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Volume 1

Review of Commercially Marketed (Spontaneous) Hypoglycemia Adverse Event Reports and Olanzapine

**Eli Lilly and Company
(January 2000)**

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Table of Contents

Volume I

1. Introduction	4
1.1. Purpose/Scope/Rationale	4
1.2. Executive summary	4
2. Methods	5
2.1. Overview/Background	5
2.2. Literature Review	5
2.3. Process of Report Finding in Clintrace	5
2.4. Definitions/Conventions	6
3. Discussion	10
4. Comparative Assessment	16
4.1. Background	16
4.1.1. Introduction	16
4.2. Commercially Marketed Olanzapine Experience vs. Risperidone	16
5. Summary	18
6. References -- Review of Commercially Marketed (Spontaneous) Hyperglycemia Adverse Event Reports and Olanzapine	19
7. Review of the Scientific Literature	20
7.1. Prevalence of Diabetes in General Population	20
7.2. Prevalence of Diabetes in Schizophrenia	20
7.3. Studies On The Effects Of Antipsychotic Agents On Insulin and/or Blood Glucose In Animals and/or Normal Volunteers	21
7.4. Reports on the Relationship between Typical Antipsychotic Agents and Hyperglycemia and/or Diabetes in Patients with Schizophrenia	22
7.5. Influence Of Weight Gain and/or Obesity On The Development Of Hyperglycemia and/or Diabetes	23
7.6. Clozapine and Hyperglycemia in Patients	24
7.7. Risperidone and Hyperglycemia in Patients	25
7.8. Olanzapine and Hyperglycemia in Patients	26
7.9. Quetiapine fumarate and Hyperglycemia in Patients	26

Olanzapine
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ZY 9453 521

7.10. Atypical Antipsychotics and Hyperglycemia in Patients26
8. References – Literature Review.....28

Volume 2

Appendix 1: Line-Listing of Adverse Event Reports

Volume 3

Appendix 2: Literature Review References

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ZY 9453 522

1. Introduction

1.1. Purpose/Scope/Rationale

In response to a query from the Switzerland Health Authority (IKS), 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 phenomenon 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. There is a clearly documented increased risk of diabetes among patients with schizophrenia. Schizophrenia is an illness with signs and symptoms that could reasonably be expected to reduce adherence to medication regimens intended to treat diabetes and therefore contribute to diabetic exacerbations. 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. From the data available, it is unclear that the incidence of new onset diabetes and exacerbations of pre-existing diabetes among patients taking olanzapine exceeds the incidence of new onset cases and exacerbations among a population with psychiatric disorders not taking olanzapine but for whom olanzapine would be an appropriate medication. The Swiss Summary of Patient Characteristics (SPC) contains a Precaution regarding hyperglycemia which reads as follows:

"In very rare cases, hyperglycemia or worsening of pre-existing diabetes have been reported under Zyprexa treatment. In some cases, a transitory weight gain was assessed as a possible predisposing factor. An adequate medical examination is advisable for patients with diabetes or related risk factors."

Given the total data, no change is warranted at this time. Reports and scientific literature regarding hyperglycemia will continue to be closely monitored.

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 section 7 below.

2.3. Process of Report Finding in Clintrace

The adverse event reporting database, Clintrace, was searched on December 6, 1999 for all spontaneous olanzapine adverse event reports entered into Clintrace from September 29, 1996 through September 30, 1999 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 332 reports were identified utilizing this search. As of September 30, 1999 an estimated 3,536,000 patients have been treated with commercial olanzapine.

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. u = unknown or not reported n = reported as no concomitant medications
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
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 Diabetes Mellitus (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 Treatment (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 History (Hx) DM	y = yes, n = no, u = unknown or possible when so specified. A family history of diabetes mellitus as reported in the text is coded y in this category. The degree of family member relatedness was not considered.

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ZY 9453 525

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

Obesity/BMI or Weight (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 weight & height were 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.
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 acute hyperglycemia/DM/DKA is reported when known.

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ZY 9453 526

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

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
<i>Resolved</i>	Resolved; Recovered; Returned to normal; Abated; [lab results show or are reported to show normal values or return to pre-olanzapine levels]
<i>Improved</i>	Improved; Stabilized; Recovering; [lab results show improvement but not yet normal]; Resolving
<i>Plateaued</i>	Stable; Unchanged; Remain at ___ level
<i>Deteriorated</i>	Deteriorated; Continued to drop; Downhill course; [lab results show deterioration]
<i>Not resolved</i>	Not resolved; Not recovered; [this category is for cases where definitive information is lacking]
<i>Unknown</i>	Report specifically states that outcome is unknown or that further information not available
<i>Death</i>	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	Cyclosporine
Acetazolamide	Dapsone
Albuterol	Diazoxide
Amitriptyline	Dopamine
Amoxapine	Doxapram
Asparaginase	Doxepin
Atenolol	Droperidol
Atorvastatin	Enalapril maleate
Bumetanide	Encainide
Calcium channel blocker NOS	Estrogen

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**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**

Chlordiazepoxide	Ethanol
Chlorpromazine	Fludrocortisone acetate
Chlorprothixene hydrochloride	Fluoxetine hydrochloride
Cisapride	Fluvoxamine
Clonidine	Furosemide
Clozapine	Gabapentin
Corticosteroids	Haloperidol
Heparin	Pentamidine
Hydrochlorothiazide	Perphenazine
Imipramine	Phenothiazines
Indapamide	Phenytoin sodium
Indomethacin	Prednisolone
Isoniazid	Prednisone
Labetalol	Progesterone
Lamivudine	Propranolol
Lamotrigine	Protriptyline hydrochloride
L-Dopa	Pseudoephedrine
Levothyroxine sodium	Quinethazone
Lisinopril	Rifampicin
Lithium	Risperidone
Methylprednisolone	Salbutamol
Metoprolol	Sertraline hydrochloride
Minoxidil	Synthroid
Mirtazapine	Theophylline
Morphine	Thiazide NOS
Nadolol	Thiothixene
Nalidixic acid	Thyroid
Naproxen sodium	Triamterene
Nicotinic acid	Trifluoperazine hydrochloride
Nifedipine	Venlafaxine hydrochloride
Norethindrone/ethinyl estradiol	Verapamil
Octreotide	Zolpidem
Oral contraceptives	
Paroxetine hydrochloride	

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3. Discussion

There were 332 reports identified as potential cases of hyperglycemia through the search method described above. These include reports from healthcare professionals as well as other nonprofessional sources. Reports might be included even when a unique patient could not be identified. Detailed line listings of these 332 reports are included in Appendix 1 and these 332 reports are summarized in Table 3.1. below.

Of the 332 reports, 9 can be considered to be reported where treatment emergent hyperglycemia was not present (Group "n" = 7; Group "other" = 2). Additionally there were 86 reports where data provided did not indicate a peak serum glucose. These reports can be considered sparse with respect to important clinical data and therefore difficult to interpret.

There remains a total of 237 cases with data available at least regarding peak serum glucose. Of these 237, there were 41 (17% of 237) who presented with a peak glucose <300mg/dL (Group "a", DM-II-like presentation). Eighteen (44%) of these had definite histories of hyperglycemia and only 4 (10%) definitely did not have such a history. Of these 41 patients, 33 (80%) definitively had one or more risk factors for development or exacerbation of diabetes and the risk factor status was unknown for the remaining 8 patients.

In addition, there were 76 (32% of 237) who presented with a peak glucose ≥ 300 to <600mg/dL (Group "b", DM-I-like presentation). Thirty-seven (49%) of these had definite histories of hyperglycemia and only 13 (17%) definitely did not have such a history. Of these 76 patients, 59 (78%) definitively had one or more risk factors for development or exacerbation of diabetes and the risk factor status was unknown for the remaining 17 patients.

Lastly, there were 120 (51% of 237) who presented with a peak glucose >600mg/dL (Group "c", clinically severe DM-I-like presentation). Twenty-one (18%) of these had definite histories of hyperglycemia and 39 (33%) definitely did not have such a history. Of these 120 patients, 99 (83%) definitively had one or more risk factors for development or exacerbation of diabetes and the risk factor status was unknown for the remaining 21 patients.

From the information contained in these reports, it is clear that a history of diabetes and/or the presence of multiple risk factors for the development of diabetes make it difficult to strongly consider olanzapine as the etiology in these cases of diabetic destabilization or development of diabetes.

Table 3.1. Presentation Groups: Summary of All Clinical Characteristics at Time of Adverse Event

N = 332		Presentation Groups: Clinical Characteristics at Time of Adverse Event (All Cases)																							
Group	Group "a"				Group "b"				Group "c"				Group "u"				Group "n"				Group "other"				
Group Definition	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 at time of adverse event				
	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	
1) Risk Factors for and/or Clinical Conditions Associated with Diabetes Mellitus Which Pre-existed Adverse Clinical Event																									
Total per Presentation Group Known to Have DM or Elevated Glucose @ Time of Adverse Event Onset AND/OR History of Prior Hyperglycemia or DM	18	4	19	41	37	13	26	76	21	39	60	120	29	5	52	86	0	0	7	7	2	0	0	2	

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N = 332	Presentation Groups: Clinical Characteristics at Time of Adverse Event (All Cases)																							
Group	Group "a"				Group "b"				Group "c"				Group "u"				Group "n"				Group "other"			
Group Definition	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 at time of adverse event			
	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total
2) Risk Factors Other Than History of DM or Hyperglycemia (continued)																								
• Family History DM																								
Yes	3	0	1	4	2	1	6	9	3	6	12	21	1	0	13	14	0	0	0	0	0	0	0	0
No	0	2	2	4	0	9	3	12	1	15	4	20	2	2	2	6	0	0	0	0	0	0	0	0
Unknown	15	2	16	33	35	3	17	55	17	18	43	78	26	3	37	66	0	0	7	7	2	0	0	2
Possible	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
• Obesity																								
Yes	7	2	8	17	17	5	10	32	13	17	22	52	5	2	18	25	0	0	0	0	0	0	0	0
No	5	0	1	6	5	2	5	12	1	8	10	19	5	1	1	7	0	0	2	2	0	0	0	0
Unknown	6	2	10	18	15	6	11	32	7	14	28	49	19	2	33	54	0	0	5	5	2	0	0	2

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N = 332	Presentation Groups: Clinical Characteristics at Time of Adverse Event (All Cases)																							
Group	Group "a"				Group "b"				Group "c"				Group "u"				Group "n"				Group "other"			
Group Definition	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 at time of adverse event			
	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total
2) Risk Factors Other Than History of DM or Hyperglycemia (continued)																								
• Weight gain while on olanzapine																								
Yes	1	1	9	11	2	4	5	11	1	8	9	18	2	0	8	10	0	0	0	0	0	0	0	0
No	0	0	0	0	3	2	2	7	1	7	5	13	2	0	0	2	0	0	1	1	0	0	0	0
Unknown	17	3	10	30	32	7	19	58	19	24	46	89	25	5	44	74	0	0	6	6	2	0	0	2
• Alcohol abuse / alcoholism; (active, acute or by history)																								
Yes	2	0	1	3	1	1	3	5	1	3	7	11	0	0	4	4	0	0	0	0	0	0	0	0
No	0	0	0	0	0	2	0	2	3	2	1	6	0	0	1	1	0	0	1	1	0	0	0	0
Unknown	16	4	18	38	36	10	23	69	17	34	52	103	29	5	47	81	0	0	6	6	2	0	0	2

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N = 332	Presentation Groups: Clinical Characteristics at Time of Adverse Event (All Cases)																							
Group	Group "a"				Group "b"				Group "c"				Group "u"				Group "n"				Group "other"			
Group Definition	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 at time of adverse event			
	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total
2) Risk Factors Other Than History of DM or Hyperglycemia (continued)																								
• Pancreatitis or other pancreatic dysfunction (acute, chronic or by history)																								
Yes	0	1	0	1	0	0	0	0	2	3	5	10	0	0	0	0	0	0	1	1	0	0	0	0
No	0	0	0	0	0	2	0	2	1	1	2	4	0	1	1	2	0	0	0	0	0	0	0	0
Unknown	18	3	19	40	37	11	26	74	18	35	53	106	29	4	51	84	0	0	6	6	2	0	0	2
• Taking drug(s) reported to elevate glucose/cause DM																								
Yes	6	1	13	20	18	10	17	45	15	24	30	69	8	2	19	29	0	0	1	1	2	0	0	2
No	6	1	1	8	14	3	3	20	4	6	20	30	13	1	4	18	0	0	1	1	0	0	0	0
Unknown	6	2	5	13	5	0	6	11	2	9	10	21	8	2	29	39	0	0	5	5	0	0	0	0

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N = 332	Presentation Groups: Clinical Characteristics at Time of Adverse Event (All Cases)																							
Group	Group "a"				Group "b"				Group "c"				Group "u"				Group "n"				Group "other"			
Group Definition	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 at time of adverse event			
	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total	Yes	No	Unk	Total
2) Risk Factors Other Than History of DM or Hyperglycemia (continued)																								
Any Risk Factor Other Than Hyperglycemia/DM or DM Diagnosis at Adverse Event Onset (Summary)																								
Yes	13	2	18	33	25	12	22	59	19	32	48	99	12	3	32	47	0	0	4	4	2	0	0	2
No	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	5	2	1	8	12	1	4	17	2	7	12	21	17	2	20	39	0	0	3	3	0	0	0	0

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4. Comparative Assessment

4.1. Background

4.1.1. 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.

4.2. 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. 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 4.1. below.

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

Table 4.1. 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.

5. Summary

Antipsychotics have been reported to be associated with hyperglycemia since the mid-1950s. There has been a resurgence of interest in this phenomenon 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. There is a clearly documented increased risk of diabetes among patients with schizophrenia. Schizophrenia is an illness with signs and symptoms that could reasonably be expected to reduce adherence to medication regimens intended to treat diabetes and therefore contribute to diabetic exacerbations. 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. From the data available, it is unclear that the incidence of new onset diabetes and exacerbations of pre-existing diabetes among patients taking olanzapine exceeds the incidence of new onset cases and exacerbations among a population with psychiatric disorders not taking olanzapine but for whom olanzapine would be an appropriate medication. The Swiss Summary of Patient Characteristics (SPC) contains a Precaution regarding hyperglycemia which reads as follows:

"In very rare cases, hyperglycemia or worsening of pre-existing diabetes have been reported under Zyprexa treatment. In some cases, a transitory weight gain was assessed as a possible predisposing factor. An adequate medical examination is advisable for patients with diabetes or related risk factors."

Given the total data, no change is warranted at this time. Reports and scientific literature regarding hyperglycemia will continue to be closely monitored.

6. References -- Review of Commercially Marketed (Spontaneous) Hyperglycemia Adverse Event Reports and Olanzapine

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