicaid. The data cut-off point for this study is August 31, 2000.

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 were 1) combined conventional antipsychotic cohort (comprised of subjects treated with all agents in this class), 2) combined atypical antipsychotic cohort, 3) cohorts of individual antipsychotics (comprised of subjects treated with a particular agent, e.g. 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 (e.g. drug) during a 2-month enrollment window (January 1, 2000 to February 29, 2000). They must not have made a claim for diabetes drug(s) for at least 12 months prior to enrollment. In addition, they must not have been dispensed an antipsychotic for at least 6 months prior to and 6 months after enrollment.

Antipsychotic agents included both conventional antipsychotics: chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, prochlorperazine, promazine, thioridazine, thiothixene, trifluoperazine, and triflupromazine, and atypical antipsychotics: clozapine, olanzapine, quetiapine and risperidone.

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 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 prior to 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 six month-period before enrollment date, 3) absence of information

on either sex or the year of birth, and 4) less than 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. Therefore, individual age was comparable across the different study groups. For example, a patient in an antipsychotic cohort determined to be 25 years of age on December 5, 1998 will be compared to a patient in the general population cohort who was 25 years of age on January 5, 2000. In addition, adjustments for age differences were addressed by including an age variable in the regression analyses.

Identification of Incident Cases of Diabetes Mellitus

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 either an antipsychotic agent in the case of the antipsychotic cohorts, or a non-antipsychotic agent, in the case of the general patient population, was considered the enrollment date for that subject. In order to identify the timing of onset of new cases of DM, the date of the first anti-diabetic agent prescribed after the enrollment date was considered the start of anti-diabetic therapy. Each patient in the antipsychotic cohort was tracked for new onset of DM from the enrollment date to the time that the antipsychotic was discontinued for more than 15 days, or until August 31, 2000 (the data set cut-off point), whichever came first.

Comparison of the Risk of Developing Diabetes between Cohorts

In order to compare the risk of deve loping DM among cohorts, both incidence density and hazard ratios were determined. As 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 likely 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 hazard ratio (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 (3 categories), gender (2 categories), and amount of exposure (5 categories). The reference categories for these covariates, represented by zero in the model, were the 18-44 group for age and female for gender. Amount of exposure was viewed as having both a duration and dose component. The duration component was the number of continuous days of treatment determined from the date of first antipsychotic filled and the last successive prescription(s) that was not separated by more than 15 days. Individual doses were determined for each subject by summing 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 18-44, 45-64, and 65 years of age and older categories on the basis that these ranges correspond with those cited for the incidence of diabetes in the United States general population [39]. In

addition, given the wide dose ranges observed in the antipsychotic cohorts, HR's of DM were determined for each dose quartile, relative to the AdvancePCS general patient population. The HR's of DM between selected antipsychotic cohorts were also determined. The alpha level for statistical significance was 0.05.

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 to the AdvancePCS patient general 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 in this cohort over 64 years of age. In general, there were more females than males in all cohorts with the exception of the clozapine cohort. The average duration of antipsychotic treatment, ranging from 67-137 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 hazard ratio (HR) for age was found for all cohorts (except the thioridazine and clozapine cohorts) and a significant HR for gender was found for the general patient population, the atypical antipsychotic and risperidone cohorts. Compared to the effect of age, the gender effect was smaller. 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 ($p\leq0.0001$).

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 to the incidence density of the 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 both the conventional and atypical antipsychotic cohorts was significantly higher in comparison to the AdvancePCS general patient population. The HRs for all individual atypical antipsychotic cohorts (clozapine, olanzapine, risperidone and quetiapine) were significantly higher than that of the AdvancePCS general patient population.

As shown in Table 4, the risk of DM for the combined conventional cohort was not significantly different from that of the combined atypical cohorts (HR=1.0; CI: 0.8-1.1; p=0.6). No significant increase in the risk of DM was observed for either the olanzapine (HR=1.1; CI: 0.9-1.4; p=0.5) or the clozapine (HR=1.3; CI:0.6-2.9; p=0.5) cohort when compared to the haloperidol cohort. The clozapine sample was very small (N=277), and lacked sufficient power to detect a significant difference in the risk of DM. The HR for the quetiapine cohort was 0.7 (CI: 0.5-0.97; p=0.03), suggesting a statistically significant lower risk of DM compared to the haloperidol cohort. The risk of DM in the risperidone cohort, relative to the haloperidol cohort, was 1.2 (CI: 1.0-1.5; p=0.04). On comparison of the two largest atypical antipsychotic cohorts, olanzapine and risperidone, the HR was 0.9 (CI: 0.8-1.1; p= 0.2).

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 as 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. While 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≤0.0001). 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). A possible explanation for this may be the differences in diagnostic entities and within-diagnosis illness severity between the patient populations commonly treated with haloperidol and quetiapine in the US.

DISCUSSION

This large pharmacoepidemiological study allows examination of at least two important questions: did patients on atypical agents experience a different risk of treatment-emergent diabetes than those on conventional antipsychotics, and were there clinically significant differences in the risks of diabetes during treatment with individual antipsychotics. Consistently, the HRs of all antipsychotic treatment cohorts studied were significantly higher than that 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 pair-wise comparisons were made between individual antipsychotics. Among 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.

For all antipsychotic cohorts, increasing age was a significant risk factor for DM. This finding is in keeping with well-established epidemiological data indicating that the prevalence of diabetes increases with age[40], with an almost two-fold increase past age forty nine [39]. Male gender was a significant predictor of increased risk of diabetes only for the combined atypical antipsychotic, risperidone and 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 contain patients who received the highest doses of antipsychotics that may define a sub-population of more severely ill patients, diagnostically homogeneous patients. Compared to other psychiatric disorders commonly treated with antipsychotics, schizophrenic patients often require higher doses of antipsychotics for adequate management of their illness. Thus, the risk of DM associated with the fourth dose quartile may be particularly relevant to those patients with schizophrenia.

Recently, there have been a number of reports on the prevalence [36] or the odds ratios [37] of DM in subjects treated with antipsychotics. Compared to the present study, these reports have been limited by relatively small sample sizes, the concurrent use of multiple antipsychotic drugs in the cohorts, the absence of a reference population, or differences in duration of antipsychotic exposure among groups. Logistic regression, used for determining odds ratios, does not control for differences in duration of antipsychotic exposure among the various antipsychotic cohorts, a crucial factor in examining possible drug effects on the risk of diabetes. An exception among recent reports is the study by Caro et al. [38], which compared the cumulative incidences and risk of DM between a cohort of olanzapine-treated patients (n=19,153) and a cohort of risperidone-treated patients (n=14,792) over a three-year period of observation. The HR for the olanzapine compared to the risperidone cohort was 1.2 (CI: 1.00-1.43) in the study by Caro et al. [38], and 0.9 (CI: 0.7-1.2) in the present study. In contrast to the present study, subjects in the Caro study were not necessarily antipsychotic-free at the onset of the observation period, and were included

even if they were taking multiple antipsychotics concurrently. In particular, patients treated concurrently with olanzapine and risperidone were automatically assigned to the olanzapine cohort. Finally, the study by Caro et al. [38] did not include an AdvnacePCS general patient population reference cohort. Despite these substantial methodological differences, the results of the present study and the study by Caro et al. [38] both support the conclusion that the risks of diabetes for the olanzapine and the risperidone cohorts were comparable.

Our study presents a number of strengths, including: 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, thus the study was not confounded by antipsychotics that were either recently or concurrently administered; 3) only patients with DM would be prescribed anti-diabetic medications for outpatient use, thus false positive identification of anti-diabetes cases in this study is expected to be very low; 4) a reference population not exposed to antipsychotic medications also enabled us to compare the rates of developing DM relative to the AdvancePCS general patient population.

The major limitation of this study was that psychiatric diagnostic information was not available in the database. Other limitations were 1) only incident cases of DM that resulted in intervention with anti-diabetic medications were identified; 2) all indications for antipsychotic prescriptions were included, regardless of psychiatric illness spectrum or severity. Further, 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 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.

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 needed 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 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 treating 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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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	8,476	3,133	38,969	277	13,863	4,196	20,633
Age Distribution									
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 (years)	52	64	72	61	60	55	55	55	64
% Male	37%	44%	41%	38%	38%	53%	39%	37%	37%

Average duration of antipsychotic treatment (days) (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 1. Characteristics of Cohorts Studied (cont.)

Table 2. Hazard Ratio of Diabetes Mellitus for Covariates in the Proportional Hazard Regression Model Stratified by Antipsychotic Cohorts

Variable	Hazard Ratio	95% confidence interval	p value
Conventional Antipsychotic Cohort (n=19,782)			
Age 45-64 years*	2.4	1.5 – 3.9	0.0003
Age ≥65 years*	3.4	2.2 - 5.3	≤0.0001
Gender (Males)**	1.0	0.8 - 1.2	0.8158
Haloperidol Cohort (n=8,476)			
Age 45-64 years	4.5	1.3 – 15.2	0.0162
Age ≥65 years	5.9	1.9 – 18.4	0.0025
Gender (Males)	1.3	0.9 - 1.8	0.1218
Thioridazine Cohort (n=3,133)			
Age 45-64 years	1.7	0.7 – 4.0	0.2061
Age ≥65 years	2.1	1.0 – 4.5	0.0610
Gender (Males)	0.8	0.5 – 1.4	0.4729
Atypical Antipsychotic Cohort (n=38,969)			
Age 45-64 years	2.8	2.0 - 4.0	≤0.0001
Age ≥65 years	6.1	4.5 - 8.2	≤0.0001
Gender (Males)	1.3	1.1 - 1.6	0.0003
Clozapine Cohort (n=277)			
Age 45-64 years	3.0	0.3 - 33.6	0.3677
Age ≥65 years	3.4	0.4 - 31.3	0.2716
Gender (Males)	0.7	0.2 - 3.2	0.6497
Olanzapine cohort (n=13,863)			
Age 45-64 years	2.6	1.5 - 4.5	0.0006
Age ≥65 years	6.5	4.2– 10.5	≤0.0001
Gender (Males)	1.3	1.0 - 1.8	0.0585

Quetiapine cohort (n=4,196)			
Age 45-64 years	1.0	0.3 - 2.9	0.9670
Age ≥65 years	3.0	1.3 – 7.0	0.0095
Gender (Males)	1.1	0.6 - 2.1	0.7649
Risperidone cohort (N=20,633)			
Age 45-64 years	3.7	2.2 - 6.2	≤0.0001
Age ≥65 years	6.6	4.2 – 10.3	≤0.0001
Gender (Males)	1.3	1.1 - 1.7	0.0010
AdvancePCS General Patient Population (N=5,816,473)			
Age 45-64 years	3.4	3.3 – 3.5	≤0.0001
Age ≥65 years	4.0	3.9 - 4.2	≤0.0001
Gender (Males)	1.1	1.1 - 1.2	≤0.0001

* For all cohorts, age 18-44 years used as reference group.

** 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.

Table 2. Hazard Ratio of Diabetes Mellitus for Covariates in the Proportional Hazard Regression Model Stratified by Antipsychotic Cohorts (cont.)

Table 3. Incidence and Hazard Ratio of DM in Patients during Treatment with Antipsychotics

COHORT	No. of new cases	No. of patients	No. of patient-years	Incidence (per 1000 patient-years)		Hazard ratio*		
				Rate	95% CI	Ratio	95% CI	p-value
CONVENTIONAL ANTIPSYCHOTICS								
All combined	307	19,782	3,645.57	84	75 - 94	3.5	3.1 - 3.9	≤0.0001
Haloperidol	133	8,476	1,568.39	85	70 - 100	3.1	2.6 - 3.7	≤0.0001
Thioridazine	62	3,133	654.28	95	71 - 119	4.2	3.2 - 5.5	≤0.0001
ATYPICAL ANTIPSYCHOTICS								
All combined	641	38,969	9,571.18	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	3,374.57	58	49 - 66	3.0	2.6 - 3.5	≤0.0001
Quetiapine	40	4,196	1,025.75	39	27 - 51	1.7	1.2 - 2.4	0.0020
Risperidone	400	20,633	5,066.90	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	--	--	--

* Cox Proportional Hazards regression analysis adjusted for age, gender and duration of antipsychotic exposure.

HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points.

Table 4. Hazard Ratio of Developing Diabetes Comparing Selected Antipsychotic Cohorts to other Antipsychotic Cohorts

TREATMENT COHORT	Number of new Cases	Number of subjects in cohort	Hazard ratio*		
			Ratio	95% CI	p-value
Atypical	641	38,969	0.97	0.84 - 1.11	0.626
vs. Typical	307	19,782	-	-	-
Clozapine	7	277	1.31	0.60 - 2.86	0.496
Olanzapine	194	13,863	1.09	0.86 - 1.37	0.479
Quetiapine	40	4,196	0.67	0.46 - 0.97	0.033
Risperidone	400	20,633	1.23	1.01 - 1.50	0.040
vs. Haloperidol	133	8476	-	-	-

*Cox Proportional Hazards regression analysis adjusted for age, gender and duration of antipsychotic exposure.

HR and 95% CI values were rounded to first decimal place except where such rounding obscured significance cut-off points.

Table 5. Hazard Ratios for Antipsychotic Cohort Dose Quartiles Relative to the AdvancePCS General Patient Population

COHORT	Mean dose/quartile ± SD	Mean age ± SD	Hazard ratio*		
			Ratio	95% CI	p-value
Conventional					
Haloperidol Q1	0.5 ± 0.3	77.1 + 30.6	2.6	1.9 - 3.7	≤0.0001
Q2	0.9 ± 0.3	75.8 + 31.5	2.9	2.0 - 4.2	≤0.0001
Q3	1.7 ± 0.7	72.6 ± 34.1	2.9	2.0 - 4.1	≤0.0001
Q4	7.0 ± 17.5	61.5 + 39.5	4.3	3.1 - 5.9	≤0.0001
Thioridazine Q1	9.9 ± 6.3	66.1 ± 39.6	2.1	1.0 - 4.5	0.0453
Q2	20.1 ± 6.3	63.6 ± 38.8	3.0	1.7 - 5.4	≤0.0001
Q3	37.3 + 14.4	60.2 + 37.9	2.9	1.6 - 5.2	0.0005
Q4	110.8 ± 151.1	54.9 ± 37.0	8.9	6.2 - 12.7	≤0.0001
Atypical					
Olanzapine Q1	1.7 ± 0.9	60.1 ± 42.2	3.4	2.6 - 4.5	≤0.0001
Q2	3.1 ± 0.7	55.0 ± 41.0	2.6	1.9 - 3.6	≤0.0001
Q3	5.3 + 2.0	53.4 + 39.6	2.5	1.9 - 3.3	≤0.0001
Q4	11.3 + 9.8	50.0 + 37.1	3.6	2.8 - 4.7	≤0.0001
Risperidone Q1	0.4 ± 0.2	70.9 ± 40.6	3.7	3.0 - 4.5	≤0.0001
Q2	0.7 + 0.1	65.1 + 43.5	3.0	2.4 - 3.8	≤0.0001
Q3	1.1 ± 0.3	63.6 ± 43.0	3.0	2.5 - 3.7	≤0.0001
Q4	2.5 ± 2.4	56.0 ± 42.2	4.0	3.3 - 4.8	≤0.0001
Quetiapine Q1	17.0 + 8.6	60.2 + 40.7	1.8	0.9 - 3.4	0.0957
Q2	34.5 ± 11.3	57.1 ± 41.2	1.4	0.7 - 2.9	0.3347
Q3	64.5 ± 24.4	53.3 ± 37.8	0.6	0.2 - 1.8	0.3938
Q4	203.7 + 245.1	49.8 + 36.4	3.1	1.9 - 5.1	≤0.0001

* 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 DM) was too small for a meaningful quartile analysis

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Diabetes Mellitus and Antipsychotic Treatment in the United Kingdom

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SUMMARY

Background: Treatment-emergent diabetes mellitus has been reported in the literature for conventional and atypical antipsychotics.

Aims : In this retrospective cohort study, we explored the UK General Practice Research database (GPRD) to determine the hazard ratio of diabetes for patients prescribed antipsychotics.

Methods : An antipsychotic cohort comprised of patients exposed to conventional and/or atypical antipsychotics (N=46,111), individual antipsychotic cohorts comprised of patients exposed to a single antipsychotic, and a general patient population cohort (N=266,272) derived from the GPRD database were studied. A Cox proportional hazard regression model using age, gender, and presence or absence of obesity was used to determine the hazard ratio (HR) of diabetes development between these cohorts.

Results: Compared to the general population cohort, patients exposed to antipsychotics had a higher risk of developing diabetes (HR=1.5; CI=1.1-1.9). The risk of developing diabetes during exposure to thioridazine and risperidone was significantly higher than that of the general patient population.

Declaration of Interest: None

INTRODUCTION

Studies over several decades have suggested that diabetes and impaired glucose tolerance (IGT) are more common among patients with major mood disorders and schizophrenia than among the general population (Cassidy, 1999; Balter, 1961; Tabata, 1987). It remains to be determined whether this disturbance in glucose homeostasis is attributable to the underlying psychiatric conditions, to the drugs used for their treatment, or both.

Treatment-emergent glucose intolerance has also been reported for conventional antipsychotics (Bugasjski, 1979; Thonnard-Neumann, 1968), as well as for atypical antipsychotics (Hagg, 1998; Wirshing, 1998; Bettinger, 2000; Sobel, 1999; Croarkin, 2000). These findings, together with the increased incidence of weight gain during treatment with some atypical antipsychotics (Stanton 1995; Taylor, 2000; Wirshing, 1999), suggest the importance of evaluating the relative risk of developing diabetes during treatment with antipsychotics. We have undertaken a retrospective cohort study to determine the incidence of diabetes mellitus (DM) in patients exposed to antipsychotics compared to a general patient population using the UK-based General Practice Research Database (GPRD).

METHODS

Study population and data source

A detailed description of the baseline population from which the GPRD data were generated has been described elsewhere (Walley, 1997; Garcia-Rodreguez, 1998). Briefly, the database is comprised of over 8 million residents in the UK enrolled by selected general practitioners who had agreed to enter patient data using computers provided by VAMP Medical irrespective of future research hypotheses. It is a longitudinal database that contains patient information on gender, age, weight, height, diagnoses, prescriptions, hospitalizations, and doctor visits. The general practices contributing information were chosen to ensure that they were representative of the UK both geographically and in the number of partners at each practice. The accuracy and completeness of these data have been validated (Jick, 1992) and this database has been used previously for an epidemiological study to determine the incidence of disease (Garcia-Rodreguez, 1998).

Identification of patients treated with antipsychotics

The study population was comprised of adults 18 years of age or older as of 1994, which were registered in standard general practices, and were prescribed an antipsychotic between January 1, 1994 and December 31, 1999 (the study period). At the time of our analyses, data after December 31, 1999 was not available. The retrospective cohorts studied included a general patient

population cohort, individual antipsychotic monotherapy cohorts, and the combined antipsychotic cohort. The general patient population cohort consisted of a random sample of subjects registered continuously during January 1, 1996 and December 31, 1997 who had received at least one prescription for any medication other than an antipsychotic during this two-year period. The individual antipsychotic cohorts were comprised of patients exposed to a single antipsychotic during the study period. The combined antipsychotic cohort included patients who were started on one or more antipsychotics regardless of disease indications during the study period. Only patients who were continuously registered for the two-year period prior to starting antipsychotics were included. Antipsychotics included in this study were clozapine, olanzapine, quetiapine, amisulpiride, risperidone, chlorpromazine, fluphenazine, methotrimeprazine, pericyazine, perphenazine, pipothiazine, promazine, thioridazine, trifluoperazine, benperidol, droperidol, flupenthixol, haloperidol, loxapine, pimozide, and zuclopenthixol.

Conventional antipsychotics were the most commonly prescribed antipsychotics in the United Kingdom, and relatively small numbers of patients were prescribed atypical antipsychotics. Consequently, the number of patients who took atypical antipsychotics in the GPRD database was small (N=2,550). To maximize the number of patients eligible for the individual atypical antipsychotic monotherapy cohorts, the requirement for continuous registration for the two-year period prior to initiation of the atypical antipsychotics was waived. Similarly, patients who had taken conventional antipsychotics prior to

initiation of atypical antipsychotics were eligible for this cohort. However, those who had taken conventional antipsychotic(s) concurrently with atyp ical antipsychotics were excluded from the individual antipsychotic monotherapy cohorts.

Identification of patients with diabetes mellitus

Any patient who had a computer-recorded diagnosis of type1or type 2 diabetes mellitus (as defined by one or more ofthe Oxford Medical Information System diagnostic codes for diabetes mellitus) or who were prescribed any hypoglycemic agent(s) indicated for the treatment of diabetes was considered as having diabetes. For a given subject, the date when the diagnosis of diabetes was first made by physician, and the date when hypoglycemic drug(s) was prescribed for the first time were determined, and the earlier date of these two was regarded as the date for a new case of diabetes. In determining the incidence of diabetes during exposure to conventional antipsychotics, patients with a personal history of diabetes prior to the first prescription of antipsychotic(s) were excluded. New cases of diabetes that occurred during the antipsychotic prescription period plus 15 days of washout period were considered as treatment-emergent diabetes. The washout period was defined as the 15 day period that immediately followed the discontinuation of a given antipsychotic drug or class of drugs. Two prescriptions separated by less than 16 days were counted as one continuous prescription.

Methods of Analysis

The Knowledge Manager software (Real Enterprise Solutions, Massachusetts, USA) in conjunction with SAS programs were used for identifying subjects eligible for various cohorts and for identifying incident cases of diabetes.

For determining incidence of diabetes during exposure and after discontinuation of antipsychotics throughout the evaluation period, patients were followed until December 31, 1999, or until they left the clinical practices at which they were registered, whichever came first. The cumulative antipsychotic treatment duration of each patient was determined and used to calculate diabetes incidence per 1000 patient-years of exposure. Based on a method described elsewhere (Lee, 1980), 95% confidence intervals for these incidences were calculated.

Cox proportional hazards regression was used to determine statistically significant ($p<0.05$) predictors of diabetes for consideration of their inclusion as covariates in the regression model, and for estimating the hazard ratios (rate ratios) of diabetes between various cohorts mentioned above. The PHREG procedure in SAS was used for fitting the proportional hazard models. The covariates for these models were age, gender, and the presence or absence of obesity. Subjects were classified as obese by a physician's diagnosis of obesity or by a body mass index equal to or greater than 30 kg/m^2 (NIH

criteria). The classification of obesity was determined during the four-year period prior to exposure to antipsychotics for the antipsychotic cohorts and between 1992 and 1995 for the general patient population cohort. The most recent body mass index or obesity diagnosis was used for each subject and 27.4% and 55.7% of patients had such information in the two-year period and four-year prior to antipsychotic exposure, respectively. The age categories 18 to 44, 45 to 64, and 65 or older (used as covariates in the regression model) showed a near doubling of incidence with each transition in age category as determined in the 1990-92 National Health Insurance Survey in the United States (National Diabetes Data Group, 1996). All three-age categories were included in the model used to determine the hazard ratio of the conventional antipsychotic cohort, the atypical antipsychotic cohort, and the general population cohort. For hazard ratio determination in the individual antipsychotic monotherapy cohorts (comprised of patients who received a single antipsychotic) only two age categories were included in the model, 65 or above, and 18 to 64. The 18 to 44-age category was not included because the trifluoperazine cohort did not have new cases of diabetes in this age category. Because the database does not contain information on ethnic origin, it was not included as a covariate in the model. The possibility that an increased frequency of physician visits might increase the probability of uncovering diabetes was evaluated. Since the hazard ratio for this covariable was equal to 1.0, whether it was included as a continuous or categorical covariate, it was not included in the regression models in this study. Family history is an

established risk factor for type 2 diabetes but examination of the GPRD database showed that this information was missing in the great majority of the patients. As less than 1% of patients had recorded family history of diabetes (OXMIS code F250A), family history was not included as a covariate in the regression model.

RESULTS

The characteristics of the general patient population and the combined antipsychotic cohorts are shown in Table 1. The mean age of patients in the general patient population cohort was less than that of the antipsychotic cohorts ($p < 0.001$). In the general population cohort, the percentage of subjects in the 65 years and older category was significantly smaller than that of the combined antipsychotic cohort ($p < 0.001$) while the percentage of subjects in the 18 to 44 and 45 to 64 year age categories was significantly larger than that of the combined antipsychotic cohort ($p < 0.001$). There were a significantly greater percentage of male subjects in the general patient population cohort ($p < 0.001$). The percentages of subjects with information on obesity were comparable between all cohorts and a significantly greater percentage of patients were classified as obese in the combined antipsychotic cohort ($p < 0.001$). The mean duration of exposure to antipsychotics in the combined antipsychotic cohort is 156 ± 244 days.

Stratified Cox regression analyses were performed to evaluate potential risk factors of diabetes for each cohort. All the covariates used for the Cox regression model in the present study are shown in Table 2. Obesity was found to have a significant effect on the risk of diabetes in the general patient population and the combined antipsychotic cohorts ($p < 0.001$). The risk of diabetes increased with age in all cohorts. Male subjects in the general patient

population cohort had a small but significantly increased risk for developing diabetes ($p< 0.001$).

The incidences of diabetes for the various antipsychotic cohorts and for the general patient population cohort are shown in Table 3. The incidence of diabetes during exposure to antipsychotics (combined cohort) was 8.6 per 1000 patient-years (CI=7.3-9.9), and this was significantly higher than the incidence of diabetes in the general patient population with no overlap of 95% CI. The risk of developing diabetes for those who took antipsychotics was 1.5 times higher than that of the general patient population (CI=1.1-1.9).

The hazard ratios of the commonly prescribed antipsychotics were determined in a combined antipsychotic cohort relative to a general patient population cohort (Table 3). Compared to the general patient population cohort, patients in the combined antipsychotic cohort had a significant higher risk of developing diabetes (HR=1.5; CI=1.1-1.9) (Table 3). During the period 1994-1999, the most commonly prescribed conventional antipsychotics in UK in descending order (% subjects exposed in parenthesis) were thioridazine (44%), flupenthixol (22%), trifluoperazine (13%), haloperidol (14%), and chlorpromazine (12%). Risperidone and olanzapine were the two most commonly prescribed atypical antipsychotics in the UK, representing 71% and 21% of the atypical antipsychotics, respectively. The hazard ratios of patients who received monotherapy of specific individual antipsychotics relative to the general patient population cohort were also determined. Among individual

conventional antipsychotic treatment cohorts, a significantly elevated risk for DM was noted only for the thioridazine monotherapy cohort, the largest monotherapy cohort. Among individual atypical antipsychotic cohorts, a significantly elevated risk for DM was observed in the risperidone monotherapy cohort. Less than 120 patients received monotherapy of clozapine, quetiapine or amisulpiride and as a result of the insufficient sample size, these monotherapy cohorts could not be analyzed.

DISCUSSION

This study suggests that patients treated with either conventional or atypical antipsychotics may have a higher risk of developing diabetes during exposure to the drugs. Though a higher risk of diabetes was temporally associated with treatment with antipsychotics, it remains to be determined whether this observation can be attributed to direct treatment effects, or other non-treatment related factors. Because of the large sample sizes of the GPRD general patient population and combined antipsychotic cohorts, relatively small differences in baseline characteristics in age, gender, and presence of obesity in patients were significantly different between cohorts. A Cox proportional hazard model used for determination of risk of developing diabetes used in this study controlled for the small differences in these baseline characteristics.

Of note is the fact that the database contained a small number of patients treated with atypical antipsychotics. In particular, the olanzapine monotherapy cohort sample size was too small for a conclusive determination of DM risk. The small number of patients prescribed olanzapine monotherapy may be largely due to the fact that olanzapine was not commercially available until the end of 1996. Additional studies with a greater number of patients who took atypical antipsychotics would be needed to assess the incidence of glucose intolerance during treatment with those atypical antipsychotic agents that were not sufficiently represented in the GPRD database at the time of this analysis.

Findings from this study are consistent with a separate epidemiology study we conducted with patients in the United States using the AdvancePCS Inc.'s prescription claim database (Buse, submitted). The AdvancePCS study confirms that treatment with antipsychotics was temporally associated with higher risks of developing diabetes than the general patient population. The AdvancePCS study contained cohorts with greater number of patients (especially in the atypical antipsychotic cohorts); therefore, the results are more relevant than the GPRD study results.

A number of strengths in the present study are noteworthy. First, individual antipsychotic monotherapy cohorts were evaluated. This avoids confounding of risk assessment by concomitant antipsychotics. If such concomitants were included in our cohorts, the results could have been confounded by imbalances in the frequency of use of such agents between cohorts. Second, it is not uncommon for subjects in the GPRD longitudinal database to have more than 5 or even 10 years of records before the evaluation period used for identifying new onset of diabetes during antipsychotic treatment. This enabled us to check the record of many patients for several years prior to the commencement of antipsychotics for excluding pre-existing diagnosis of diabetes or treatment with diabetes medications.

The present study has the following limitations. First, the number of patients who received atypical antipsychotics was relatively small. Thus, the small number of new cases of diabetes and the number of patients who took atypical antipsychotics other than risperidone may have been too small for accurate determination of the risks of diabetes during treatment with those drugs. Second, unlike the conventional cohort that was comprised of antipsychotic naive patients, the atypical cohort consisted mainly of patients who had prior exposure to conventional antipsychotics. If the mechanism for treatment-emergent diabetes is the same in patients treated with both classes of antipsychotics, the individual atypical antipsychotic cohorts may have been enriched with subjects who had developed diabetes while taking conventional antipsychotics. Therefore, these patients would not have been counted as new cases of DM during subsequent treatment periods with atypical antipsychotics potentially resulting in an under estimation of DM risk in the individual atypical cohorts. Conversely, if the risk of diabetes is of a cumulative nature, a period of exposure to conventional antipsychotics prior to an atypical antipsychotic could result in an overestimation of the risk for the individual atypical cohorts. Third, paucity of information on the family history of diabetes in this database precluded a meaningful inclusion of this variable in our Cox regression model. Fourth, antipsychotic doses in the treatment cohorts were not evaluated in this analysis. Finally, the diagnosis of diabetes in this retrospective study was ascertained by a physician's diagnosis or by a recorded use of a glucose-lowering drug in the database. Without the primary clinical

data, an unqualified diagnosis of diabetes is uncertain. However, it is reasonable to assume that a patient diagnosed with diabetes or one receiving a glucose-lowering drug has a high likelihood of having diabetes.

Obesity and increasing age are well established as risk factors for type 2 DM. (Dixon, 2000). This was confirmed by the present study, in both the general patient population and the antipsychotic cohorts. Male subjects in the general patient population cohort had a small but significantly increased risk for developing diabetes. This is in contrast with other data collected in the UK that both sexes have an equal likelihood of being diagnosed with diabetes (UK Diabetes Information Audit and Benchmarking Services, 2000). However, reports of a slightly higher incidence of DM in males in the 1970s and in females in the 1950s and 1960s have also been published (UK Prospective Diabetes Study IV, 1988).

While there appears to be an increased risk of developing diabetes during treatment with antipsychotic drugs, the mechanism is unclear. Potential mechanisms for increasing glucose intolerance include a reduction in the production or secretion of insulin or by an increase in insulin resistance. Though weight gain has been commonly observed during treatment with some antipsychotic drugs, the relationship between weight gain and subsequent development of diabetes during specific drug use cannot be determined from the present study as the weight of a relatively small percentage of subjects was

recorded during antipsychotic exposure. In addition, correlating the weight gain during treatment with various antipsychotics from other studies to their risk of developing diabetes in this study was not feasible as only the hazard ratios of the thioridazine and risperidone antipsychotic cohorts were statistically significant.

Patients with psychiatric disorders present unique challenges in determining the potential for altered glucose metabolism during antipsychotic treatment. For example, obtaining fasting glucose levels is quite difficult due to reduced compliance with fasting. While serial glucose tolerance tests would be valuable in assessing the likelihood of altered glucose metabolism such studies are also potentially difficult due to the nature of the underlying psychiatric illness.

In conclusion, the present study suggests a higher risk of developing diabetes during treatment with antipsychotic drugs. The sample sizes of thioridazine and risperidone cohorts were sufficiently large to discern a significant increase in the risk for diabetes relative to the general patient population cohort. Though the sample size of other individual antipsychotic cohorts were not adequately powered to discern a significant treatment effect, the 95% confidence interval of their hazard ratios suggest an estimation of diabetes risk temporally associated with these agents. Further epidemiological studies

utilizing databases with larger number of subjects who were treated with atypical antipsychotic are needed.

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Table 1. Characteristics of the Major Cohorts Studied

	General patient population	Combined antipsychotic cohort
Number of subjects	**266,272**	**46,111**
Mean age, years (SD)	**50.9 (17.9)**	**58.7 (21.4) ***
18 to 44 years of age	**41% ***	**31%**
45 to 64 years of age	**33% ***	**25%**
65 years of age and older	**26%**	**44% ***
Proportion Male	**42% ***	**39%**
Proportion obese **	**13%**	**15% ***

* $p<0.001$, relative to the general patient population.

** Based on the number of subjects with body mass index greater than or equal to 30 kg/meter^2 or with a diagnosis of obesity during the four year-period prior to the commencement of antipsychotics.

Table 2. Proportional Hazard Analysis Of Diabetes Mellitus For Covariates In The Cox Regression Model, Stratified By Cohort

Variable	Hazard Ratio	95% confidence interval	p value
Combined Antipsychotic Cohort (N= 46,111)			
Presence of Obesity	3.1	1.9 - 5.1	≤0.0001
Age ≥65 years*	4.9	2.2 - 1 1.0	≤0.0001
Age 45-64 years*	4.0	1.7 – 9.1	0.001
Gender (male)	1.0	0.6 - 1.6	0.99
General Patient Population Cohort (N= 266,272)			
Presence of Obesity	4.7	3.9 - 5.7	≤0.0001
Age ≥65 years	5.02	3.7 - 6.7	≤0.0001
Age 45-64 years	3.3	2.5 - 4.4	≤0.0001
Gender (male)	1.6	1.3 - 1.9	≤0.0001

* Age 18-44 years used as reference

Table 3. Incidence and Hazard Ratio of Diabetes in Patients while taking Antipsychotics

COHORT	Number of new cases	Number of patients	Mean days of exposure (SD)	Number of patient-years	Incidence (per 1000 patient-years)		Hazard ratio*		
					Rate	95% CI	Ratio	95% CI	p-value
All antipsychotics combined**	170	46,111	156 (244)	19,720	8.6	7.3 - 9.9	1.5	1.1 - 1.9	0.007
CONVENTIONAL ANTIPSYCHOTICS									
Thioridazine only	56	15,008	175 (245)	7,172	7.8	5.7 - 9.9	1.5	1.009 - 2.3	0.045
Fluopenthixol only	13	7,950	116 (174)	2,538	5.1	2.3 - 8.0	0.86	0.4 - 2.0	0.86
Trifluoperazine only	12	3,848	159 (250)	1,675	7.2	3.0 - 11.3	1.2	0.5 - 3.0	0.66
Chlorpromazine only	5	3,294	128 (217)	1,156	4.3	0.5 - 8.2	0.37	0.05 - 2.6	0.37
Haloperidol only	13	3,550	109 (178)	1,059	12.3	5.5 - 19.1	1.6	0.7 - 4.0	0.28
ATYPICAL ANTIPSYCHOTICS									
Risperidone only	16	1,702	229 (296)	1,067	15.0	7.5 - 22.5	3.2	1.4 - 7.1	0.006
Olanzapine only	2	528	194 (188)	279	7.2	0 - 17.3	2.0	0.3 - 14.5	0.48
GENERAL PATIENT POPULATION									

	1,589	269,272	--	430,892	3.7	3.4 - 4 .0	1.0	--	--

* Results from Cox proportional hazards analyses with age, gender and obesity as covariates. Reference group was the general patient population cohort. Three age categories were included as a covariate in the model for the antipsychotic combined cohort, but only two age categories for individual antipsychotic monotherapy cohorts.

** Includes antipsychotics not listed in this table that were less commonly prescribed in the UK.

Table 3 cont.

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Hyperglycemic Clamp Assessment of Insulin Secretory Responses in Normal Subjects Treated with Olanzapine, Risperidone, or Placebo

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Hyperglycemic Clamp Assessment of Insulin Secretory Responses in Normal Subjects Treated with Olanzapine, Risperidone, or Placebo.

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Running head: Insulin secretion with antipsychotics

Abstract

The goal of this study was to evaluate the effect of olanzapine or risperidone treatment on beta cell function in healthy volunteers.

Subjects were randomly assigned to single-blind therapy with olanzapine 10 mg/day (n=17), risperidone 4 mg/day (n=13), or placebo (n=18) for 15 to 17 days. Insulin secretion was quantitatively assessed at baseline and endpoint using the hyperglycemic clamp.

Weight increased significantly ($p < 0.01$) in the olanzapine (2.8 ± 1.7 kg) and risperidone (3.1 ± 2.1 kg) treatment groups. An increase (~25%) in insulin response to hyperglycemia and a decrease (~ 18%) in the insulin sensitivity index was observed after treatment with olanzapine and risperidone. The change in insulin response was correlated ($r=0.5576$, $p=0.019$) with change in body mass index (BMI). When the impact of weight change was accounted for by multivariate regression analyses, no significant change in insulin response or insulin sensitivity was detected following treatment with olanzapine or risperidone.

We found no evidence that treatment of healthy volunteers with olanzapine or risperidone decreased the insulin secretory response to a prolonged hyperglycemic challenge. Results of this study do not support the hypothesis that olanzapine or risperidone directly impair pancreatic beta cell function.

Introduction

The newer atypical antipsychotics, such as clozapine, olanzapine, risperidone, quetiapine, and ziprasidone are effective therapy for schizophrenia and are considered by many as first line therapy. These drugs act as antagonists at multiple receptors including members of the dopaminergic, serotonergic, adrenergic, muscarinic, and histaminergic families (1, 2). Although the precise mechanism of action remains uncertain, the relatively high affinity for serotonergic receptors ($5HT_{2C}$) and relatively low dopaminergic (D_2) activity are believed to contribute to the improved efficacy and increased tolerability of these newer drugs. The serotonergic and histaminergic binding characteristics may contribute to weight gain that can be observed during treatment with these medications.

In addition to weight gain, a number of reports have suggested an association between the atypical antipsychotics and abnormalities in glucose homeostasis including diabetes mellitus, diabetic ketoacidosis (DKA), or hyperosmolar nonketotic syndrome (reviewed in 3 and 4; 5, 6, 7, 8, 9). A variety of mechanisms have been postulated to account for an association between atypical antipsychotics and abnormalities of glucose metabolism (discussed in 3 and 4). Most invoke a weight-related decrease in insulin sensitivity or a direct drug effect that results in decreased insulin sensitivity or that impairs pancreatic beta cell function (e.g. decreases insulin secretion). Although weight gain is an obvious concern, hyperglycemia with severe metabolic decompensation has been reported in the absence of weight gain and in individuals without obvious risk factors for diabetes (3, 4). A direct drug effect has also been hypothesized based on case reports of patients presenting with DKA that are able to discontinue all anti-diabetic therapy following

cessation (positive de-challenge) of the suspected antipsychotic and a very small number of cases in which hyperglycemia is reported to return shortly after reintroduction of the antipsychotic (positive re-challenge) (3, 4).

The possibility of a link between schizophrenia or it's therapy and diabetes is not new (10). The first reports pre-date introduction of pharmacological therapy (11, 12) and increased following widespread use of the phenothiazine derivatives (13-19). Some of the available data suggested that chlorpromazine might impair insulin secretion in man; however, this finding was not consistently observed.

Given the above considerations and the almost universal requirement for inadequate beta cell function (absolute or relative) in the development of severe metabolic decompensation (DKA or hyperosmolar state) (20), we directed initial efforts toward clarifying whether subjects treated with olanzapine or risperidone experienced decreased insulin secretion. Using the highly sensitive hyperglycemic clamp, we examined insulin responses during a prolonged hyperglycemic challenge in healthy volunteers before and after 15-17 days of treatment with olanzapine, risperidone, or placebo.

Methods

Patient Population

Subjects were healthy men and women between the ages of 18 and 65 years, without pre-existing conditions that could significantly alter glycemic status. At enrollment, subjects were required to have a history of normal glucose metabolism, a normal physical examination, a fasting glucose of <6.1 mmole/L, and a BMI (body mass index) of ≤ 30 kg/m^2. All subjects provided written informed consent after the study procedures and possible treatment adverse effects were fully explained. The protocol was approved by the Indiana University School of Medicine Institutional Review Board.

Subjects with significant co-morbid illness, recent hospitalization, a first degree family history of type 1 or type 2 diabetes mellitus, previous exposure to antipsychotic medication, or current use of recreational drugs were excluded. Pregnant or lactating women and sexually active women of childbearing age not actively practicing birth control were also excluded.

Study Design

Between 2 and 25 days prior to initiation of the study, medical history was recorded and subjects were screened with a physical examination and clinical laboratory tests. Two to four days before the baseline clamp, subjects were admitted to an inpatient facility for diet stabilization with an isocaloric diet (~25-35 Kcal/kg) adjusted for activity level, smoking status, and satiety. The diet had a caloric distribution of 55% carbohydrate,

30% fat, and 15% protein, with a daily salt intake of 6 grams. This diet was followed for at least 2 days prior to the hyperglycemic clamps and subjects were requested to maintain this diet throughout the active treatment phase.

After the baseline clamp, subjects were randomly assigned to single-blind treatment (investigative staff performing clamps were blinded) with olanzapine 10 mg/day, risperidone 4 mg/day, or placebo. Medications were begun at half maximal dose and titrated over 4 days after which subjects were allowed up to three hospital release passes (72 hours each). Subjects were readmitted at least 48 hours prior to the final clamp and had to undergo a urine drug screen for recreational substances upon each readmission. Subjects unable to tolerate the maximum dose of study drug or with a positive urine drug screen upon readmission were discontinued.

Hyperglycemic Clamp

Subjects underwent hyperglycemic clamps (21), at baseline prior to randomization and after 15 to 17 days of treatment with olanzapine, risperidone, or placebo. Subjects were requested to refrain from alcohol and vigorous exercise for 24 hours and from tobacco for 12 hours prior to the clamp. Following a 9 hour fast, each subject began the clamp procedure at approximately 7:00 AM.

Subjects were studied in the supine position with catheters inserted in an ante-cubital vein for infusion of glucose and potassium, and into a dorsal hand vein, in a retrograde fashion, for drawing blood samples. The hand was warmed to 60-70 C using a heating pad to obtain arterialized venous blood. Approximately 10 minutes after catheter

insertion, two sets of baseline blood samples were obtained 10 minutes apart for measurement of glucose, insulin, and C-peptide.

After baseline samples were obtained, the hyperglycemic clamp was initiated with a 15-minute priming dose of 20% (w/v) glucose. This priming dose was based on previous studies in which the mass of glucose required to increase glycemia to the target level (11.1 mmole/L) was empirically derived using a modification of the Andres method (21). Half of the total glucose mass was infused during the first 5 minutes, the remainder during the next 10 minutes, and then the infusion rate was decreased by half to prevent exceeding target glycemia. Plasma glucose values were determined at 5-minute intervals using a bedside glucose analyzer and the glucose infusion rate adjusted to maintain the target level of glycemia. The procedure was continued for a total of 240 minutes after initiation of the glucose infusion. Sampling for insulin and C peptide was performed at 2-minute intervals from 0 through 10 minutes, at 15 to 30 minute intervals from 10 to 120 minutes, and at 20-minute intervals during the final two hours. Blood glucose levels at steady-state varied by less than 5%. To prevent hypokalemia, potassium was infused during the studies at a maximum rate of 0.0038 mEq/kg/min as tolerated.

Fasting measurements of glucose, insulin, and C peptide were calculated as the mean of the 0 and -10 minute values collected prior to the clamp. The insulin responses to hyperglycemia were evaluated as first-phase (0 to10 minutes), second-phase (10 to 240 minutes) and total insulin response (TIR, 0 to 240 minutes). In each of these intervals, insulin response is measured by a weighted average of the insulin concentrations measured during that time interval after subtracting the baseline (fasting) concentration.

The weight of each measurement was proportional to the time interval between that measurement and the previous one so that the weighted average represents the average concentration during the whole time interval. The total C peptide response (TCR, 0 to 240 minutes) was similarly quantitated. An insulin sensitivity index was calculated by dividing the steady-state (180 to 240 minutes) average glucose infusion rate (M, mmoles/L/kg body weight/minute) by the average insulin concentration (I, pmole/L).

Analysis of Blood Samples

Insulin was assayed using the Abbott IMX MEIA system (Abbott Laboratories, Abbott Park, IL) which has an intra-assay CV of 2.5 - 4.0% and an inter-assay CV of 4.4 - 6.0%. C-peptide was analyzed by the BioData ^{125}I C-peptide tracer/C-peptide specific primary antibody system (Polymedco, Inc., Cortland Manor, NY).

Statistical Methods

An analysis of variance (ANOVA) model was used to examine the baseline to endpoint changes in fasting measures (glucose, insulin, and C peptide) as well as the first-phase, second-phase, and total (0 to 240 minute) insulin and C peptide responses during the hyperglycemic clamps. Treatment effects on study variables were examined using a t-test comparing the change during treatment with olanzapine or risperidone against that of placebo.

The above analyses were repeated with BMI change included as a covariate. Changes in study variables in the absence of weight gain were calculated from the linear regression analyses with therapy and BMI change as covariates.

All tests of hypotheses were two-sided with 5% level of significance.

Results

A total of 73 subjects were screened and complete data was available for 48 subjects. Among subjects completing the protocol, there were no significant differences in baseline characteristics between the treament groups except that there were no females and 30% fewer total subjects in the risperidone arm (Table 1). Fewer subjects randomized to risperidone completed the protocol due to study discontinuations (3 patients withdrew consent, 1 patient became pregnant, 1 patient had a positive drug screen and 1 patient's samples could not be analyzed) with blinded replacement. There was no apparent association between study discontinuations in the risperidone group and adverse events reported. There was one subject discontinuation in both the olanzapine and placebo treated groups (both patients withdrew consent). We did note among subjects completing the protocol that somnolence was reported frequently among those receiving active therapies (35% olanzapine, p=0.008 vs. placebo and 31% risperidone, p=0.023 vs. placebo).

In the placebo group, weight, fasting glucose, and fasting insulin did not change significantly while fasting C peptide was slightly lower at endpoint (Table 2). Weight increased significantly (~ 3 kg, $p < 0.01$ within group) from baseline to endpoint in both the olanzapine and risperidone treatment groups (Table 2). Although subjects were requested to maintain an isocaloric diet of fixed composition throughout the study, they were allowed up to 9 days as outpatients. Diet composition and caloric intake were not closely monitored during the outpatient phases and weight gain is likely a consequence of increased food intake in the two active therapy groups. We also observed significant

increases (~ 38%) in fasting insulin and C peptide (~ 10-20%) in both the olanzapine and risperidone treatment groups. Increases in fasting insulin of a comparable magnitude have been described in other short term studies of hypercaloric feeding (22) and with high carbohydrate diets (23).

Hyperglycemic Clamp

Hyperglycemic clamps were performed at baseline and after 15 to 17 days of treatment. Plasma glucose levels were clamped at 11.1 mmole/L for 240 minutes in both studies. The glucose infusion rate required to maintain this level of hyperglycemia over the course of the clamp were unchanged at the final study for all treatment groups (Table 3 and data not shown).

Pancreatic beta cell function was assessed by quantitating insulin responses during the hyperglycemic challenge. Mean insulin levels during the studies were slightly lower during the final clamps in the placebo group while mean insulin levels were slightly higher for the two active therapy groups (Figure 1). Mean C peptide levels were unchanged in all three treatment groups.

Insulin responses during the hyperglycemic clamps were evaluated as first-phase, second-phase, and total insulin response (TIR). For the placebo group, first-phase (–4.8 ± 44.4 mmole/L; 3.4%), second-phase (–82.2 ± 163.2 mmole/L; 17.9%), and TIR (Figure 1) insulin responses were slightly lower at endpoint than at baseline. Significant increases in the mean change in first-phase (69.0 ± 95.4 mmole/L; 38.7%) and second-phase (117.0 ± 201 mmole/L; 22.3%), and TIR (Figure 1) insulin responses were noted for the

olanzapine group ($p < 0.01$ within group). Changes of comparable magnitude were observed in the risperidone group for first-phase (35.4 ± 54.0 mmole/L; 30.2%) and second-phase (90.0 ± 171.6 mmole/L; 22.5%) and TIR (Figure 1) insulin responses. Quantitation of the mean change in total C peptide response (TCR) confirmed that no significant changes occurred in any of the groups from baseline to endpoint.

Although the hyperglycemic clamp is primarily used to assess insulin secretion, an index of insulin sensitivity can be obtained from steady-state data. The ratio (M/I) of the mean glucose infusion rate (M, which at steady-state is a measure of glucose utilization) to average insulin level (I), provides an index of insulin sensitivity that has been shown to correlate with direct measures obtained from a euglycemic clamp (24, 25). Data collected during the final hour of the clamps were used to calculate the insulin sensitivity index. Similar results were obtained using the third hour data (results not shown).

The mean glucose infusion rate (M) and insulin (I) at steady-state did not significantly change in the placebo group (Table 3). There was also no significant change in the steady-state M but an increase (~ 15%) in mean insulin (I) in the two active therapy groups. These data clearly demonstrate that even after four hours of continuous stimulation, subjects treated for 15 to 17 days with olanzapine or risperidone were able to maintain an appropriate insulin response.

The increase in steady-state insulin without concurrent change in M resulted in slightly lower indices of insulin sensitivity in the active therapy groups. The magnitude of the decrease in insulin sensitivity observed with both drugs (~18%) was identical; however, the within-group baseline to endpoint changed achieved statistical significance only for

the olanzapine group (p=0.038, n=17 within olanzapine group; and p=0.157, n=13 within risperidone group). The change in M/I in the olanzapine and risperidone groups was not significantly different from the placebo group.

Impact of Weight Gain

Significant weight gain was observed in the olanzapine and risperidone treatment groups and as expected, we found that changes in the clamp TIR (r=0.5576, p=0.02) were correlated with BMI change. A similar relationship between BMI change and the change in fasting insulin was observed (r=0.645, p=0.08). To determine whether patients treated with olanzapine or risperidone experienced a weight-independent effect on fasting insulin levels, insulin secretion during the hyperglycemic clamps, or insulin sensitivity indices, multivariate regression analyses were performed to predict mean changes in these variables in the absence of weight gain (no change in BMI). These analyses revealed that in the absence of weight gain, neither treatment with olanzapine nor risperidone was associated with a significant change in fasting insulin or clamp results (Table 4).

Thus, we found no evidence supporting a weight-independent effect on insulin secretion or on insulin sensitivity during treatment with olanzapine or risperidone.

Discussion

Using the gold standard for assessing insulin secretory capacity, we found no evidence that patients treated with the atypical antipsychotic drugs, olanzapine or risperidone, experienced a direct impairment of insulin secretion. An increase in the total insulin response (TIR) during the clamp was seen with both drugs and was most likely related to weight gain observed during therapy. Importantly, even when the impact of weight gain was accounted for, we found no evidence that patients treated with olanzapine or risperidone experienced decreased insulin or C peptide responses during the hyperglycemic challenge.

We observed significant increases in TIR but no changes in TCR in the active therapy groups. The relationship between insulin secretion, insulin clearance, and peripheral C peptide levels is quite complex (26); however, the results of this study are suggestive of a weight-related decrease in insulin clearance. Modulation of the insulin clearance in response to body fat or weight changes has been described by others (27, 28). Regardless, the absence of a decrease in insulin or C peptide levels during the hyperglycemic clamps strongly argues against a direct negative effect of these antipsychotic drugs on pancreatic beta cell function.

Case reports of diabetes temporally associated with antipsychotic treatment in the absence of weight gain (3, 4) have been offered as evidence of a direct drug effect on glucose homeostasis. However, neither obesity nor weight gain are pre-requisites for the development of diabetes (29) and weight loss may actually precede diagnosis of this disease (30, 31). Therefore, caution should be exercised in invoking a direct drug effect

in cases of new-onset diabetes in antipsychotic-treated patients that do not experience weight gain.

Cases of positive de-challenge following episodes of DKA in patients with psychosis treated with atypical antipsychotics have also been interpreted as supporting a direct drug effect (3, 4). Although classically considered a hallmark of autoimmune type 1 diabetes, DKA does occur in patients with type 2 diabetes and can be the presenting abnormality (32-35). The natural history for this subgroup of patients with type 2 diabetes is interesting and relevant to the evaluation of diabetes during treatment with olanzapine and risperidone. For some patients with type 2 diabetes that present with DKA, after resolution of the acute event, it is not uncommon to observe a period in which normoglycemia is maintained in the absence of anti-diabetic therapy or adequately managed with oral agents alone. It is also noteworthy that in many instances physicians have been unable to identify a triggering event which might have contributed to the metabolic decompensation. Given this pattern of disease, it is likely that some cases of positive de-challenge may simply reflect the natural history of a subgroup of patients with type 2 diabetes. Reports of positive re-challenge with antipsychotics have been very infrequent making conclusions in these cases difficult (36, 37, 38, 39).

Two limitations of the current study warrant specific comment. First, healthy non-psychiatric subjects were studied in this protocol. As the prevalence of diabetes in schizophrenics appears to exceed that of the general patient population (10), it could be argued that non-psychiatric subjects do not possess the same susceptibility to pancreatic dysfunction during treatment with antipsychotics as patients with schizophrenia. Results

of the current study cannot rule out this possibility and ultimately, large-scale epidemiological studies will be required to clarify whether patients receiving atypical antipsychotics exhibit higher rates of diabetes or greater tendency for a DKA prone subtype of type 2 diabetes than patients receiving other therapies or the nonpsychiatric population. Another potential limitation is the relatively short duration of drug exposure (17 days at maximum) employed in this protocol. At the time this study was initiated, at least 6 of 35 published case reports of diabetes during treatment with atypical agents recorded glycemic abnormalities within 30 days of exposure (3, 4). Furthermore, in a small prospective study of clozapine-treated patients, changes in glucose tolerance were reported in some subjects within one week of initial therapy (40). Therefore, we believed that 15 to 17 days would provide adequate exposure, particularly with use of the prolonged hyperglycemic challenge.

In summary, healthy volunteers treated with olanzapine or risperidone for 15 to 17 days exhibited very similar changes in insulin levels (fasting and clamp) that appear to be largely related to weight gain. We found no evidence that patients treated with either drug experienced decreased insulin secretion or significant weight-independent effects on insulin sensitivity as assessed by the hyperglycemic clamp. Overall, these data do not support a direct effect of olanzapine or risperidone to decrease insulin secretion or insulin sensitivity.

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Table 1

Subject Characteristic	Olanzapine N=17	Risperidone N=13	Placebo N=18
Male/Female	13/4	13/0	13/5
Ethnic Background (Caucasian/African American/Other)	11/6/0	11/1/1	13/5/0
Age years	33.1 (6.1)	28.0 (6.5)	31.2 (9.7)
BMI kg/m^2	24.4 (3.6)	24.2 (2.5)	24.1 (2.5)
Glucose mmole/L	5.0 (0.37)	5.09 (0.31)	5.08 (0.33)
Insulin pmole/L	49.8 (34.2)	41.4 (14.4)	55.2 (27.6)
C peptide nmole/L	0.72 (0.39)	0.68 (0.22)	0.76 (0.31)

Table 2

	Weight kg	Glucose mmole/L	Insulin pmole/L	C peptide nmole/L
Olanzapine	2.8 (1.7) *, [a]	0.02 (0.53)	19.8 (54.6) **, [b]	0.15 (0.34) **, [a]
Risperidone	3.1 (2.1) *, [a]	0.14 (0.44)	15.0 (28.2) [c]	0.07 (0.21) [b]
Placebo	0.5 (1.2)	-0.08 (0.31)	-13.8 (17.4)	-0.15 (0.17) **

* $p<0.01$ within group, ** $p\leq0.04$ within group

[a] $p < .001$ vs. PLC, [b] $p \leq .02$ vs. PLC, [c] $p < .05$ vs. PLC

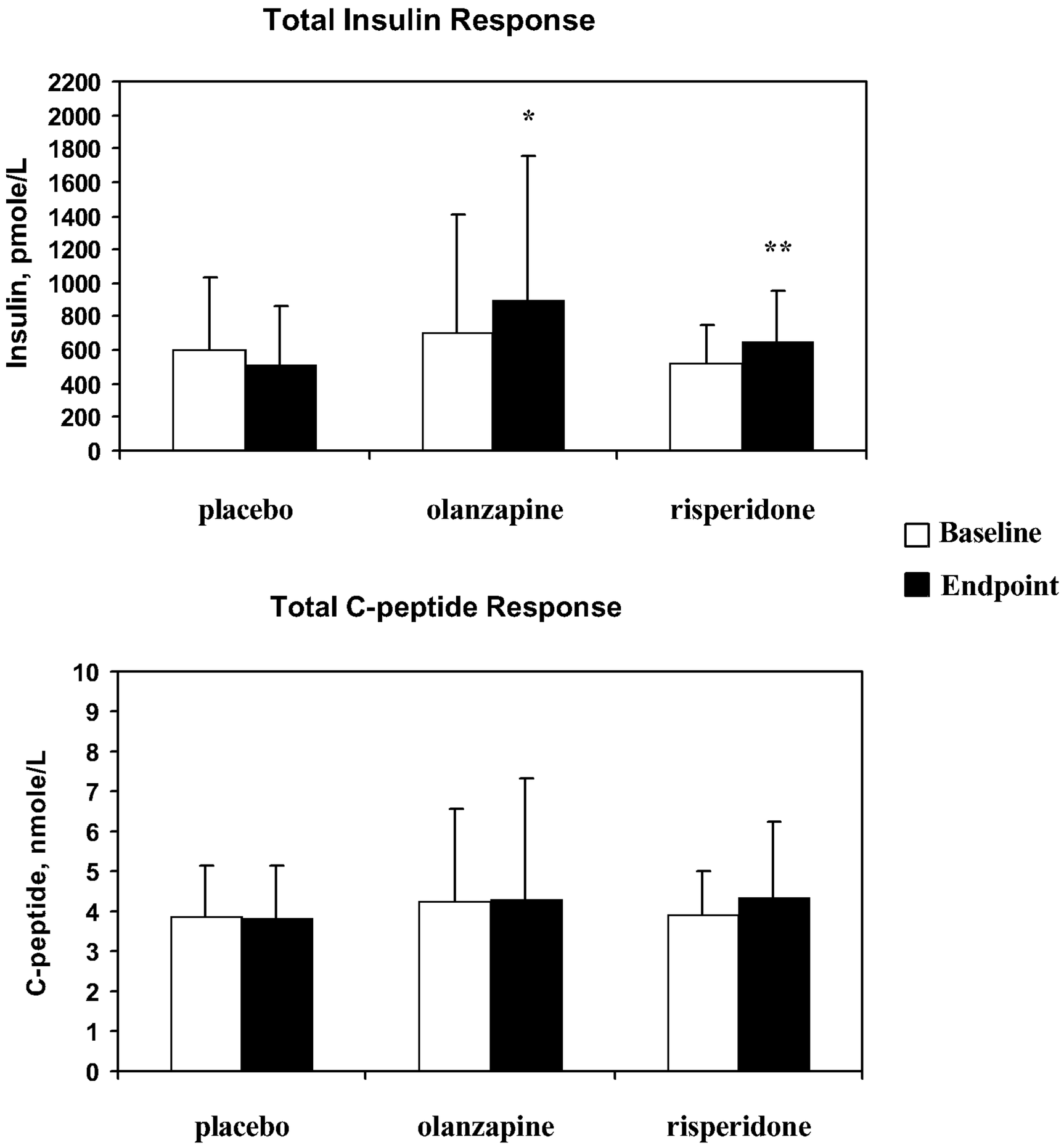


Figure 1

* $p < 0.01$ within group; $p < 0.001$ vs. PLC

** $p=0.054$ within group; $p=0.014$ vs. PLC

Table 3.

Therapy	Change in M, mmole/min/kg ($x10^{-3}$)	Change in I, pmole/L	Change in M/I ($x10^{-5}$)
Olanzapine	-2.4 (16.0)	111.0 (266.4)	-4.63 (11.0) *
Risperidone	-7.8 (11.6)	81.6 (266.4)	-3.7 (7.4)
Placebo	0.3 (16.0)	-112.8 (260.4)	0.92 (7.4)

* $p < 0.05$ within group

Table 4.

	Change in Fasting Insulin pmole/L	Change in TIR pmole/L	Change in TCR nmole/L	Change in M/I $x10^{-5}$
Olanzapine	2.4 (54.6)	42.6 (327.6)	-0.18 (1.94)	1.9 (13)
Risperidone	-3.6 (28.2)	-24.0 (310.8)	0.17 (1.84)	2.8 (12)
Placebo	-16.8 (17.4)	-111.6 (221.4) *	-0.11 (1.31)	2.8 (8.3)

* $p < 0.05$ within group

Figure Legends

Table 1. Baseline characteristics of study subjects. Results for each characteristic are expressed number of individuals or as means (SD) prior to randomization.

Table 2. Changes in weight and fasting measures of glucose, insulin, and C peptide. Within individual baseline to endpoint change in weight and fasting values were calculated and results expressed as mean (SD) for each therapy group.

Figure 1. **Total Insulin and Total C-peptide Responses.**. The total insulin response (TIR, 0 to 240 minutes,) to hyperglycemia was evaluated and is expressed as pmole/L insulin and AUC calculated as described in methods. Total C peptide response (TCR, 0 to 240 minutes) is also shown and is expressed as nmole/L. Results from the baseline (white bars) and endpoint (black bars) hyperglycemic clamps are shown and are expressed as means (SD).

Table 3. Baseline to Endpoint Change in Steady-State Glucose Infusion Rate, Insulin Levels and Insulin Sensitivity Index. Data collected the final hour of the clamps were used to calculate the steady-state glucose infusion rate (M, mmole/kg body weight/min) and steady-state insulin level (pmole/L) and an insulin sensitivity index (M/I). Results are shown as the group mean change from baseline in M, I, and M/I. Standard deviations are shown in parentheses.

Table 4. Multivariate regression analyses were performed with therapy and BMI change as covariates. Results from these analysis are presented as the LS (Least Square) mean (SD) change from baseline to endpoint for fasting insulin, TIR, TCR, and M/I where BMI change = 0.

Global Response Document
Blood Glucose Changes and Olanzapine

OLANZAPINE - BLOOD GLUCOSE CHANGES

SUMMARY

The summary below includes condensed key information for easy review. Information excluded may pertain to trial methods and limitations, patient population, non-endpoint results, and statistical information; more detailed information is included in the global response document that follows this summary.

- A number of antipsychotic medications, including olanzapine, have been temporally associated with treatment-emergent diabetes mellitus and related disorders in published reports, product labeling, and other documents. Information from controlled trials is needed because anecdotal reports are of little use in estimating the frequency of adverse events, the relative likelihood of events during treatment with one agent or another, or the nature of the relationship of the event to treatment.

- One of the largest sources of controlled data on this topic is the olanzapine clinical trial database. During head-to-head trials, clinically diagnosed treatment-emergent diabetes mellitus occurred at similar incidence in patients on olanzapine (0.5%) compared to haloperidol (0.4%) and in patients on olanzapine (0.6%) compared to risperidone (0.6%).

- Across controlled schizophrenia trials with active comparators (maximum exposure 52 weeks), mean random plasma glucose increased from 3.2 to 4.6 mg/dl[0.18 to 0.26 mmol/L] in patients treated with olanzapine. While the increase in mean glucose during treatment with olanzapine was significantly less than that observed with clozapine, it was not significantly different from that observed on risperidone and it was statistically greater than that observed on haloperidol.

- Because it may be difficult to make conclusions regarding the clinical significance of relatively small mean random glucose changes, a second analysis explored the estimated likelihood of an individual experiencing a random glucose value at or above any of four potentially important thresholds: 126, 140, 160, and 200 mg/dl (7.0, 7.8, 8.9, 11.1 mmol/L, respectively). The likelihood of reaching any of those thresholds while on olanzapine did not significantly differ from haloperidol or risperidone. Patients treated with clozapine were significantly more likely to experience elevation at or above the 126 (7.0 mmol/L) or 140 mg/dL (7.8 mmol/L) thresholds than patients treated with olanzapine.

- A large epidemiologic study was also conducted using prescription claims data from the Advance PCS database in the United States. In this study, comparable increases in risk of diabetes were observed in patients treated with both conventional and atypical antipsychotics in comparison to a reference population. Diabetes risk was comparable in olanzapine vs haloperidol-treated patients, as well as in olanzapine vs risperidone-treated patients.

- Olanzapine, risperidone, and placebo have been compared in a randomized study in normal volunteers using a hyperglycemic clamp, which is a very sensitive method for assessing insulin

secretion. Impairment of insulin secretion could potentially be a link to diabetic ketoacidosis, but such a link was not substantiated in this research. The study found no evidence that either olanzapine or risperidone directly impair pancreatic beta cell function and hence do not support this type of connection to diabetic ketoacidosis.

- Attention to the issue of altered glucose homeostasis is advisable because it is quite clear that diabetes mellitus is common in the general population and in psychiatric practice. A number of factors can contribute to the overall diabetes risk for an individual patient (e.g., family history, ethnicity, age, obesity, behavioral factors, and baseline glycemic control). Importantly, a series of reports over many decades suggest that psychiatric illness itself may be a meaningful risk factor, with rates of diabetes at least double those in reference populations. It remains unclear how much, if any, of this risk is associated with treatment, and whether such putative risk varies across treatments.

- In conclusion, information available to date, from head-to-head randomized clinical trials and one large epidemiological study does not support a clinically important increased of risk of treatment-emergent glucose elevations with olanzapine compared to other psychotropic medications. However, the common occurrence of diabetes does support the prudence of attending to the general health of psychiatric patients, including glycemic control.

INTRODUCTION

An association between schizophrenia and diabetes was implicated as early as the mid-1920's[1]. A more recent body of evidence similarly points to an association between bipolar disorder and diabetes[2, 3]. In addition, since the mid-1950's, psychotropic drugs including antipsychotics have been reported to be associated with hyperglycemia[4]. Recently, a resurgence of interest in this area has occurred due to several case reports suggesting that some atypical antipsychotics may alter glucose metabolism. This potential issue raises the question of how to balance expected efficacy with the potential of altered glucose control and other safety parameters (e.g., Extrapyramidal Symptoms, Tardive Dyskinesia, QTc prolongation, Prolactin, Weight Gain, Cognition).

The following review includes clinical experience with olanzapine, including prospective randomized trials initially designed to assess psychotropic effects, and later analyzed to evaluate random glucose changes. In these trials, the likelihood of clinically important random glucose elevations did not differ significantly among patients treated with olanzapine, risperidone, or haloperidol. Overall, significantly greater glucose elevations were observed during treatment with clozapine.

TREATMENT-EMERGENT GLYCEMIC ADVERSE - INTEGRATED OLANZAPINE CLINICAL TRIAL DATABASE

Unlike case reports or case series, clinical trial data are obtained prospectively from randomized double-blind studies, which reduces bias and the likelihood of confounding factors. Below is a report of treatment emergent adverse events related to glycemic control from 2500 olanzapine-treated patients during the initial registration trials (Table 1). In this analysis, the following COSTART standardized event terms were analyzed: hyperglycemia, diabetes mellitus, diabetic

acidosis, and hypoglycemia[5[MJB1]].

TABLE 1: INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS RELATED TO GLYCEMIC CONTROL IN OLANZAPINE TREATMENT GROUPS

COSTART Term	OLANZAPINE (N=2,500)	
	N	%
Hyperglycemia	16	0.64
Diabetes Mellitus	16	0.64
Diabetic Acidosis	1	0.04
Hypoglycemia	4	0.16

Rates of treatment emergent adverse events relative to other treatments can also be informative. The olanzapine database includes head-to-head comparisons in schizophrenia against clozapine, haloperidol, and risperidone. Table 2 reports the number of patients who had diabetes mellitus recorded as an adverse event in the clinical trial. As seen in this table, the incidence of treatment-emergent diabetes mellitus (reported as an adverse event) was not significantly different during treatment with olanzapine, compared to haloperidol or risperidone[5[BJ2]].

TABLE 2: INCIDENCE OF TREATMENT EMERGENT DIAGNOSIS OF DIABETES

STUDY	DRUG	N	INCIDENCE OF ADVERSE EVENT	P-VALUE
OLANZAPINE VS. HALOPERIDOL (1 YEAR)**	Haloperidol	261	0.4%	Not Significant
	Olanzapine	927	0.5%	
OLANZAPINE VS. RISPERIDONE (6 MONTHS)	Risperidone	167	0.6%	Not Significant
	Olanzapine	172	0.6%	

** Included in this analysis were those patients who had completed at least 6 weeks of a one-year double-blind olanzapine vs haloperidol study.

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

The American Diabetes Association recommends use of fasting glucose measurements to diagnose diabetes. In contrast, the World Health Organization recommends use of the 2-hour OGTT for diagnosis. Both organizations accept a random glucose > 200 mg/dl (11.1 mmol/L) with symptoms on two occasions as diagnostic of diabetes[8].

Predictive Value of Random Glucose

Diabetes can be diagnosed by several different methods including by fasting glucose, random glucose, or 2-hour oral glucose tolerance test measurements (OGTT). All of these approaches have certain limitations. There is currently considerable discussion regarding the impact of using fasting glucose alone to diagnose diabetes. Multiple reports have demonstrated that use of fasting

glucose alone may significantly underestimate the true prevalence of diabetes and impaired glucose tolerance as defined by a 2-hour OGTT[6-8]. However the OGTT has also been shown to have a high intra-individual variability resulting in low reproducibility[9, 10]. Likewise, the measurement of random glucose also has important limitations. Notably, in any individual, a random glucose is more variable than a fasting plasma glucose and random glucose measurements are not recommended by the American Diabetes Association for diabetes screening in the general population, because the positive predictive value is fairly low due to the relatively low sensitivity of this test. However, in populations with increased risk for diabetes, a number of reports have concluded that random capillary glucose measures may be useful for screening due to high specificity. The specificity of using a random glucose cutoff of $\geq$ 145 mg/dl (8.0 mmol/L) has been shown to be 95%[11, 12]. Further, epidemiological data have shown that risk of future diabetes can be predicted based on random plasma glucose (eg. random glucose $\geq$ 6.1 mmol/L[110 mg/dl] is associated with approximately a 2.7 fold greater incidence of future diabetes compared to those with random glucose < 6.1 mmol/L[110 mg/dl])[13]. Thus, there is evidence that random glucose may have a role in the assessment of hyperglycemia.

Analysis of random glucose measurements in the olanzapine clinical trials database were not intended to diagnose or to screen for diabetes or impaired glucose tolerance in the treatment groups. The random glucoses were used as a tracking variable to assess in a relatively large population, trends in glycemia over time in different treatment groups.

ACTIVE COMPARATOR OLANZAPINE CLINICAL TRIAL DATABASE

Glycemia Analyses of Head to Head Clinical Trial Database

A first set of analyses compared the mean change in random plasma glucose, which was measured periodically during head-to-head clinical trials of olanzapine in patients with schizophrenia (Table 3). Over an observation period of 18 to 52 weeks, a mean random glucose increase of 3.2 mg/dL to 4.6 mg/dL (0.18 to 0.26 mmol/L) was observed in olanzapine-treated patients. This increase was significantly more than observed with haloperidol, not significantly different from that seen with risperidone, and significantly less than observed with clozapine. These analyses controlled for a number of factors, including age, time of exposure to antipsychotic therapy, baseline BMI, baseline glucose, and change in BMI during treatment.

TABLE 3: MEAN RANDOM GLUCOSE CHANGE DURING HEAD-TO-HEAD STUDIES IN SCHIZOPHRENIA [14[JB3]]

CHANGE FROM BASELINE TO ENDPOINT IN LEAST SQUARES MEAN OF RANDOM GLUCOSE ACROSS CONTROLLED TRIALS

Study	Treatment	N	Glucose Change (mg/dL)	p-value
Vs. risperidone (26 week)	Olanzapine	172	4.51 ± 1.79 mg/dL(0.25 mmol/L)	Not Significant*
	Risperidone	167	2.58 ± 1.12 mg/dL (0.14 mmol/L)	
Vs. haloperidol (52 week)	Olanzapine	1737	4.56 ± 0.57 mg/dL (0.25 mmol/L)	<0.01**
	Haloperidol	792	0.22 ± 0.93 mg/dL (0.01 mmol/L)	
Vs. clozapine (18 week)	Olanzapine	88	3.17 ± 1.36 mg/dL (0.18 mmol/L)	<0.01**
	Clozapine	85	13.22 ± 2.19 mg/dL 0.73 mmol/L)	

*p=0.0626; **p= 0.0001

In patients entered in two, six-week placebo-controlled schizophrenia trials, a mean increase in random plasma glucose of 0.8mg/dL (.045 mmol/L) from baseline to endpoint was observed in patients treated with olanzapine (n=248). This was significantly different from the mean baseline to endpoint decrease of 1.3 mg/dL (.072 mmol/L) observed in placebo-treated patients (n=118). However, this placebo comparison was less informative than comparison to active controls due to the high drop out rate and the fact that many of the placebo-treated subjects had been treated recently with antipsychotic drugs[14].

Interpreting the clinical significance, if any, of a difference in group mean change of random glucose levels should be approached with caution. First, changes in mean random glucose may reflect something other than altered glucose control, such as an increased appetite or eating frequency, which would be reflected in a change in random glucose values. Second, the distribution of random glucose changes may be more clinically informative than mean glucose changes. Therefore, an additional analysis of the olanzapine clinical trial database was conducted to examine the rate of potentially, clinically significant elevations of glucose in patients treated with olanzapine compared with other antipsychotics.

Likelihood of increases in random plasma glucose above potentially clinically significant thresholds in Patients treated with Olanzapine vs. Other Antipsychotics

Table 4 reviews the potential clinical significance of several random blood glucose thresholds. These thresholds were derived from the recommendations of the American Diabetes Association at the time the study was conducted and were used in analyses reported below[15].

TABLE 4: REVIEW OF GLUCOSE THRESHOLDS

Glucose (mg/dL)	Glucose (mmol/L)	Interpretation
110	6.1	Fasting plasma glucose upper limit of normal
126	7.0	Fasting plasma glucose diagnostic of diabetes *
140	7.8	Random capillary glucose (finger stick) suggests need for further evaluation, and formerly considered suggestive of diabetes mellitus on fasting plasma glucose
160	8.9	Random plasma glucose suggests need for further evaluation
200	11.1	Random plasma glucose diagnostic of diabetes**

* With confirmation on a subsequent day

** If present on two occasions, with symptoms

The objective of this second set of analyses was to explore the likelihood of individual patients crossing glucose thresholds of 126, 140, 160, or 200 mg/dL (7.0, 7.8, 8.9, 11.1 mmol/L). It should be recognized that progressively fewer cases were identified as the thresholds increased thereby affecting the power to detect differences in the likelihood of crossing the higher thresholds. While lower random glucose thresholds can be expected to be more sensitive in identifying patients with impaired glycemic control, these lower thresholds would also be more likely to be crossed by patients with adequate glycemic control who happened to have had their glucose measured in close temporal proximity to a meal[14].

Results of this analysis indicate that the likelihood of random glucose elevations while on olanzapine when compared to haloperidol and risperidone were not statistically different at any examined threshold (126, 140, 160, and 200 mg/dL[7.0, 7.8, 8.9, 11.1 mmol/L]). However, the likelihood of having glucose levels at or above the 126 mg/dl (7.0 mmol/L) and 140 mg/dl (7.8 mmol/L) thresholds was significantly less (approximately one-third) in patients treated with olanzapine compared to patients treated with clozapine[14].

In summary, the results of the threshold analysis show the likelihood of potentially clinically significant glucose elevation during olanzapine treatment may be less than on clozapine and not significantly different from haloperidol or risperidone[14].

Mean Change in Fasting Glucose Compared to Ziprasidone

Pfizer Inc. has conducted a six week head-to-head study with up to 160 mg/day of ziprasidone (n=104) or up to 15 mg/day of olanzapine (n=112) in patients with schizophrenia or schizoaffective disorder. No significant change in fasting glucose was seen from baseline to endpoint in patients treated with olanzapine or with ziprasidone. Between treatment groups, there were no differences in fasting glucose[16].

GLUCOSE CHANGES AND BODY WEIGHT

In the clinical trial database analysis, the differences in mean glucose changes observed between

patients treated with olanzapine vs. respective comparators were only partially accounted for by weight gain during treatment. This finding is not surprising, given that obesity is only one of several factors contributing to the risk of diabetes[5[JAB4]].

STRENGTHS AND LIMITATIONS OF OLANZAPINE DATABASE ANALYSIS

All research findings should be considered in light of the scientific method employed. The analyses described above contribute significantly to available information on the issue of altered glucose homeostasis because they include a large number of patients who participated in prospective, blinded comparative clinical trials. Treatment assignment was randomized, avoiding some of the potential bias inherent if one selects patients already receiving a particular treatment.

On the other hand, these post-hoc analyses of prospectively collected data have a number of limitations, such as: (1) use of random glucose values, as discussed above, (2) maximal treatment exposure was one year, and shorter for most patients; (3) in the categorical analyses, power was reduced at the higher thresholds (e.g. 200 mg/dL[11.1 mmol/L]) because so few patients met or exceeded those glucose values; (4) patients participating in research clinical trials may be healthier on average than the overall population of patients in treatment, possibly resulting in under representation of higher risk groups (i.e. due to age, ethnicity, or concurrent medical conditions).

POST-MARKETING EXPERIENCE WITH OLANZAPINE

*Spontaneous Adverse Event Database**[5[MJB5]]***

Adverse events reported during open clinical use of a medication are relatively uninformative when attempting to compare the frequency of a particular event during treatment with one drug with another. Nevertheless, spontaneously reported adverse events are tracked because they can provide signals of potential safety issues after market approval. In a review of olanzapine 's spontaneous safety database between September 27, 1996 through April 30, 2000, the following COSTART terms were used to capture reports potentially related to glucose dysregulation: Acidosis, Diabetes Mellitus, Diabetic Acidosis, Diabetic Coma, Glucose Tolerance Decreased, Glycosuria, Hyperglycemia, Ketosis, and/or Lactic Acidosis. As of April 30, 2000, the estimated worldwide patient exposure to olanzapine was approximately 4.5 million.

The reporting rate frequency of these events potentially related to glucose dysregulation (including cases of diabetes mellitus, ketoacidosis, and hyperosmolar coma) in the olanzapine spontaneous safety database was found to be "very rare", defined as a frequency of <0.01% according to guidelines published by the Council for International Organizations of Medical Sciences (CIOMS). Most reports of glucose dysregulation during olanzapine treatment were in patients with one or more risk factors for diabetes, such as family/personal history of diabetes, pancreatic disorders or alcoholism, obesity, weight gain during treatment, or treatment with drugs that have been temporally associated with hyperglycemia.

PREVALENCE AND RISK FACTORS FOR DIABETES

When discussing the question of drug therapy and whether or not it has a relationship to diabetes, it is important to consider the prevalence of diabetes in the overall population. In fact, prevalence

data from the early 1990's indicate that diabetes may be present in up to 7.8% of the US adult population (a third of whom are undiagnosed) and an additional 6.9% have fasting glucose levels in the range of impaired fasting glucose[17]. Further, the estimated prevalence of diabetes among adults worldwide in 1997 was 2.5%[18]. Studies from the late 1990's also suggest that the prevalence of diabetes continues to increase[19].

Several factors have been associated with increasing the risk of diabetes. Intrinsic factors include a family history, age ≥45 years, ethnicity (increased risk for non-Caucasians), and a previous history of glucose intolerance[15]. Other variable factors have included dyslipidemia, lack of exercise, hypertension, and obesity[15, 20, 21]. In a two-decade epidemiological study, the incidence of diabetes was approximately 1%/year greater among those with the greatest weight increase compared with the lowest-risk group[20]. However, adults with normal body mass index can also develop diabetes and clearly not all obese adults will develop diabetes[20, 22].

Though not well established, other factors such as alcoholism, diet, and hyperprolactinemia have been implicated as diabetes risk factors[20, 21, 23]. As discussed below, one potentially very important factor is presence of a serious psychiatric illness.

PREVALENCE OF DIABETES IN THE PSYCHIATRICALLY ILL POPULATION

Recent data indicate that patients with certain mental illnesses have a prevalence of type 2 diabetes mellitus 2 to 4 times higher than the general population. Studies in populations with schizophrenia have shown a prevalence of elevated blood glucose levels ranging from 2.5 to 24.5%[24-27], but always substantially higher than the reference group. Further, two reports suggest increased prevalence of diabetes mellitus in bipolar disorder relative to reference populations[2, 3]. Thus, diabetes is not only of clinical concern in the general population, but it also represents an important major health concern for patients with mental illness. A number of factors may contribute to the apparent increased prevalence of diabetes in the mentally ill such as a behavioral and/or lifestyle issues, or an underlying genetic vulnerability to diabetes that may or may not be shared with the psychiatric disorder itself.

ANTIPSYCHOTIC DRUGS AND GLUCOSE DYSREGULATION

While it is reasonably clear that type 2 diabetes is more common in patients with mental illness, debate persists over whether this can be attributed to the underlying disease or to pharmacotherapy. Some speculate on predisposition for diabetes related to the illness itself[2] especially as abnormalities in glucose control were highlighted in the first half of the 20th century, predating modern psychopharmacology[28-30]. Several reports have been unable to demonstrate a definitive association between diabetes and the use of antipsychotics[24, 26, 31, 32], though as discussed below, other authors have proposed such an association.

LITERATURE SUMMARY

As mentioned above, several reports in the literature have associated psychotropic agents with diabetes or related events. McKee et al[25] found that 15 of 16 patients with schizophrenia receiving high doses of chlorpromazine had diabetes, suggesting a relationship between antipsychotic usage and the development of diabetes. Of the older, typical antipsychotics, case

reports have demonstrated a temporal association between diabetes and several of the typical antipsychotics including: chlorpromazine[31, 33, 34], loxapine[35], and phenothiazines in general[33]. In any case, a 1991 epidemiological report demonstrated elevated rates of diabetes in patients with schizophrenia, which predates widespread use of the newer atypical antipsychotic agents[36].

Case Reports of glucose dysregulation with Atypical Antipsychotics

Of the atypical antipsychotics, case reports demonstrating a temporal association with glucose dysregulation (diabetic ketoacidosis, hyperosmolar coma and new diagnosis or exacerbation of previously diagnosed diabetes) have been reported for clozapine[37-56], olanzapine[42,56-70], risperidone[71-73], and quetiapine[74-75]. These case reports were identified by searching the medical literature using the following databases: Medline, Derwent Drug File, Biosis Previews, SciSearch, PsycInfo, Embase through October 2001. Based on case reports, many of the patients that may develop glucose dysregulation in a temporal association with treatment have risk factors for type 2 diabetes based on race, obesity, or family history. The number of case reports temporally associated with a particular agent cannot establish whether the rate of events on that agent differ from either the base rate in the study population or from the incidence rate associated with another treatment. Ultimately, such comparative data can only be obtained from large head-to-head trials such as those described above or, better yet, from large-scale epidemiological studies. Appendix 1 contains a summary of the case report literature.

EPIDEMIOLOGICAL DATA

Strengths and Limitations of Epidemiological Studies

Due to their large sample size compared to prospective clinical trials, epidemiological studies provide the power to examine and quantitate relatively rare events and examine specific subpopulations. These studies may also apply less rigorous exclusion criteria than clinical trials, leading to a greater generalizability of results. Limitations of epidemiological studies in general are that treatment assignment is not randomized and limited information is often available regarding each individual patient. To investigate the frequency of diabetes mellitus in a large population of patients treated with antipsychotics, a retrospective cohort study was conducted using the Advance PCS prescription claims database. A description of the study and a summary of the results are presented below.

A retrospective cohort study of diabetes and antipsychotics in the US using the Advance PCS prescription claim database

Methods

The Advance PCS (PCS) prescription claim database processed over 300 million prescription claims per year for over 50 million members covered by over 2000 employers and managed care plans within the United States. Ten percent of patients on antipsychotics are on Medicaid, with also some representation of the over 65 Medicare population (In the US these cover individuals with medical/psychiatric disabilities, or social assistance, respectively). This large database was used to identify large cohorts of patients treated with antipsychotic monotherapy, regardless of

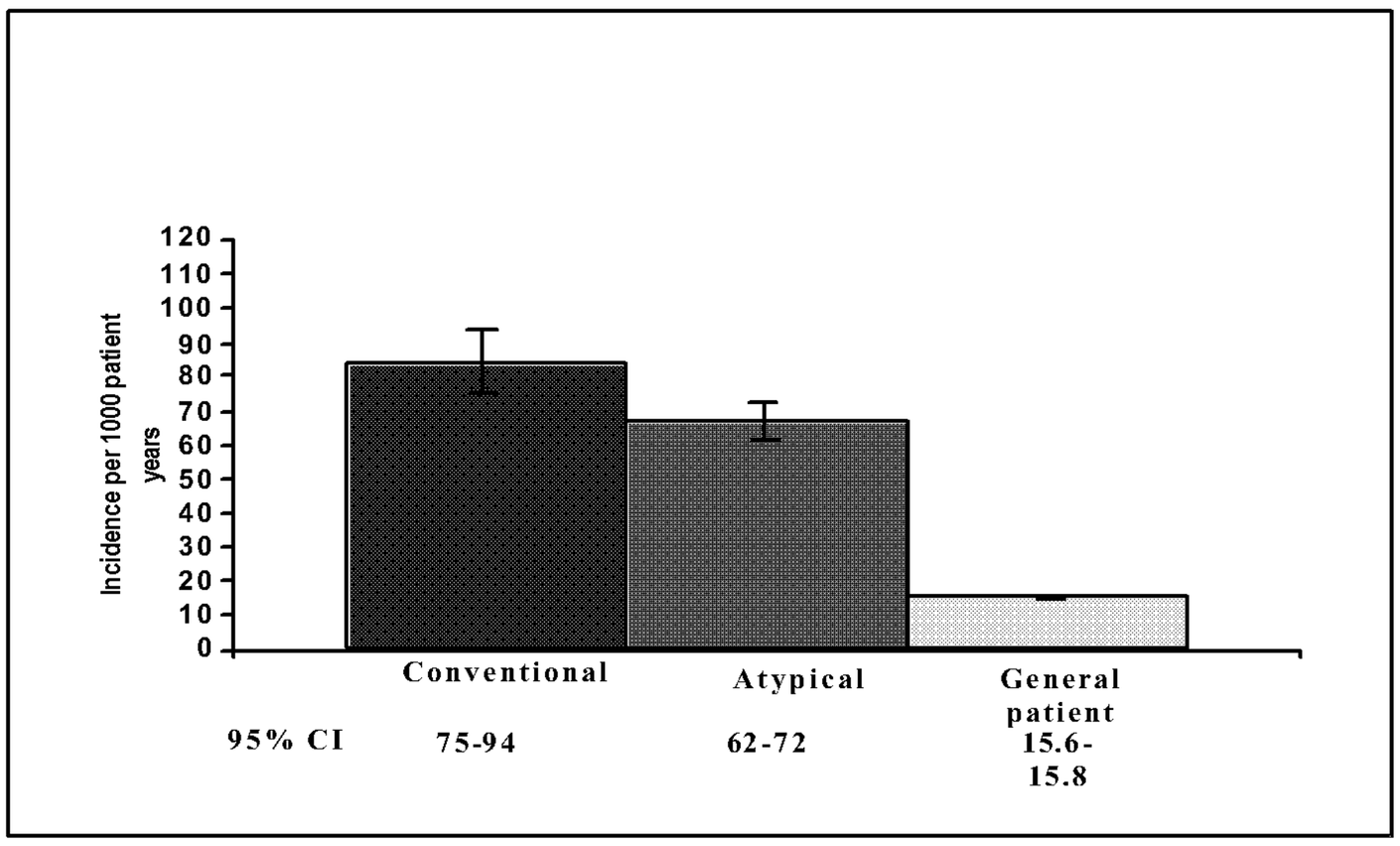
indication. The cohorts studied were: conventional antipsychotics as a class (n=19,782), haloperidol (n=8,476), thioridazine (n=3,133), atypical antipsychotics as a class (n=38,969), olanzapine (n=13,863), risperidone (n=20,633), quetiapine (n=4196), and clozapine (n=277). New onset of diabetes mellitus during antipsychotic exposure was identified by claim(s) for any medication(s) indicated for the treatment of diabetes.

Cox proportional hazard regression (controlling for age and gender) was used to determine the hazard ratio (HR) of diabetes in the antipsychotic cohorts relative to the general PCS patient population and relative to other selected antipsychotic cohorts[76].

Results

Compared to the general PCS patient population, the incidence of diabetes mellitus was significantly increased in both the conventional and atypical groups (Figure 1).

FIGURE 1: ANNUALIZED INCIDENCE OF DIABETES MELLITUS DURING ANTIPSYCHOTIC TREATMENT



When selected antipsychotic cohorts were compared to each other, there was no significant increase in risk of diabetes in the conventional versus the atypical cohorts (HR=0.966;CI0.8-1.1; p=0.6). Upon comparison of single atypical antipsychotic cohorts and the haloperidol cohort, a statistically significant increase in risk of diabetes was observed during treatment with risperidone (HR=1.2, CI: 1.0-1.5; p=0.04), but not during treatment with olanzapine (HR=1.09;CI: 0.9-1.4;p=0.5). On comparison of the olanzapine cohort relative to the risperidone cohort, no statistically significant difference in risk of diabetes was observed. The risk of diabetes was lower in the quetiapine cohort (HR=0.67). However, this included patients treated with a range of doses, reflected in the relatively low mean quetiapine dose (79.9 mg daily). When a secondary analysis was done of the 25% of subjects receiving the highest dose ranges of each of the treatments being considered, the risk of diabetes was found to be comparable across all treatments, including quetiapine, and ranging between 3-4 times the risk observed in controls not receiving antipsychotic medications[76].

Limitations

The limitations of this study include (1) the PCS database did not contain disease diagnostic information. Thus all prescriptions for a single antipsychotic were included, regardless of diagnosis or illness severity, (2) risk factors for diabetes (such as body mass index and family history) were not captured in this database, (3) the average duration of antipsychotic treatment was relatively brief, ranging from 68 to 137 days and the average daily doses of antipsychotic cohorts were low, and (4) due to the nature of the database, only new cases of diabetes that resulted in intervention with anti-diabetes medications were included.

Other Epidemiological Studies of Antipsychotics and diabetes Mellitus

Other epidemiological prevalence studies have been recently conducted. Mahmoud et al examined prescription claims data from two large mixed indemnity and managed health care plans in the United States and determined the hazard ratios for developing diabetes during exposure to antipsychotic medications. They reported an increased risk of developing diabetes in patients exposed to both high and low potency conventional antipsychotics, clozapine, and olanzapine[77]. Caro and colleagues retrospectively examined treatment emergent diabetes during exposure to either risperidone or olanzapine from prescriptions claims and physician diagnosis from the Regie de l' Assurance Maladie de Quebec (RAMQ). Their results showed a numerically greater incidence of diabetes in the olanzapine (1.7%) compared to risperidone (1.5%) cohort. On the basis of an odds ratio of 1.08 (95% CI: 0.89-1.31) and hazard ratio of 1.2 (95% CI: 1.0-1.43), the authors concluded that the risk of treatment emergent diabetes was higher among patients treated with olanzapine versus risperidone[78]. Both of these studies were limited by the fact that they included patients on multiple antipsychotic medications and did not include reference populations.

Conclusions/Summary

While these studies may differ with respect to methodology patient cohorts, and rank ordering of risk to patients compared to the PCS study, they generally are consistent in finding relative risks that are comparable or differ by only a small magnitude. In general, epidemiologic studies reported to date have shown a higher risk for antipsychotic-treated patients than reference populations, when these were included. What remains unclear is whether this increased risk is related to factors inherent to those conditions commonly treated with antipsychotics (e.g. shared genetic vulnerability) or to extrinsic factors such as lifestyle, behavior or drug therapy.

EVALUATION OF GLYCEMIC PARAMETERS AND OTHER LABORATORY-BASED REPORTS

To date, most preclinical trials and studies evaluating glycemic parameters have been carried out in very small samples and confounded by serious methodological limitations to be adequately informative about the glycemic changes in patients treated with olanzapine relative to other treatment options. More meaningful basic research is needed on this issue. The relevance of any preclinical or basic research ultimately still needs to be evaluated in the context of actual clinical trials and epidemiological studies.

Cross-sectional study on glycemic parameters

In a recent article, Melkersson and colleagues measured glucose and a variety of metabolic factors in 14 patients treated with olanzapine[79]. However, this study adds little to the understanding of effects of the drug on glucose homeostasis. Three of the patients had fasting glucose levels above the normal range, and one of the three patients had a glucose level greater than126 mg/dL (6.99 mmol/L), suggestive of diabetes. The study also reported weight increase and elevated insulin levels in many subjects. However, because the study was cross-sectional, no inference can be made upon how any particular laboratory parameter changed during treatment with olanzapine. Another methodological flaw was the failure to assure fasting status at the time glucose was measured. Lastly, there was no appropriate control group studied. Instead, results were compared to the "normal" range of laboratory values.

Preclinical Studies

A recently published study investigated the in vitro effects of antipsychotic medications on pancreatic insulin release. Based on reports that older antipsychotic medications (chlorpromazine, pimozide, haloperidol) may decrease insulin secretion, Melkersson and colleagues studied laboratory responses of isolated rat pancreatic islets during exposure to one of seven different antipsychotics or without addition (control). They measured basal (unstimulated) and glucose stimulated insulin release during one or four hours of exposure. No significant effects on insulin release were observed for any drug during one hour of exposure

In the four hour exposure experiments, no significant effect compared to controls was observed for basal or glucose stimulated insulin release with five of the tested medications (olanzapine, chlorpromazine, perphenazine, zuclopenthixol, or risperidone). Islets incubated with haloperidol for four hours released less insulin in response to glucose than did controls. Basal insulin release from islets incubated with clozapine for four hours was significantly greater than controls while glucose stimulated release by islets incubated with clozapine was not different from controls. The authors speculate that if clozapine similarly stimulates insulin release in vivo, the elevated insulin levels might stimulate appetite, promote weight gain, and thereby predispose to developing diabetes. Although these data are interesting in vivo human homeostatic mechanisms for regulating insulin release and production are complex and are not fully modeled by an in vitro rat experiment. Therefore, caution is recommended before interpreting these data as demonstrating that clozapine is diabetogenic or as definitive in identifying potential effects of these agents on in vivo insulin release[80].

Glucose Tolerance Tests

Two poster presentations concerning glucose homeostasis and antipsychotic medications have employed variants of glucose tolerance testing. Both were small studies using similar procedures that pose significant methodological concerns. Additionally, the findings of these studies were somewhat contradictory, likely illustrating that inherent design issues preclude generalizing these findings to other patients taking these medications.

The first study, by Prior et al used standard glucose tolerance test procedures[81]. In this study, eligible patients taking one of three medications were studied: olanzapine (N=9), risperidone

(N=10), clozapine (N=9). The measurements included plasma glucose at baseline (fasting), 30, 60 and 120 minutes after administration of 75 gm of oral dextrose. At baseline, all patients had normal fasting glucose levels. During the glucose tolerance test, 67% of clozapine patients, 40% of risperidone patients, and 0% of olanzapine-treated patients had abnormal glucose levels. These data should be interpreted with great caution because of serious study limitations including lack of a control group, small group size limiting statistical evaluation, and non-randomized selection of subjects (i.e., they were already on treatment).

A second somewhat similar and as yet unpublished study by Newcomer et al used a non-standard glucose tolerance test (GTT) consisting of only 50 gm of dextrose and glucose measurements at baseline (fasting), 15, 45 and 75 minutes[82]. Apparently subjects on established pharmacotherapy were enrolled, precluding the evaluation pre-treatment glycemic indices. Thirty-one healthy untreated patients were compared to 32 patients with schizophrenia treated with olanzapine (n=3), risperidone (n=5), clozapine (8), and traditional antipsychotic drugs (n=16). Patients on clozapine and olanzapine had mean fasting plasma glucose levels at baseline that were well within the normal range, yet statistically significantly higher than baseline levels for healthy controls. At 75 minutes, mean glucose levels for the clozapine and olanzapine-treated groups apparently were not significantly different from the risperidone group, yet remained significantly greater than mean glucose levels in healthy untreated controls. Data derived from the three patients treated with olanzapine in this non-randomized, cross-sectional study have no clear clinical significance.

A more recent abstract from this group reports on the post-hoc addition of more subjects to this study (treated n=48; healthy controls n=31), now including 12 olanzapine-treated patients. The abstract reports that each treatment group receiving antipsychotic medication had abnormal glucose tolerance testing results compared to normal controls. Results among olanzapine-treated patients did not differ compared to risperidone-treated patients; however, the former had significantly greater glucose elevation compared to those on typical antipsychotics[83].

The preliminary results from an additional unpublished glucose tolerance testing study has also been reported. Henderson and colleagues used frequently sampled intravenous glucose tolerance testing (FSIVGTT), obviating confounds regarding gut effects of psychotropics. Glucose and insulin levels were collected after glucose challenge, and the Bergman's Minimal Modal Analysis (MINMOD) is used for glucose effectiveness and insulin sensitivity. Patients on established treatment with several atypical antipsychotics were compared. No differences were found on glucose effectiveness, but rank ordering on insulin sensitivity was clozapine < olanzapine < risperidone. There was not a normal control group in this preliminary study, but historical norms appear to fall between results for olanzapine and risperidone-treated patients. The key consideration in interpreting these results is that because of the cross-sectional design, it is not possible to interpret what changes, if any, occurred during treatment or if pre-treatment vulnerability to diabetes was equivalent between treatment groups[84].

Hyperglycemic Clamp Study

A number of cases of new onset diabetes mellitus with ketoacidosis or hyperosmolar state have been reported in patients using atypical antipsychotic drugs. If medications were in some way interfering with insulin secretion, they potentially would contribute to such complications. The goal

of this Lilly-sponsored study was to determine if atypical antipsychotics have a direct effect on pancreatic beta cell function, causing decreased insulin secretion. Unlike several of the experiments reported in paragraphs above, treatment assignment was randomized. This decreases the potential confounds of baseline individual risk factors. The hyperglycemic clamp, the gold standard for quantitating insulin secretion, was used for this study. The hyperglycemic clamp is, loosely speaking, a stress test for the pancreas. Glucose is infused over an extended period of time and plasma glucose is maintained in a hyperglycemic range. This stimulates insulin secretion, and clamp studies are sensitive instruments for detecting impaired capacity to secrete insulin in response to glucose challenge. Healthy volunteers were randomly assigned to treatment with olanzapine 10 mg/day (N=17), risperidone 4 mg/day (N=13), or placebo (N=18) for 15 to 17 days. Insulin secretion was quantitatively assessed at baseline and endpoint using the hyperglycemic clamp. We found no evidence that treatment of healthy volunteers with olanzapine or risperidone was associated with a decrease in the insulin secretory response to a prolonged hyperglycemic challenge. This study did not find that olanzapine or risperidone directly impair pancreatic beta cell function, and therefore does not support a hypothesis linking the agents to diabetic ketoacidosis via impairment of insulin secretion[5[BJ6]].

CONCLUSION

Anecdotal reports and small case series have temporally associated a number of psychotropic medications, including olanzapine, with changes in glucose regulation. However, the conclusions derived from these reports need to be evaluated in light of larger, randomized clinical trials. Across clinical trials, treatment-emergent diabetes mellitus was observed in fewer than 1% of olanzapine-treated patients, and the incidence was similar among the active comparators haloperidol and risperidone. The analyses of random plasma glucose showed a mean increase during olanzapine treatment in the range of 3.2 to 4.6 mg/dL (0.18 to 0.26 mmol/L). This increase in mean glucose during olanzapine treatment was significantly less than that observed on clozapine, not significantly different from that observed on risperidone, and significantly greater than that observed on haloperidol. However, the clinical significance of such changes in random glucose is unclear. Therefore, a second analysis assessed the likelihood of an individual's experiencing an increase in random glucose to or above any of four potentially important random plasma glucose thresholds. That analysis found no significant differences for patients treated with olanzapine compared to haloperidol or risperidone. Patients on olanzapine were significantly less likely compared with those on clozapine to experience elevation at or above the 126 mg/dl (7.0 mmol/L) or 140 mg/dL (7.8 mmol/L) thresholds.

Results from a large epidemiological study of the incidence and risk of developing diabetes during treatment with antipsychotics showed a higher risk among antipsychotic-treated patients than controls, and indicated that the risk of developing diabetes was comparable across the most widely used agents. The findings of several smaller studies also seem compatible with these overall conclusions[85-87]. It cannot be ascertained whether the observed increased risk of diabetes mellitus reflects factors related to antipsychotic treatment, and/or factors related to elevated background rates of diabetes mellitus among the seriously mentally ill.

Preclinical research and study of other parameters such as insulin levels and glucose tolerance testing may be informative. Unfortunately, available studies are limited, of those that are available, the majority have methodological shortcomings. Clinical studies and research attention to the

issue of antipsychotic drugs and glucose homeostasis is advisable because diabetes mellitus is observed frequently in psychiatric practice as it is in the general population with increasing prevalence. Known risk factors for diabetes mellitus include a positive family history, non-caucasian ethnic background, age > 45 years old, obesity, previous history of glucose intolerance, hypertension, and low HDL and/or high triglyceride levels.

Importantly, a series of reports over many decades suggest that psychiatric illness itself may be a meaningful risk factor, with rates of diabetes at least double those of reference populations. Glycemic control may be one of several safety factors (i.e., along with rates of EPS, risk of TD, potential for QTc prolongation, prolactin elevation, propensity for weight gain, effects on cognition, etc.) that must be appropriately balanced against expected efficacy when selecting appropriate pharmacotherapy intervention for psychiatric disorders.

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Appendix 1: Summary of Case Report Literature of Atypical Antipsychotics and Hyperglycemia and/or Diabetes

Appendix 1 contains a summary of case reports including cases of diabetic ketoacidosis, type 1 DM, and/or type 2 DM in temporal association with clozapine, olanzapine, risperidone, and quetiapine as of June 2001. The diagnosis and baseline obesity (ie. classification of obesity and ideal body weight) are reported as defined by the authors of the report.

TABLE 1: SUMMARY OF CLOZAPINE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES

Case	Max. Drug Dose	Duration of Clz treatment before HG onset	Age/Race/Sex	Baseline Obesity	DM History	Family History	Weight change from baseline	Blood Glucose at time of Diagnosis	Diagnosis	Concomitant Medications
Case 1[37]	**900 mg**	**2 months**	**41/AA/M**	**NR**	**No**	**NR**	**NR**	**829 mg/100 ml**	**Hyperglycemia**	**Ranitidine Benztropine**
Case 2[38]	**250 mg**	**6 weeks**	**34/AA/F**	**NR**	**No**	**IDDM**	**NR**	**1,224 mg/100 ml**	**DKA**	**Lithium Benztropine**
Case 3[39]	**400 mg**	**1 month**	**42/NR/M**	**Obese (130kg)**	**Slight increase. glucose at baseline**	**NIDDM**	**NR**	**447 mg/dl**	**DKA**	**No other meds**
Case 4[40]	**500 mg**	**5 weeks**	**46/AA/M**	**NR**	**No**	**Positive history, not specified**	**NR**	**762 mg/100 ml**	**DKA**	**Lithium Verapamil Bethanechol**
Case 5[41]	**425 mg**	**2 months**	**32/AA/M**	**11% over IBW**	**No**	**IDDM & NIDDM**	**8 lb increase Over 5 weeks**	**930 mg/dl**	**DKA**	**Ephedrine**

AA – African-American, AC – Afro-Caribbean, C – Caucasian, F – Female, M – Male, NR – Not reported, IDDM – Insulin dependent diabetes mellitus, NIDDM – Non-insulin dependent diabetes mellitus, HCTZ – hydrochlorothiazide, IGT – Impaired glucose tolerance, IBW -- Ideal body weight, DKA --Diabetic Ketoacidosis

TABLE 1: SUMMARY OF CLOZAPINE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES (CONT.)

Case	Max. Drug Dose	Duration of Clz treatment before HG onset	Age/Race/Sex	Baseline Obesity	DM History	Family History	Weight change from baseline	Blood Glucose at time of Diagnosis	Diagnosis	Concomitant Medications
Case 6[41]	**450 mg**	**5 weeks**	**44/AA/M**	**42% over IBW**	**No**	**No**	**3 lb increase. Over 5 weeks**	**494 mg/dl**	**Hyperglycemia**	**Risperidone HCTZ Lithium Clonidine**
Case 7[41]	200 mg	2weeks	51/C/M	NR	NIDDM	NR	No weight change	300 to 500 mg/dl	Hyperglycemia	Glyburide
Case 8[41]	900 mg	4 months	51/AA/M	NR	NIDDM	NR	No weight change	139 to 311 mg/dl	Hyperglycemia	Glyburide Lisinopril
Case 9[42]	150 mg	2 months	47/AA/M	9% over IBW (borderline obesity)	IGT	No	24 lb (11%) increase over 8 weeks	NR	Hyperglycemia	None reported
Case 10[42]	400 mg	18 months	32/AA/M	No obesity	No	No	56 lb(37%) increase over 18 months	NR	DKA	None reported
Case 11[42]	100 mg	6 months	43/AA/M	12% over IBW	No	NIDDM	7 lb(4%) increase over 20 weeks	100 to 200 mg/dl	Hyperglycemia	None reported
Case 12[42]	200 mg	5 weeks	41/AA/M	38% over IBW	No	No	No weight change	1,028 mg/dl	Hyperglycemia	None reported

AA – African-American, AC – Afro-Caribbean, C – Caucasian, F – Female, M – Male, NR – Not reported, IDDM – Insulin dependent diabetes mellitus, NIDDM – Non-insulin dependent diabetes mellitus, HCTZ – hydrochlorothiazide, IGT – Impaired glucose tolerance, IBW -- Ideal body weight, DKA --Diabetic Ketoacidosis

TABLE 1: SUMMARY OF CLOZAPINE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES (CONT.)

Case	Max. Drug Dose	Duration of Clz treatment before HG onset	Age/Race/Sex	Baseline Obesity	DM History	Family History	Weight change from baseline	Blood Glucose at time of Diagnosis	Diagnosis	Concomitant Medications
Case 13[43]	300 mg	5 months	30/AC/M	NR	No	No	NR	24.9 mmol/L	DKA	Minocycline
Case 14[44]	400 mg	1 month	50/C/F	NR	No	type 2	NR	1,000 mg/dl	DKA	Valproic Acid
Case 15 [45]	200 mg	3 months	31/C/ M	29 kg/m^2	No	No	3 kg increase over 3 months	42 mmol/L	DKA	No other meds
Case 16 [46]	150 mg	18 days	48/C/M	NR	No	NR	NR	267 mg/dl	Hyperglycemia	Lithium Clonzapam Niacin Pantothenic acid Multivitamin Chromium Picolonate
Case 17 [47]	25 mg	2 weeks	57/NR/F	NR	No	NR	NR	320 mg/dl	Hyperglycemia	None reported
Case 18 [48]	NR	16	40/AC/M	Mildly obese	No	No	NR	55 mmol/L	DKA	None reported
Case 19 [49]	450 mg	NR	28/NR/F	NR	NIDDM	NR	NR	NR	Gestational Diabetes	None

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TABLE 1: SUMMARY OF CLOZAPINE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES (CONT.)

Case	Max. Drug Dose	Duration of Clozapine treatment before HG onset	Age/Race/Sex	Baseline Obesity	DM History	Family History	Weight change from baseline	Blood Glucose at time of Diagnosis	Diagnosis	Concomitant Medications
Case 20 [50]	300 mg	10 days	50/NR/M	NR	NR	NR	NR	23.5 mmol/L	DKA	No meds noted
Case 21 [51]	325 mg	3 months	30/AA/M	NR	No	No	NR	19 mmol/L	DKA	No meds noted
Case 22 [53]	900 mg	First detected after 17 months	45/NR/M	24% over IBW	No	No	23 kg increase	173 mg/dl	Hyperglycemia	NR
Case 23[54]	800 mg	First detected after @ 4 years	54//NR/M	29.3% over IBW	No	No	24 kg increase	327 mg/dl	Hyperglycemia	Docusate Naproxen Diazepam Metoprolol Simvastatin Psyllium Nitroglycerin Levofloxacin Lisinopril
Case 24[55]	300 mg	67 days	38/AA/M	104 kg and184cm	No	No	20 lb weight gain during 2 months prior to starting therapy	776 mg/dl	Hyperglycemia	Sertraline
Case 25 [56]	NR	6 months	38/NR/M	NR	No	No	Weight loss of 3 kg	25 mmol/L	Hyperglycemia	NR

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TABLE 2: SUMMARY OF OLANZAPINE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES

Case	Max. Drug Dose	Duration of Olz treatment Prior to HG	Age/Race/ Sex	Baseline Obesity **[CLW16]**	DM History	Family History	Weight Change from Baseline	Blood Glucose at time of Diagnosis	Diagnosis	Concomitant Medications
Case 1 [42]	250 mg [CLW17](possible typographical error)	3 months	38/AA/M	Obese 42% over IBW	No	No	14 lb(5%) increase over 12 weeks	NR	Hyperglycemia	None reported
Case 2 [42]	25 mg	3 months	56/C/M	Obese 25% or 27[CLW18]% over IBW	No	No	No weight change	NR	Hyperglycemia	None reported
Case 3 [57]	10 mg	3 months	31/C/M	BMI 40 kg/m^2 [CLW19]	No	No	8 lb decrease on Olanzapine	36 mmol/L	DKA	3 other neuroleptics – not specified
Case 4 [58]	10 mg	Unclear ? within a month	45/AA/M	NR	NIDDM tx with glyburide	NR	25% increase over 16 weeks	300 to 400 mg/dl	Hyperglycemia	Glyburide Nifedipine Fluoxetine
Case 5 [59]	20 mg	6 weeks	32/AA/M	Ht 67" Wt 99.5 kg Obesity	No	No	NR	290 mg/dl	Hyperglycemia	Beclomethasone nasal spray
Case 6 [60]	30 mg	8 months	50/AA/M	Mild obesity, 227 lb	No	No	Increase to 248 lb over 5months, then decreased to 205 lb by the end of tx	1,200 mg/dl	DKA	Nifedipine Divalproex Sodium
Case 7 [61]	10 mg	6 months	42/C/F	BMI 24.5 kg/m^2[CLW20]	No	NIDDM	71 lb increase to BMI 36	1,274 mg/dl	DKA	Valproic Acid

AA – African-American, AC – Afro-Caribbean, C – Caucasian, F – Female, M – Male, NR – Not reported, IDDM – Insulin dependent diabetes mellitus, NIDDM – Non-insulin dependent diabetes mellitus, HCTZ – hydrochlorothiazide, IGT – Impaired glucose tolerance, IBW -- Ideal body weight, DKA --Diabetic Ketoacidosis

TABLE 2: SUMMARY OF OLANZAPINE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES (CONT).

Case	Max. Drug Dose	Duration of Olz treatment Prior to HG	Age/Race/Sex	Baseline Obesity **[CLW21]**	DM History	Family History	Weight Change from Baseline	Blood Glucose at time of Diagnosis	Diagnosis	Concomitant Medications
Case 8 [61]	10 mg	17 months	40/C/F	BMI 27.2 kg/m^2 Mildly obese	No	No	10 to 15 lb increase over 18 months	1,160 mg/dl	DKA	Over the counter cold medicine
Case 9 [61]	10 mg	5 months	41/C/F	Obesity	No	No	NR	766 mg/dl	Hyperglycemia	Valproic Acid Medroxyprogesterone
Case 10 [61]	20mg	5 weeks	47/C/M	Obesity	No	NIDDM	30 lb increase over 5 weeks (BMI – 40kg/m^2)	878 mg/dl	Hyperglycemia	Clonazapam Carbamazepine
Case 11 [61]	10 mg	6 months	43/C/M	185 lb Obese	No	No	25 lb increase (BMI – 32 kg/m^2)	567 mg/dl	Hyperglycemia	Lamotrigine Lithium Paroxetine
Case 12 [61]	10 mg	6 months	39/C/M	BMI 39.1 kg/m^2 Obesity	No	NIDDM	6 lb decrease	686 mg/dl	Hyperglycemia	Lithium Valproic Acid Hydrochlorothiazide/Triamterene Lisinopril Levothyroxine Atorvastatin Lorazepam

AA – African-American, AC – Afro-Caribbean, C – Caucasian, F – Female, M – Male, NR – Not reported, IDDM – Insulin dependent diabetes mellitus, NIDDM – Non-insulin dependent diabetes mellitus, HCTZ – hydrochlorothiazide, IGT – Impaired glucose tolerance, IBW -- Ideal body weight, DKA --Diabetic Ketoacidosis
BMI -- Body Mass Index

TABLE 2: SUMMARY OF OLANZAPINE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES (CONT.)

Case	Max. Drug Dose	Duration of Olz treatment Prior to HG	Age/Race/Sex	Baseline Obesity	DM History	Family History	Weight Change from Baseline	Blood Glucose at time of Diagnosis	Diagnosis	Concomitant Medications
Case 13 [61]	10 mg	3.5 months	38/C/M	Obesity BMI 31.3 kg/m^2	No	NIDDM	No weight change	372 mg/dl	Hyperglycemia	Sertraline
Case 14 [62]	NR	4months	12.5/NR/M	NR	NR	NR	NR	NR	DKA	NR
Case 15 [63]	20 mg	3 months	19/NR/F	Obese BMI 25.3 kg/m^2	Borderline OGTT	No	NR	338 mg/dl	Hyperglycemia	Metoprolol Lorazepam Bezafibrate
Case 16 [63]	20 mg	15 days	24/NR/M	Normal body wt.	No	NR	NR	500 mg/dl	DKA	None reported
Case 17 [64]	NR	12 days	54/AA/F	BMI 25 kg/m^2	NIDDM	NR	13 kg increase over 14 weeks	536 mg/dl	Glucose dysregulation	None reported
Case 18 [56]	20mg	6 months	55/NR/M	BMI 28 kg/m2		Type 2 DM	7 kg weight loss	19 mmol/L	Hyperglycemia without acidosis	None reported
Case 19 [56]	NR	3 months	41/NR/M	BMI 40 kg/m2	NR	No	4 kg weight loss	36 mmol/L	DKA	None reported

AA – African-American, AC – Afro-Caribbean, C – Caucasian, F – Female, M – Male, NR – Not reported, IDDM – Insulin dependent diabetes mellitus, NIDDM – Non-insulin dependent diabetes mellitus, HCTZ – hydrochlorothiazide, IGT – Impaired glucose tolerance, IBW -- Ideal body weight, DKA --Diabetic Ketoacidosis
BMI -- Body Mass Index

TABLE 2: SUMMARY OF OLANZAPINE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES (CONT.)

Case 20 [65]	25 mg	7 months	51/C/M	85.5 kg (7% over IBW)	No	No	No weight gain	1596 mg/dl	Hyperosmolar hyperglycemic nonketotic coma	Gabapentin Isosorbide Venlafaxine Lansoprazole
Case 21 [66]	10 mg	6 weeks	31/AA/M	100 kg	No	DM (type unknown)	12 kg weight increase	509 mg/dl	Diabetes Mellitus	Nitroglycerin Albuterol Fluoxetine Divalproex Mirtazapine Benztropine Temazepam
Case 22 [66]	15 mg	4 months	44/C/M	NR	No	DM (type unknown)	NR	936 mg/dl	Diabetes Mellitus	Divalproex Sertraline Propranolol
Case 23[67]	15 mg	Unk	16/Hisp/F	NR	Unk	Type II DM	30 lb weight increase	669 mg/dl	DKA	Imipramine Risperidone Venlafaxine
Case 24 [68]	NR	NR	42/C/M	120.8 kg	No	No	NR	>700 mg/dl	DKA	Atenolol Docusate sodium Olanzapine Paroxetine Valproic acid
Case 25 [69]	NR	12 months	38/NR/NR	NR	No	NR	NR	NR	Diabetes Mellitus And ketoacidosis	NR
Case 26[70]	2.5 mg	6 weeks	79/C/F	48.1 kg	IGT	NR	NR	496 mg/dl	Hyperglycemia	Cloprednole

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TABLE 3: SUMMARY OF RISPERIDONE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES

Case	Max. Drug Dose	Duration of Risp treatment before HG onset	Age/Race/Sex	Baseline Obesity	DM History	Family History	Weight change from baseline	Blood Glucose at time of Diagnosis	Diagnosis	Concomitant Medications
Case 1[71]	4 mg	NR	42/C/M	NR	No	No	NR	565 mg/dl	DKA	Fluoxetine Trazadone
Case 2 [73]	8 mg	15 months	52/AA/M	216 lg (BMI 30.1)	No	Type II DM	2 lb decrease	436 mg/dl	Diabetes Mellitus	NR
Case 3 [73]	6 mg	31 months	50/Latino/M	177 lbs (26.9)	NR	NR	65 lb gain (increase BMI of 37%)	158 mg/dl	Type II DM	NR

AA – African-American, AC – Afro-Caribbean, C – Caucasian, F – Female, M – Male, NR – Not reported, IDDM – Insulin dependent diabetes mellitus, NIDDM – Non-insulin dependent diabetes mellitus, HCTZ – hydrochlorothiazide, IGT – Impaired glucose tolerance, IBW -- Ideal body weight, DKA --Diabetic Ketoacidosis
BMI -- Body Mass Index

TABLE 4: SUMMARY OF QUETIAPINE CASE REPORTS OF HYPERGLYCEMIA (HG) AND/OR DIABETES

Case	Max. Drug Dose	Duration of Quet treatment before HG onset	Age/Race/Sex	Baseline Obesity	DM History	Family History	Weight change from baseline	Blood Glucose at time of Diagnosis	Diagnosis	Concomitant Medications
Case 1[74]	200 mg	1 month	42/C/M	NR	No	No	NR	607 mg/dl	Diabetes Mellitus	Lithium Gabapentin Clonazepam Venlafaxine
Case 2 [75]	400 mg	16.5 weeks	30/AA/M	100kg (BMI 32.3)	No	No	5 kg increase	21.2 mmol/L	Diabetes Mellitus	Clonazepam Divalproex Loxapine Fluphenazine

AA – African-American, AC – Afro-Caribbean, C – Caucasian, F – Female, M – Male, NR – Not reported, IDDM – Insulin dependent diabetes mellitus, NIDDM – Non-insulin dependent diabetes mellitus, HCTZ – hydrochlorothiazide, IGT – Impaired glucose tolerance, IBW -- Ideal body weight, DKA --Diabetic Ketoacidosis
BMI -- Body Mass Index

Global Response Document
Acute Complications or Presentations of Diabetes – DKA & HHNS

OLANZAPINE – ACUTE COMPLICATIONS OR PRESENTATIONS OF DIABETES MELLITUS - DIABETIC KETOACIDOSIS AND HYPERGLYCEMIC HYPEROSMOLAR NON-KETOTIC SYNDROME

TYPE 1 VS. TYPE 2 DIABETES MELLITUS

The two most common types of diabetes mellitus (DM): Type 1, an autoimmune disease characterized by progressive destruction of pancreatic islets and loss of insulin production, and type 2, characterized by insulin resistance (decreased effectiveness of insulin) and pancreatic insufficiency with inadequate production of insulin. In type 1 diabetes there is an absolute insulin deficiency while in type 2 insulin production is inadequate to overcome the increased insulin requirements imposed by decreased hormone effectiveness[1-2].

Type 1 diabetes is generally thought of as a childhood disease however, there is growing appreciation that type 1 diabetes may present later in life. Type 2 diabetes is the most common form of diabetes, accounting for >90% of diagnoses. While it was previously considered to be a disorder of adults[3], type 2 diabetes is becoming increasingly common in children and adolescents[4].

RISK FACTORS FOR TYPE 2 DIABETES MELLITUS

Risk factors for type 2 diabetes include obesity (BMI ≥ 27 kg/m^2), previous history of glucose intolerance, gestational diabetes, birth of infant > 9 lbs, polycystic ovary syndrome, certain ethnic backgrounds and aboriginal groups, family history of diabetes and certain lipid abnormalities (HDL ≤ 35 mg/dl (0.90 mmol/L) or triglycerides ≥ 250 mg/dl (2.82 mmol/L)[3,5]. The risk for diabetes also increases with age and a sedentary lifestyle[3,5].

ACUTE COMPLICATIONS OR PRESENTATIONS OF DIABETES MELLITUS

The two most common acute complications of diabetes are diabetic ketoacidosis (DKA) and hyperglycemic, hyperosmolar non-ketotic syndrome (HHNS). Both DKA and HHNS may be the presenting complaint in patients not previously known to be diabetic although the frequency of this type presentation is not known. DKA represents a potentially life threatening acute complication or presentation of diabetes and is the metabolic consequence of severe insulin deficiency (inadequate insulin to suppress ketogenesis). It is most commonly associated with type 1 diabetes. However, it does occur in type 2 diabetic patients. DKA is usually associated with precipitating factors such as non-compliance with diabetic therapy or poor glycemic control, intercurrent illness (infection, severe diarrhea, vomiting, myocardial infarction etc.) or trauma[7].

DKA results from insulin deficiency, absolute as in type 1 or a relative deficiency as in type 2. Clinically, these patients present with lethargy, hyperventilation (Kussmaul's respiration), fruity odor to the breath (from acetonemia), nausea and vomiting, abdominal pain, thirst and polyuria. As dehydration becomes pronounced, patients display decreased urine output, dry mucus membranes and poor skin turgor, and tachycardia. Presence of large urine ketones, serum ketones, lowered arterial pH, and lowered serum bicarbonate level are characteristic of DKA. Generally these

patients have a relatively short prodrome of symptoms, from hours to days[2]. DKA is a medical emergency that requires immediate treatment, with a mortality rate of 3 to 10%[7].

HHNS is generally associated with type 2 diabetes. It is also a result of inadequate insulin but there appears to be enough insulin to prevent development of ketosis. Rising glucose concentrations create a hyperosmolar driven polyuria which will perpetuate the hyperosmolar state if adequate hydration is not maintained by the patient and if glycemic control is not achieved. Precipitating conditions are similar to those for DKA[6].

Patients that present with HHNS tend to be older individuals, have a longer symptomatic period (days to a week or so), and have much higher glucose levels than typically seen in DKA. Patients with HHNS tend to be individuals who have difficulty caring for themselves, are unable to keep themselves hydrated, or require care from other family members, caregivers, or healthcare professionals. Clinically these patients display dehydration, decreased level of consciousness, and absence of marked ketosis and acidosis[2]. Because this condition develops insidiously, it may be initially misdiagnosed as with DKA. HHNS is a medical emergency that requires immediate treatment, with a mortality rate of approximately 10 to 20%[7]. Table 1 summarizes the laboratory criteria for DKA and HHNS[8,9].

Table 1. Laboratory Criteria for DKA and HHNS[8,9]

	DKA	HHNS
Plasma glucose (mg/dl)	>250	>600
Arterial pH	<7.30	>7.30
Serum bicarbonate (mEq/l)	<15-18	>20
Serum ketones	Positive at > 1:2 dilution	Negative to small
Urine ketones*	Positive, >3	Negative to small
Effective serum osmolality (mOsm/kg)$^{\Psi}$	Variable	>320
Anion gap$^{\phi}$	>10-12	<12

*Nitroprusside reaction method;$^{\Psi}$calculation: 2[measured Na (mEq/l)] + glucose (mg/dl)/18;$^{\phi}$calculation: $(Na+) - (Cl^- + HCO_3^-)$ (mEq/l).

In both DKA and HHNS, the metabolic consequences of insulin deficiency may be further complicated by concurrent lactic acidosis (e.g. from infections or circulatory collapse), starvation ketosis, or alcoholic ketoacidosis. Also, it is possible to have a mixed DKA/HHNS physiology occurring within a single patient.

RISK FACTORS FOR DKA/HHNS

Most reports of DKA/HHNS during olanzapine treatment have been in patients with one or more risk factors for diabetes. These include family/personal history of diabetes, pancreatic disorders or alcoholism, obesity, weight gain preceding olanzapine treatment or during olanzapine treatment, or concomitant treatment with drugs that have also been temporally associated with glucose dysregulation (including conventional antipsychotics-phenothiazines, e.g., chlorpromazine, thioridazine etc., other atypical antipsychotics, as well as drugs such as beta blockers and thiazide diuretics)[10-23]. The great majority of cases of DKA /HHNS reported in temporal association with olanzapine treatment are consistent with type 2 diabetes.

POST-MARKETING EXPERIENCE WITH OLANZAPINE

The reporting rate frequency of events potentially related to glucose dysregulation (including cases of diabetes mellitus, ketoacidosis, and hyperosmolar coma) in the olanzapine spontaneous safety database was found to be "very rare", defined as a frequency of <0.01% according to guidelines published by the Council for International Organizations of Medical Sciences (CIOMS). A direct causal relationship with olanzapine treatment has not been established[25].

LILLY-SPONSORED INVESTIGATIONS

Since both DKA and HHNS are conditions where insulin deficiency (absolute or relative) is present, Lilly conducted a study to clarify whether olanzapine could impair pancreatic insulin secretion. The methodology for this study (known as a "hyperglycemic clamp") represents the most sensitive procedure to study this issue. In this study, there was no evidence of decreased insulin secretion in subjects treated with olanzapine.

CONCLUSIONS

Cases of DKA or HHNS have been reported in temporal association with olanzapine treatment. These reports are very rare (e.g., occurring in less than 0.01% of patients treated with olanzapine). A direct causal relationship has not been established. Current evidence does not indicate that olanzapine has an inhibitory effect on pancreatic insulin secretion.

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US Medical Letter

Natural History, Diagnosis, and Management of Diabetes

ZYPREXA®--DIABETES MELLITUS: NATURAL HISTORY, DIAGNOSIS, AND MANAGEMENT EXECUTIVE SUMMARY

The following is a summary of the attached medical letter. This does not contain the complete information provided in the medical letter, but places key information in a condensed form for easy review. Information excluded may pertain to trial methods and limitations, patient population, non-endpoint results, and statistical information.

- In the United States, diabetes mellitus is a significant and growing health concern, affecting about 8% of the population and costing billions in health care dollars. Given the increasing number of people with diabetes in this country, a brief review is provided.
- About 90% of patients with diabetes have type 2 diabetes, the form of the disease characterized by both insulin resistance and relative insulin deficiency.
- Diabetes is the sixth leading cause of death by disease in the United States, and a leading cause of disability. Uncontrolled diabetes can result in neuropathy, nephropathy, retinopathy, stroke, and/or myocardial infarction. Individualized treatment, including lifestyle modification and pharmacologic therapy if necessary, can improve glucose control and forestall complications of diabetes.
- Risk factors for developing type 2 diabetes include: family history, obesity, ethnic background, age, sedentary lifestyle, hypertension, and dyslipidemia. In addition, patients with mental illness may have increased risk for the development of diabetes.
- Symptoms of type 2 diabetes vary widely among patients, but may include the following: increased thirst and hunger, frequent urination, tiredness, frequent infections, slow healing, blurred vision, tingling or numbness in extremities, and sexual dysfunction.
- The American Diabetes Association now recommends screening every 3 years all people over the age of 45 by measuring a fasting plasma glucose. Patients with risk factors or symptoms should be screened at a younger age and/or more frequently. In addition, the American Association of Clinical Endocrinologists (AACE) recommends that screening begin at age 30 in asymptomatic individuals with risk factors for diabetes. This recommendation clearly applies to most patients with severe mental illness.

- Diagnostic criteria for diabetes include any of the following: fasting plasma glucose ≥126 mg/dL (confirmed on a separate day), casual (random) plasma glucose ≥200 mg/dL, or a glucose level ≥200 mg/dL 2 hours after ingesting glucose during a standard oral glucose tolerance test. Currently, fasting plasma glucose is the screening test recommended by the American Diabetes Association.
- Managing diabetes requires a multi-system approach that not only focuses on controlling plasma glucose levels, but also managing significant cardiovascular risk factors such as blood pressure, lipid abnormalities, and cigarette smoking, all of which significantly contribute to diabetes-related mortality.
- Lifestyle changes are an integral part of diabetes management, and should be included in any therapeutic regimen. Important aspects include proper nutrition, exercise, weight management, and smoking cessation.
- Useful medications for managing type 2 diabetes include oral anti-diabetic agents, alone or in combination, and insulin therapy.
- With the increasing prevalence of diabetes, anyone treating patients may find it helpful to review risk factors and presenting symptoms of diabetes.

DIABETES MELLITUS: NATURAL HISTORY, DIAGNOSIS, AND MANAGEMENT:
A REVIEW FOR CLINICIANS IN PSYCHIATRY
PREPARED BY ELI LILLY AND COMPANY U.S. MEDICAL DIVISION

Due to the large and increasing prevalence of diabetes mellitus in the United States, a review of diabetes is timely and relevant for all health care professionals. The following information regarding diabetes and its management is intended as an overview that we hope you will find useful. This overview will include the pathophysiology of diabetes mellitus, epidemiology and risk factors, diagnostic criteria, disease course and outcomes, and management strategies. Risk factors and presenting symptoms are covered in more detail than management strategy. The information contained in this letter is by no means all-inclusive, and specific patient management should be approached in a case-by-case manner, including consideration of referral to a specialized diabetes care team.

PATHOPHYSIOLOGY

Diabetes mellitus is a complex metabolic disorder involving altered fat, protein, and glucose metabolism brought about by a relative or absolute deficiency of insulin. Insulin is a protein hormone secreted from β-cells of the pancreas in response to increasing glucose levels. Insulin, in turn, allows glucose to enter insulin-responsive cells where it is metabolized to produce energy. Insulin also plays an important role in fat and protein metabolism.

Type 1 diabetes accounts for about 10% of diabetes, and involves an absolute insulin deficiency brought about by an autoimmune attack on the β-cells. The decreasing level of circulating insulin leads to hyperglycemia and symptoms of the disease. Although type 1 diabetes can develop in individuals at any age, it is most common in people under 30 years of age. Patients with type 1 diabetes have an absolute requirement for insulin, without which uncontrolled hyperglycemia and ketoacidosis will occur, ultimately leading to death[1-2].

Type 2 diabetes represents about 90% of all known diabetes, and is characterized by peripheral insulin resistance (insulin use is less efficient because cells lose some of the ability to respond to insulin) and relative insulin deficiency. If enough insulin is produced, even in the face of insulin resistance, glucose levels remain normal. However, type 2 diabetes is a progressive disorder that ultimately leads to decreased β-cell function and relative insulin deficiency[2]. As a consequence, early in type 2 diabetes there is a state of relative insulin deficiency; insulin levels are high but not high enough to compensate for the degree of insulin resistance. Glucose uptake by tissues such as muscle and fat is impaired as is insulin's ability to suppress glucose production by the liver[2].

Subsequent information provided in this letter focuses on type 2 diabetes, as it is far more prevalent than type 1[3].

EPIDEMIOLOGY AND RISK FACTORS

Diabetes is a significant and growing health concern. In the United States, an estimated 15.7 million people have diabetes[3]. Studying a large sample of American adults in the late 1980's and early 1990's, Harris and colleagues estimated diabetes prevalence of 7.8% and over a third of these individuals were unaware that they had diabetes[4]. Five to 10% of those with diabetes are type 1 diabetics, while type 2 diabetes represents 90 to 95% of this population. Approximately 798,000 new cases of diabetes are diagnosed each year[3]. By 2025, the total number of American adults with diabetes is estimated to reach 21.9 million, with an estimate of 300 million adults worldwide[5]. Based on trends in American lifestyles, the increasing rate of diabetes is not expected soon to abate[6].

Risk factors for developing type 1 diabetes include genetic predisposition (siblings or children of patients with type 1 diabetes are at greatest risk for the disease) and the environment, where exposure to certain viruses may precipitate an autoimmune response that ultimately destroys the pancreatic β-cells. As with type 1 diabetes, the precise cause of type 2 diabetes is unknown. However, several major risk factors for developing type 2 diabetes have been identified and are presented below (Table 1). The risk for type 2 diabetes increases significantly with age. Nearly 18.4% of the United States' population, or 6.3 million people, age 65 and older have diabetes. Weight gain, duration of obesity, and truncal distribution of obesity contribute to increased risk for diabetes. Sedentary lifestyle with chronic lack of physical activity also predisposes to type 2 diabetes.

Presence of these risk factors increases the likelihood that a patient may develop diabetes. The more risk factors present, the greater the probability that diabetes may occur. Reducing risk factors may delay the onset of diabetes[7,8].

TABLE 1. Major risk factors for type 2 diabetes[3,9]

Parent or sibling with diabetes
Obesity (BMI ≥27kg/m^2)
Ethnicity (African-American, Hispanic-American, Native-American, Asian-American, and Pacific Islander)
History of impaired fasting glucose or impaired glucose tolerance
Hypertension (adult blood pressure ≥140/90 mmHg)
Triglyceride level ≥250 mg/dL (2.82 mmol/L) and/or
HDL cholesterol ≤35 mg/dL (0.90 mmol/L)
History of gestational diabetes or delivery of a baby weighing >9 lbs
Polycystic ovary syndrome

TYPE 2 DIABETES AND PSYCHIATRIC DISORDERS

Recent data indicate that patients with certain mental illnesses (at least schizophrenia and possibly bipolar disorder) have a substantially higher prevalence of type 2 diabetes mellitus than in the general population. Although the degree of excess diabetes varies, in every available report the prevalence of diabetes was higher in psychiatric cohorts than the non-mentally ill reference groups[10-14]. Thus, diabetes is not only of great concern in the general population; it potentially represents an even more prevalent health concern for patients with mental illness.

Since the mid-1950's, psychotropic drugs, including antipsychotics, have been reported to be associated with hyperglycemia[15]. The nature of the relationship between mental illnesses, psychotropic treatment, and impaired glucose tolerance or diabetes remains unclear. Based on available data, those factors associated with higher risk of diabetes in the general population (e.g., genetic predisposition, advanced age) appear to increase the relative risk of diabetes within the psychiatric population as well. Though perhaps not well established, some risk factors such as obesity and sedentary life style may be more prevalent within psychiatric cohorts than in the general population. As in the general population, screening for risk factors may assist clinicians in determining which individuals may be at heightened risk for diabetes.

DIAGNOSIS

Signs and Symptoms

Only about half of patients with type 2 diabetes have been diagnosed. Thus, in its earliest stages of increasing hyperglycemia, people are unaware they have the disease. With this insidious onset of diabetes, the diagnosis may be delayed an average of 4 to 12 years[4]. Unfortunately, at the time the diagnosis is made about 50% of patients already have diabetes complications[16]. As hyperglycemia gradually worsens, some or all of the classic symptoms of diabetes may appear (Table 2).

TABLE 2. Prominent symptoms of type 2 diabetes mellitus[3]

- Feeling tired
- Increased hunger
- Increased thirst
- Increased urination
- Slow healing of cuts and wounds
- Unexplained weight loss
- Frequent infections
- Problems with sexual function
- Blurred vision
- Dry itchy skin
- Numbness or tingling in hands or feet

The American Diabetes Association (ADA) recommends that screening for diabetes in symptomatic individuals begin at age 45 and be repeated every 3 years. Those with risk factors should be screened sooner and more frequently than every 3 years. Other groups suggest even more aggressive screening for diabetes. The current guidelines from the American Association of Clinical Endocrinologists (AACE) suggest that patients with any risk factors should be screened beginning at age 30[3]. No available guidelines specifically address screening in psychiatrically ill patients. With the observations cited above that serious mental illness may be a diabetes risk factor, interpreting the ADA and AACE guidelines suggests screening should begin before age 45, quite possibly as soon as Age 30.

Currently, the screening test that the ADA recommends is a fasting plasma glucose. It has potential advantages over oral glucose tolerance testing because the former is easier, faster, more convenient, more acceptable to patients, and less expensive. However, when the fasting plasma glucose suggests borderline abnormality, e.g., >110 mg/dL but <126 mg/dL, an oral glucose tolerance may clarify the diagnosis[9]. Glycosylated hemoglobin (HbA_{1c}) levels are useful for monitoring the long-term control of diagnosed diabetes but are not recommended for screening or for the diagnosis of diabetes.

DIAGNOSTIC CRITERIA

According to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus in 2001[17], a diagnosis can be made when any one of the following three methods is used and confirmed on a subsequent day:

1. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.

OR

2. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal.

OR

3. Two-hour posts load plasma glucose ≥200 mg/dL during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

These diagnostic criteria are supported by the ADA[9]. Signs and symptoms of diabetes, especially in patients with risk factors, should prompt testing to determine if the disease is present[3]. In addition to the above diagnostic criteria, the ADA has recommended in the past that patients with random blood glucose levels above 160 mg/dL should be formally screened for potential diabetes. More recently, the ADA has noted that a postprandial glucose level rarely exceeds 140 mg/dL in non-diabetic individuals[18].

DISEASE COURSE AND OUTCOMES

Diabetes is an important contributor to mortality and disability[3].

Acute Complications

Acute complications in type 2 diabetes are uncommon, but include diabetic ketoacidosis (DKA) and hyperglycemic, hyperosmolar nonketotic syndrome (HHNS). DKA is far more common in type 1 patients but may be observed in type 2 diabetes. Even when type 2 diabetes presents with DKA, it may stabilize, such that subsequently a patient may maintain adequate glucose control without pharmacotherapy for months or longer. Hyperglycemic hyperosmolar non-ketotic state is generally seen in type 2 rather than type 1 diabetes. Timely detection and effective treatment of type 2 diabetes can forestall these acute complications.

DKA results from insulin deficiency. Although in type 2 though there may be substantial insulin produced, it may be insufficient to prevent DKA in some circumstances, such as non-compliance with antidiabetic treatment, infection, myocardial infarct, cerebrovascular accident, acute pancreatitis, and so forth. Clinically, patients in DKA often show prodromal symptoms in the hours to days preceding the diagnosis of DKA. The patient may present with lethargy, hyperventilation (Kussmaul respirations), fruity odor to the breath (from acetonemia), nausea and vomiting, abdominal pain, thirst, and polyuria or (if already dehydrated) decreased urine output, dry mucus membranes, poor skin turgor, and tachycardia. Presence of urine ketone, serum ketones, lowered arterial pH, and/or lowered serum bicarbonate levels are diagnostic for DKA (Table 3).

Diabetic ketoacidosis can be life threatening with mortality estimated to be 3 to 10%[19]. There have been a number of reports of DKA in psychiatric patients[20-25]. Though reported information tends to be incomplete, several features suggest that some or many of these cases involved type 2 diabetes (e.g., high glucose at presentation, prominent risk factors for type 2 diabetes, resolution without need for continuous insulin treatment).

Compared to type 2 patients with DKA, those with HHNS tend to be older, have a longer symptomatic period, and have much higher glucose levels. Typical patients with HHNS have difficulty caring for themselves, especially an impaired ability to consume fluids to offset losses due to polyuria. Clinically these patients display dehydration, neurological depression, and absence of marked ketosis[2]. Because HHNS has an insidious onset, it may be misdiagnosed initially and be confused with starvation ketosis or lactic acidosis[19].

TABLE 3: Selected laboratory findings in DKA and HHNS[26]

	DKA	HHNS
Plasma glucose (mg/dL)	>250	>600
Arterial pH	<7.30	>7.30
Serum Ketones	Positive at >1:2 dilution	Negative or small
Urine Ketones	At least 3+ positive	Negative or small
Serum osmolality (mOsm/kg)	Variable	>320

Long Term Complications

Diabetes can result in a number of long-term complications. These complications are classified as microvascular and macrovascular. Microvascular complications include retinopathy, nephropathy, and neuropathy. Macrovascular complications include cardiovascular disease and stroke. Compared to non-diabetic individuals, people with diabetes have a two- to four-fold increased risk of stroke and/or cardiovascular death. Smoking, hypertension, sedentary lifestyle, and dyslipidemia increase the morbidity and mortality associated with diabetes[15]. Smoking heightens the risk of macro and microvascular complications of diabetes[27]. Adequate control of blood pressure reduces progression of nephropathy and cardiovascular disease. Additionally, both diabetes and dyslipidemia are risks for developing atherosclerotic vascular disease[28].

MANAGEMENT STRATEGIES

The ADA recommends a team approach to managing diabetes. This team should include physicians (including a podiatrist and ophthalmologist or optometrist), nutritionists, pharmacists, and nurses with expertise in diabetes care. This physician-coordinated team should set treatment goals, assess quality of therapy, and define referral patterns to appropriate specialists[16]. While no specific recommendations have been formulated for psychiatric patients with diabetes, it is reasonable to anticipate that management strategies applicable to the general population will be useful. Therefore, psychiatric patients can benefit from a broad-based approach to their general health that includes referral to a diabetes management team, in addition to their ongoing psychiatric treatment.

Non-Pharmacologic Strategies

Persistent hyperglycemia is the hallmark of poorly controlled diabetes, and glycemic control is the main focus of management goals[19]. In both type 1 and type 2 diabetes, many of the complications are a result of hyperglycemia. The Diabetes Control and Complications Trial (DCCT) in type 1 subjects, and the UKPDS in type 2 patients showed that controlling hyperglycemia delayed or prevented microvascular disease. Thus, it is believed that keeping glucose levels as close to normal as possible is the best defense against complications related to hyperglycemia. Suggested goals are 80 to 120 mg/dL before meals, and 100 to 140 mg/dL at bedtime; however, these goals may vary with individual needs[1,19]. Meal planning, weight loss, and exercising are occasionally sufficient to control blood glucose levels for patients with type 2 diabetes and are considered first line treatment[1,28]. However, these measures may not be enough to control hyperglycemia over time.

Pharmacologic Strategies

The next step, in addition to these life-style changes, is the initiation of pharmacologic therapy. Monotherapy with an oral agent is usually considered the first pharmacologic step; however, for some patients initiation of insulin may be considered an alternative. In the United States, oral anti-diabetic medications fall into the following classes: sulfonylureas, biguanides, meglitinides, α-glucosidase inhibitors, and thiazolidinediones[29,30]. Listed below are the oral anti-diabetic agents currently available in the United States (Table 4).

TABLE 4. Oral anti-diabetic agents currently available in the United States[29,30]

Drug Class	Brand Name	Generic Name
Sulfonylureas	Amaryl®	glimepiride
	DiaBeta®	glyburide
	Diabinese®	chlorpropamide
	Glucotrol®	glipizide
	Glucotrol XL®	glipizide
	Glynase® PresTab®	glyburide (micronized)
	Micronase®	glyburide
	Orinase®	tolbutamide
	Tolinase®	tolazimide
	Dymelor®	acetohexamide
Biguanides	Glucophage®	metformin
	Glucophage®XR	metformin
Meglitinides	Prandin®	repaglinide
	Starlix®	nateglinide
α-glucosidase inhibitors	Glyset™	miglitol
	Precose®	acarbose
Thiazolidinediones	Actos®	pioglitazone
	Avandia®	rosiglitazone
Combination	Glucovance®	glyburide/metformin

Sulfonylureas principally act by stimulating the insulin secretion from β-cells. Agents in the meglitinide class also act by stimulating insulin secretion, but do so more quickly than sulfonylureas. Biguanides act primarily by reducing hepatic glucose output, but also have been shown to reduce intestinal glucose absorption and increase insulin sensitivity in peripheral tissues. Alpha-glucosidase inhibitors delay the absorbtion of glucose in the intestine by inhibiting the breakdown of complex carbohydrates. Thiazolidinediones exert their effect by increasing insulin sensitivity in peripheral tissues and by reducing hepatic glucose production[15,31].

Patient characteristics, side effect profiles of each agent, as well as effects on blood pressure and lipids should be considered when selecting the appropriate therapy. Due to the different mechanisms by which these agents act, combination therapy should be considered when blood glucose levels are not adequately controlled[15,29,30].

At the point when oral agents no longer sufficiently control glucose levels, insulin should be added to the regimen. Insulin may be used alone or along with oral agent(s). Insulins are grouped according to their time-action profile, which define their onset, peak and duration of action. A comparison of the pharmacokinetics of various biosynthetic human

insulin products is available below (Table 5). The goal of insulin treatment is to replace insulin levels in a way that best matches normal physiology. Thus, the choice of insulin formulations, the injection timing, and the variable dosing required must be tailored to the individual patient[17].

TABLE 5. Time-action profiles of various human insulins[17,32]

Classification	Type of Insulin	Onset (hrs)	Peak (hrs)	Effective Duration (hrs)
Rapid acting	Lispro	0.25	0.5-1.5	2-4
Short acting	Regular	0.5-1	2-3	4-6
Intermediate acting	NPH	2-4	4-10	10-16
	Lente	3-4	4-12	12-18
Long acting	Ultralente	6-10	minimal	20-24
	Glargine	1-2	minimal	20-24

Patient Monitoring

One of the most important advances in diabetes treatment was the introduction of home blood glucose monitoring in the early 1980s. With that technology, comprised of finger-stick glucose measurements several times each day, patients became capable of more closely controlling their blood glucose levels by adjusting insulin dosing, meal patterns or physical activities. Like all aspects of diabetes care, the frequency of home glucose measurements should be individualized. Glycosylated hemoglobin (HbA_{1c}) levels are useful for monitoring the long-term control of diabetes. The HbA_{1c} is a measure of the relative amount of glucose attached to hemoglobin and reflects overall glucose levels during the preceding 2 to 3 months. It is recommended that HbA_1 be measured every 3 months. HbA_{1c} levels <7% is generally the goal of therapy although the specific therapeutic goal must be individualized[28].

In addition to controlling blood glucose levels, modifying other risk factors can decrease long-term effects of diabetes. Smoking cessation should be encouraged; as the cardiovascular burden of smoking, especially in combination with diabetes, heightens the risk of macrovascular complications, leading to morbidity and premature death. Hypertension should be controlled through lifestyle changes, or pharmacologic agents when appropriate. The primary goal of anti-hypertensive therapy for adults is to decrease blood pressure to below 140/90 mmHg. Modifying lifestyle or using pharmacologic agents when necessary should also address Dyslipidemia. The current primary goal for adults with diabetes is to lower LDL cholesterol to <100 mg/dL, and to lower triglyceride levels to <150 mg/dL[14]. A secondary goal is to raise HDL cholesterol to >45 mg/dL in men and >55 mg/dL in women[27,28].

CONCLUSION

Diabetes is a chronic, complex disease that affects millions of people nationwide, resulting in considerable morbidity and mortality. It is important for health care practitioners to know which patients may be at risk for developing diabetes and to know the symptoms of the disease. Patients with severe psychiatric illness appear to be at particular risk for diabetes. Screening for diabetes is now recommended for all adult Americans, which

allows for earlier detection and appropriate treatment that will ultimately decrease long-term complications of the disease. Diabetes is best managed through a team approach that addresses all aspects of diabetes care. Managing diabetes should be highly individualized, with particular focus on modifying lifestyle and appropriately using pharmacologic agents, including insulin. By controlling glucose levels, blood pressure, and abnormal lipid profiles, patients with diabetes can reduce their risk of long-term complications of this disease.

ZYPREXA, olanzapine, Lilly

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Treatment-Emergent Diabetes Clinical Trial Analysis

Risk Factors for Treatment Emergent Glucose Abnormalities in Schizophrenic Patients

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Schizophrenia is associated with an increased burden of diabetes mellitus. Reasons for this association remain uncertain. The objective of this analysis was to characterize risk factors for diabetes in individuals with schizophrenia.

We retrospectively examined a large database pooled from multiple randomized, double-blind clinical trials of antipsychotic medications for the treatment of patients with schizophrenia..

Subject demographics and the following risk factors for diabetes (age ≥ 45 years, body mass index (BMI) of ≥ 27 kg/m^2, use of anti-hypertensive medications, non-caucasian ethnic background, and evidence of abnormal glucose tolerance) were assessed in 5013 non-diabetic subjects (olanzapine n=3068, haloperidol n=1164, risperidone n=364, clozapine n=211 or placebo n=206). Family history of diabetes and specific lipid profiles were not available for evaluation.

Random glucose values obtained during the observation period (205 ± 283 days; range 3 to 1775 days) were used to identify subjects with treatment emergent diabetes (TED, two random glucose values ≥ 200 mg/dl at any time during the observation period, final glucose ≥ 200 mg/dl, clinical diagnosis of diabetes, or initiation of anti-diabetic medications). Individuals without repeated glucose values ≥ 140 mg/dl were were considered to have normal glucose tolerance (NGT).

Comparing entry characteristics, patients in the TED cohort (n=94) were substantially older (44 vs. 37 years), more obese (BMI 31.5 vs. 25.8 kg/m^2), and had higher mean non-fasting glucose levels (127 vs. 94 mg/dl) than the NGT cohort (n=4637). In addition, the TED cohort was enriched with non-Caucasian patients (38 vs. 27%) and patients with hypertension (23 vs. 9%). At entry into the clinical trials, only 9.6% of the TED cohort was without identifiable risk factors for diabetes compared to 39% for the NGT cohort. The TED cohort was also enriched in subjects with multiple risk factors for diabetes; 25% vs. 5% with ≥ 3 risk factors in the TED and NGT the groups, respectively.

Conclusions: Risk factors for diabetes in patients with schizophrenia overlap those of the general population. Physicians should use this information when assessing individual patient risk and prospectively considering diabetes screening programs and preventative interventions.