Appendix 2, Vol 1

Review of Commercially Marketed (Spontaneous) Olanzapine Hyperglycemic Adverse Event Reports

Eli Lilly and Company (August 1999)

Table of Contents

1 Introduction 3
1.1 Purpose/Scope/Rationale 3
1.2 Executive summary 3
2 Methods 4
2.1 Overview/Background 4
2.2 Literature Review 4
2.3 Process of Report Finding in Clintrace 4
2.4 Definitions/Conventions 5
3 Reports of (*Spontaneous)* Hyperglycemia Adverse Events Associated with Commercially Marketed Olanzapine 8
4 Discussion 26
5 Comparative Assessment 28
5.1 Background 28
5.1.1 Introduction 28
5.2 Commercially Marketed Olanzapine Experience vs. Risperidone 28
6 Summary 30
7 References 31

1 Introduction

1.1 Purpose/Scope/Rationale

In response to a query from the Health Canada Health Protection Branch (HPB), a review was undertaken of all spontaneous information potentially relating to hyperglycemia for patients treated with olanzapine. It is important to mention that the reporting of hyperglycemia does not imply a causal relationship.

1.2 Executive summary

Antipsychotics have been reported to be associated with hyperglycemia since the mid-1950s. There has been a resurgence of interest in this phenomena since the wider use of clozapine in North America. With cases of hyperglycemia reported in temporal association with olanzapine some cases have the clinical characteristics consistent with presentations expected with Type II diabetes while others have clinical characteristics consistent with presentations expected with Type I diabetes. A majority of cases are confounded by a frank history of diabetes and/or risk factors for diabetes. The estimated incidence for only the single event term "Diabetic Ketoacidosis: associated with olanzapine clearly exceeds that with risperidone. The estimated incidence of all the various potential manifestations of diabetes associated with olanzapine does not clearly exceed similar estimated incidence figures with risperidone.

2 Methods

2.1 Overview/Background

2.2 Literature Review

A review of the literature with regards to schizophrenia and diabetes was undertaken. The results of this review are included in Appendix 2, Volume 2

2.3 Process of Report Finding in Clintrace

The adverse event reporting database, Clintrace, was searched on July 16, 1999 for all spontaneous olanzapine adverse event reports entered into Clintrace from September 29, 1996 through September 30, 1998 that contain one or more of the following COSTART (the Coding Symbol and Thesaurus for Adverse Reaction Terms) terms: ACIDOSIS, DIABETES MELLITUS, DIABETIC ACIDOSIS, DIABETIC COMA, GLUCOSE TOLERANCE DECREASED, GLYCOSURIA, HYPERGLYCEMIA, KETOSIS, and/or LACTIC ACIDOSIS. A total of 197 reports were identified utilizing this search.

Clintrace is a computerized system established by Eli Lilly and Company in 1998 to replace the Drug Experience Network created in 1983 for the world-wide collection, storage, and reporting of adverse events involving Lilly products. Clintrace includes clinical trial events described as "serious" according to the United States Food and Drug Administration (FDA) regulations as well as serious and nonserious events reported spontaneously from postmarketing experience (including scientific literature and media reports). By FDA regulations "serious" refers to any adverse event that results in death, is permanently or severely disabling, requires or prolongs inpatient hospitalization, results in congenital anomaly, is life-threatening or is significant for any other reasons. The coding of events entered in Clintrace is based on the Coding Symbol and Thesaurus for Adverse Reaction Terms (COSTART) dictionary. It should be noted that a causal relationship between a reported adverse event and a particular drug(s) cannot be established with certainty. In addition, the accumulated case reports cannot be used to calculate the event incidence.

2.4 Definitions/Conventions

Table 2.4.1. Definitions/Conventions Used In Review of Clintrace Cases

Case ID/Mfg#	**The unique identification number for a spontaneous report that is assigned by the manufacturer.**
Sex	m = male, f = female, u = unknown
Race	w = White/Caucasian, b = Black, as = Asian, h = Hispanic, m = Multiracial, na = Native American, u = Unknown, other
Age	The age of the patient at the time of the event.
Concomitant Drugs/Prescription Medications as symptoms developed	All concomitant systemic medication that the patient was taking at the time of the event or within 24 hours preceding the onset of the event. If the report is unclear about the time frame a particular drug was taken, then this is denoted in brackets. All medications are listed by generic name.
COSTART Terms	COSTART term
On olanzapine at time of symptom onset and/or beginning of event?/Duration	y = yes, on olanzapine n = no, not on olanzapine u = unknown
Duration	The period of time the patient was on olanzapine up to the date of the onset of symptoms and/or beginning of event; reported by days, weeks, months, years. U = unknown – Examples: y/6 weeks; y/u; u; n [information about when olanzapine was discontinued in relation to event]
Known to have DM at time of adverse event?	Y = yes, n = no, u = unknown In order to enter y in this category, the record must be clear that the patient was known to have pre-existing current diabetes mellitus at the time of the adverse event on olanzapine. This judgment is based on text and concomitant medication history. In order to enter n in this category it must be clearly stated in the record that patient had no history of diabetes mellitus.
Prior Hyperglycemia/DM; Type or Tx	y = yes, n = no, u = unknown Type 1; Type 2; gestational; hyperglycemia; while on [medication], insulin dependent; diet controlled. The entries in this category are based upon text and/or laboratory data indicating prior hyperglycemia or diabetes mellitus.
Family Hx DM	y = yes, n = no, u = unknown A family history of diabetes mellitus as reported in the text is coded y in this category. The degree of relatedness was not considered.
Obesity/BMI or Wt	y = yes, n = no, u = unknown Obesity was defined as a BMI > 27.8 kg/m^2 for males and > 27.3 kg/m^2 for females; or > 120% of desirable body weight (when that measurement was listed in the text). BMI's were calculated and recorded for all patients when height was not listed. The patient was listed as obese if so indicated in the text even if height and/or weight were not reported. On a few occasions the patient was listed as obese based solely on the body weight. BMI reported as kg/m^2 and weight reported in kg.
Weight gain while on olanzapine	y = yes, n = no, u = unknown If yes; the amount of reported weight gain is listed in kg if known. This category reports weight gain while on olanzapine irrespective of the presence or absence of obesity.
Alcohol abuse/-ism; (active/acute or by hx)	y = yes, n = no, u = unknown If yes; the status of alcohol usage is reported if known.

Table 2.4.1. Definitions/Conventions Used In Review of Clintrace Cases (concluded)

Pancreatitis or other pancreatic dysfunction; (acute, chronic or by hx)	y = yes, n = no, u = unknown If yes; the type or status is reported if known.
Taking drug(s) reported to elevate glucose/cause DM	Name drug(s) n = none, u = unknown All drugs taken by the patient (listed in the concomitant drugs/prescription medication section of the Hyperglycemia/Diabetes Mellitus Table) were checked against a list of drugs reported to be associated with: Hyperglycemia; Diabetes Mellitus; Diabetes Mellitus, increase; Diabetes Mellitus, precipitation of latent; Diabetic Acidosis; and Diabetic Ketoacidosis. Drugs were selected for entry into this category based on their inclusion on the list. The incidence data of the above reported adverse effects were not considered as a criteria for selection.
Peak Glucose Level at Time of Adverse Event	The highest reported glucose levels (reported as mg/dl) as well as clinical presentation are used for selection in this category. a. Glucose > 126 to < 300 mg/dl without acute hospitalization or acidosis. May already be in hospital for other reason when glucose level measured.
	b. Glucose > 300 to < 600 mg/dl without acute hospitalization or acidosis. May already be in hospital for other reason when glucose level measured.
	c. Glucose > 600 mg/dl and/or acute/severe hyperglycemic presentation with hospital/ICU admission and/or acidosis. If the category can be determined, a y is entered in the appropriate cell, followed by the glucose level [eg. y; 697] or u if unknown [eg. y; u]. If no glucose level or definitive information about clinical presentation is available, a u is entered in all 3 cells.
Therapy	d = diet, o = oral hypoglycemic agent, i = insulin, n = none, u = unknown. The therapy of the hyperglycemia/DM/DKA is reported when known.
Outcome of Hyperglycemia/DM; olanzapine status; Therapy status	The outcome of the event is described as far as follow-up data allows. Outcomes: Resolved, Improved, Plateaued, Deteriorated, Not resolved, Unknown, Death.
Outcome of Hyperglycemia/DM; Olanzapine status; Therapy status	The outcome of the event is described as far as follow-up data allows. Outcomes: Resolved, Improved, Plateaued, Deteriorated, Not resolved, Unknown, Death. If the patient was a known diabetic with stable blood sugars on insulin or an oral agent prior to the event and returns to the pre-event status then the event can be considered resolved even though the patient still has diabetes. In addition to the outcome, the patient's olanzapine status is indicated if known; on olanzapine, off olanzapine, rechallenge information. The therapy status at the time of outcome determination is also listed if known; on insulin, off insulin, on oral agent(s), off oral agent(s) etc.

Table 2.4.2. Methodology Used In Determination of Outcome

Outcome Examples	Text Examples
Resolved	Resolved; Recovered; Returned to normal; Abated; [lab results show normal values]
Improved	Improved; Stabilized; Recovering; [lab results show improvement but not yet normal]
Plateaued	Stable; Unchanged; Remain at xx level
Deteriorated	Deteriorated; Continued to drop; Downhill course; [lab results show deterioration]
Not resolved	Not resolved; Not recovered; [this category is for cases where definitive information is lacking]
Unknown	Report specifically states that outcome is unknown or that further information not available
Death	Death

Table 2.4.3. Concomitant Drugs Reported To Be Associated With: Hyperglycemia; Diabetes Mellitus; Diabetes Mellitus, Increase; Diabetes Mellitus, Precipitation Of Latent; Diabetic Acidosis, Diabetic Ketoacidosis

Acebutolol	Levothyroxine sodium
Amiodarone hydrochloride	Lisinopril
Amitriptyline	Lithium
Atenolol	Methylprednisolone
Atorvastatin	Metoprolol
Bumetanide	Mirtazapine
Chlordiazepoxide	Nadolol
Chlorpromazine	Naproxen sodium
Chlorprothixene hydrochloride	Nifedipine
Cisapride	Norethindrone/ethinyl estradiol
Clonidine	Paroxetine hydrochloride
Clozapine	Perphenazine
Doxepin	Phenytoin sodium
Droperidol	Progesterone
Enalapril Maleate	Propranolol
Estrogen	Protriptyline hydrochloride
Fludrocortisone acetate	Pseudoephedrine
Fluoxetine hydrochloride	Risperidone
Fluvoxamine	Salbutamol (Albuterol)
Furosemide	Sertraline hydrochloride
Haloperidol	Thiothixene
Heparin	Thyroid
Hydrochlorothiazide with Triamterene	Triamterene
Imipramine	Trifluoperazine hydrochloride
Indapamide	Venlafaxine hydrochloride
Labetalol	Verapamil
Lamivudine	Zolpidem
Lamotrigine	

3 Reports of (*Spontaneous*) Hyperglycemia Adverse Events Associated with Commercially Marketed Olanzapine

4 Discussion

As can be seen from Table 4.1. below 117 patients presented with a glucose of <600 mg/dl without hospitalization or acidosis or an unknown glucose but still without hospitalization or acidosis. Of these 117 patients 59 had definitive history of diabetes. In addition, of these 117, 70 had definitive risk factors for diabetes and risk factor status was unknown for the remaining 47. In other words, over half of these patients were known diabetics and none could be clearly identified as not having risk factors for diabetes.

There were 73 patients who presented with a glucose >600 mg/dl or were hospitalized or were acidotic. Here only 12 were known diabetics (although the diabetic status of 33 was not reported). However, 60 of these 73 patients with more severe presentations had known risk factors for diabetes and none were definitely without risk factors. Given these data it is difficult to conclude safely on the basis of the data, that olanzapine was the etiology for these patients' hyperglycemia.

Table 4.1. Presentation Groups: Summary of All Clinical Characteristics at Time of Adverse Event

	Group "a."			Group "b."			Group "c."			Group "u."			Group "n"			Group "other"		
	a. >126 to <300 mg/dl without acute hospitalization or acidosis			b. >=300 to < 600 mg/dl without acute hospitalization or acidosis			c. > 600 mg/dl and/or severe hyperglycemic presentation with hospital / ICU admission and/or acidosis			Unknown peak glucose			No mention of hyperglycemia as adverse event			Elevated baseline but no glucose > 126 @ time of AE		
	Known to have DM or elevated glucose @ time of adverse event onset AND/OR Hx of Prior Hyperglycemia or DM			Known to have DM or elevated glucose @ time of adverse event onset AND/OR Hx of Prior Hyperglycemia or DM			Known to have DM or elevated glucose @ time of adverse event onset AND/OR Hx of Prior Hyperglycemia or DM			Known to have DM or elevated glucose @ time of adverse event onset AND/OR Hx of Prior Hyperglycemia or DM			Known to have DM or elevated glucose @ time of adverse event onset AND/OR Hx of Prior Hyperglycemia or DM			Known to have DM or elevated glucose @ time of adverse event onset AND/OR Hx of Prior Hyperglycemia or DM		
	Yes	**No**	**Unk**	**Yes**	**No**	**Unk**	**Yes**	**No**	**Unk**	**Yes**	**No**	**Unk**	**Yes**	**No**	**Unk**	**Yes**	**No**	**Unk**
	12	2	9	27	5	15	12	28	33	20	3	24	0	0	6	1	0	0
Additional Risk Factor(s): Family history DM, Obesity, Weight gain while on olanzapine, Alcohol abuse/ -ism, Pancreatitis or other pancreatic dysfunction, and/or Taking Drugs known to elevate glucose																		
Yes	8	0	8	16	5	9	12	24	24	8	2	14	0	0	5	1	0	0
No	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unk	4	2	1	11	0	6	0	4	9	12	1	10	0	0	1	0	0	0

5 Comparative Assessment

5.1 Background

5.1.1 Introduction

In order to put the material in proper context, it is necessary to compare the olanzapine spontaneous adverse event experience with another relevant database. Therefore, individual and pooled hyperglycemia events in the olanzapine FDA adverse event database was compared to the risperidone FDA adverse event database.

5.2 Commercially Marketed Olanzapine Experience vs. Risperidone

For general comparative purposes, the risperidone spontaneous adverse event database held at the U.S. Food and Drug Administration was obtained under the Freedom of information Act (FOI). Risperidone represents an excellent candidate for comparison because it is distinct in chemical structure, is in the same therapeutic class and has been approved for marketing quite recently. The database was current for reports received through June 1998. For olanzapine, reports through June 1998 were considered and for risperidone, reports through April 1998 were considered. This results in using one month of reporting data past the month in which the last periodic reporting data was available from the FDA for both drugs. The cumulative new patients treated with risperidone were then estimated by the same vendor, using a comparable proprietary algorithm, that provides the estimates of patients treated with olanzapine (see Section 4.1.2.). Risperidone new patient exposures since launch were estimated to be 2,041,000 through April 1998 and new patient exposures for olanzapine were estimated at 1,581,000 through June 1998.

As detailed clinical information was not available to assess individual cases in the risperidone database and as that database may be subject to duplication of reports on the same patient, a comparison was made of the incidence of all unique reports (as opposed to unique cases/patients) where a MedDRA Preferred Term suggested hyperglycemia. *All unique* MedDRA terms for olanzapine and risperidone were first reviewed. The following MedDRA terms potentially suggestive of hyperglycemia were identified: DIABETIC COMA NOS, DIABETIC KETOACIDOSIS, KETOACIDOSIS, METABOLIC ACIDOSIS NOS, ACIDOSIS NOS, INSULIN RESISTANCE, DIABETES MELLITUS NOS, DIABETES MELLITUS INSULIN-DEPENDENT, DIABETES MELLITUS NON INSULIN-DEPENDENT, DIABETES MELLITUS AGGRAVATED, DIABETES MELLITUS INADEQUATE CONTROL, GESTATIONAL DIABETES, HYPERGLYCAEMIA NOS, BLOOD GLUCOSE INCREASED, GLUCOSE TOLERANCE DECREASED, GLYCOSURIA PRESENT,

and KETONURIA PRESENT. Unique reports (not unique cases/patients) were then identified.

A comparison of the incidence of all identified reports by hierarchy of MedDRA terms are displayed below in Table 1.

Except for the single event term "Diabetic Ketoacidosis", the estimated reporting incidence for individual events and total events with olanzpaine does not clearly exceed the incidence seen with risperidone.

Table 5.1. Estimated Reporting Incidence per 100,000 Patients for Terms Potentially Suggestive of Hyperglycemia

	Olanzapine Incidence per 100,000	Risperidone Incidence per 100,000
Diabetic Coma NOS	1.265	0.490
Diabetic Ketoacidosis	12.018	0.490
Ketoacidosis	6.325	7.349
Metabolic Acidosis NOS	0.000	0.490
Acidosis NOS	1.898	1.960
Insulin Resistance	0.633	0.000
Diabetes Mellitus NOS	11.385	18.618
Diabetes Mellitus Insulin-Dependent	1.265	0.980
Diabetes Mellitus Non Insulin-Dependent	0.633	0.000
Diabetes Mellitus Aggravated	0.633	1.470
Diabetes Mellitus Inadequate Control	0.000	0.490
Gestational Diabetes	0.633	0.000
Hyperglycaemia NOS	46.806	36.747
Blood Glucose Increased	6.958	0.980
Glucose Tolerance Decreased	0.000	1.470
Glycosuria Present	0.000	0.490
Ketonuria Present	0.000	1.470
Totals	**90.449**	**73.493**

Olanzapine has estimated 1,581,000 patient exposures through June 1998.
Risperidone has estimated 2,041,000 patient exposures through April 1998.

ZY 1971 1513

6 Summary

Antipsychotics have been reported to be associated with hyperglycemia since the mid-1950s. There has been a resurgence of interest in this phenomena since the wider use of clozapine in North America. With cases of hyperglycemia reported in temporal association with olanzapine some cases have the clinical characteristics consistent with presentations expected with Type II diabetes while others have clinical characteristics consistent with presentations expected with Type I diabetes. A majority of cases are confounded by a frank history of diabetes and/or risk factors for diabetes. The estimated incidence for only the single event term "Diabetic Ketoacidosis: associated with olanzapine clearly exceeds that with risperidone. The estimated incidence of all the various potential manifestations of diabetes associated with olanzapine does not clearly exceed similar estimated incidence figures with risperidone.

7 References

DuFour DR. Clinical Use of Laboratory Data: A Practical Guide. Philadelphia: Williams & Wilkins; 1998:21, 24, 85-97, 452-453, 479, 494-495, 500.

Mayfield J. Diagnosis and Classification of Diabetes Mellitus: New Criteria. *American Family Physician.* 1998 (October 15);58(6):1355-1362.

Peters AL and Schriger DL. The New Diagnostic Criteria for Diabetes: The Impact on Management of Diabetes and Macrovascular Risk Factors. *The American Journal of Medicine.* 1998 (July 6);105(1A):15S-19S.

Objective:

1. Identify the distribution of the duration of olanzapine therapy at time of diagnosis of hyperglycemia

2. Determination of the mean, median, and range of the duration of olanzapine therapy at time of diagnosis of hyperglycemia

3. Determine whether the probability of positive dechallenge was lower if the duration of olanzapine therapy was greater than 2 months as compared to that of less than 2 months

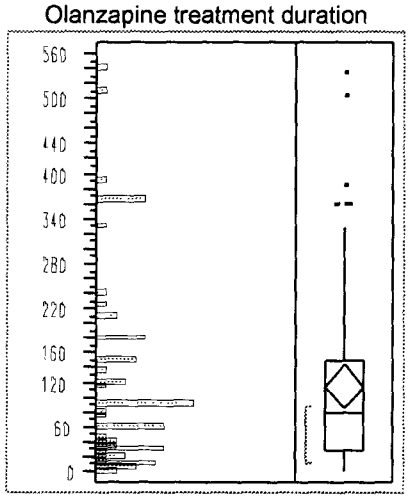
METHODS

1. The file HPB glucose-2 was used as basis of the following analysis
2. Patients with history of hyperglycemia prior to the initiation of olanzapine therapy were excluded from analysis
3. For the purpose of this analysis only, positive dechallenge is defined as resolution of hyperglycemia upon the discontinuation of olanzapine in the absence of hypoglycemic drug therapy (oral or subcutaneous).

RESULTS

1. Distribution of treatment duration with olanzapine at the time of diagnosis of hyperglycemia

126 patients who had either no history or unknown history of hyperglycemia were analyzed.



ZY 1971 1516

X axis: number of days of olanzapine therapy at the time of diagnosis of hyperglycemia (in 10 days increments)
Y axis: number of subjects for a given treatment duration.

	Quantiles	
maximum	100.0%	540.00
	99.5%	540.00
	97.5%	513.00
	90.0%	365.00
quartile	75.0%	150.00
median	50.0%	82.00
quartile	25.0%	30.00
	10.0%	11.20
	2.5%	1.90
	0.5%	1.00
minimum	0.0%	1.00

Moments	
Mean	115.9333
Std Dev	123.6042
Std Error Mean	14.2726
Upper 95% Mean	144.3722
Lower 95% Mean	87.4945
N	75.0000
Sum Weights	75.0000

Information on olanzapine treatment duration was available in 75 patients:
Mean duration of olanzapine therapy at time of diagnosis of hyperglycemia: **116 days**
Median duration: 82 days
Range of duration: 1-540 days

8 (11%) of the 75 patients were exposed to olanzapine for 12 months or more at time of diagnosis of hyperglycemia. If these outliers were excluded, then the mean olanzapine exposure time was 81 days.

52 of the 75 patients (69%) were exposed to olanzapine for 4 months or less at the time of diagnosis of hyperglycemia.

Average age: 40
Median age: 40
Range of age: 12-78 years

2. Lack of dependency of positive dechallenge (reversibility) on the duration of olanzapine therapy

36 patients had been treated with olanzapine for 60 days or less at the time of diagnosis of hyperglycemia. The hyperglycemia in 6 patients resolved completely upon discontinuation of olanzapine and cessation of diabetic drugs. The hyperglycemia in 11 patients did not resolve (i.e. still required hypoglycemic drugs).

39 patients were known to be exposed to olanzapine for more than 60 days at the time of diagnosis of hyperglycemia. Hyperglycemia resolved in 11 patients. 19 patients required hypoglycemic drugs after discontinuation of olanzapine.

Among patients with known glycemic control state after discontinuation of olanzapine, the percentage of patients with resolution of hyperglycemia (without the need for hypoglycemic drugs) was very similar between those who were treated for more than 60 days with olanzapine as compared to those who were treated for lesser duration.