«Date»

«addresseename»
«address»

Dear «salutation»:

Your request for information regarding Zyprexa® (olanzapine) and hyperglycemia has been forwarded by your Lilly representative, «salesrepname». We appreciate the opportunity to be of service to you. Zyprexa is indicated for the management of the manifestations of psychotic disorders as demonstrated in clinical trials with schizophrenic patients. Prescribing information is enclosed for your review.

The effect of Zyprexa on glucose and glycemic control in non-diabetics, in patients with impaired glucose tolerance, or in diabetics has not been systematically studied. The following summarizes the case report literature of antipsychotic drugs and hyperglycemia, and reviews the clinical trial and post-marketing experience of Zyprexa and hyperglycemia.

LITERATURE EVALUATION

The prevalence of diagnosed diabetes is estimated to be 5.1% in the general adult population (≥20 years of age), the prevalence of undiagnosed diabetes is approximately 2.7%, and the prevalence of impaired glucose tolerance (i.e., borderline diabetes) is 6.9% within the U.S. population[1]. The prevalence of diabetes in the U.S. schizophrenic population has been estimated to be 24.5%, considerably higher than that in the general population[2]. Similarly, the prevalence of diabetes in an Italian schizophrenic population has been found to be 15.8%, as compared to the prevalence 2.1% in the Italian general population[3]. In that same study of Italian schizophrenics[3], the prevalence of diabetes was higher in those schizophrenic patients not receiving antipsychotic therapy than in those

receiving antipsychotics. This difference was statistically significant ($p<.05$) and remained significant after controlling for variables such as age, sex, and cumulative duration of antipsychotic treatment.

The incidence of diabetes in a given population is reflective of the risk of developing the disease. In the U.S., the average annual incidence rate (1990 to 1992) for diabetes in the general adult population was estimated to be 2.4 cases per 1,000 people (0.24%). When the cases are stratified by age, the incidence increases as age increases. The annual incidence ranges from 1.8 cases per 1,000 at age 25 to 44 (0.18%) to 8.6 cases per 1,000 at age 65 to 74 (0.86%). The percentage of new cases is higher in women (58%) than in men (42%). Likewise the incidence of diabetes is highest in those patients of African American, Hispanic or Native American descent[4].

In addition to age, sex and ethnic background, risk factors which may have an impact on the development of diabetes and hyperglycemia are a family history of diabetes and obesity. Additional factors which may alter glycemic control are concomitant lithium therapy, alcoholism, pancreatic disorders, binges with highly concentrated sugar snacks or beverages, severe illness (sepsis, hepatic failure, neuroleptic malignant syndrome), and pregnancy with obesity.

In addition to diabetes, there are multiple other conditions that can result in the development of hyperglycemia. For example, pancreatic insufficiency due to alcohol abuse, chronic pancreatitis, hemochromatosis, cystic fibrosis, and various malignancies of the pancreas can lead to hyperglycemia. Additionally, endocrine disorders such as acromegaly, Cushing's Syndrome, pheochromocytoma, hyperaldosteronism, hyperparathyroidism, hyperthyroidism as well as renal insufficiency, and hepatic insufficiency can also result in this event. Since impaired glucose tolerance is frequently under-recognized, dietary indiscretion and fluctuating activity levels can also lead to sporadic presentation of hyperglycemia in some people.

As of October 31, 1999, case studies have reported at least a temporal association between hyperglycemia and phenothiazines[5,6,7], haloperidol[8], loxapine[9], quetiapine[10] clozapine[11-18], and Zyprexa[18-25]. These reports have not been controlled for multiple diabetic risk factors or concomitant medications. Additionally, in a review of commonly prescribed antipsychotics, the following antipsychotics include reports pertaining to hyperglycemia in their FDA approved product labeling: chlorpromazine, clozapine, haloperidol, quetiapine, perphenazine, risperidone, thiothixene, and Zyprexa (Table 1)[26].

TABLE 1. Adverse Events Related to Hyperglycemia in Commonly Prescribed Antipsychotics per FDA Approved Package Labeling

Antipsychotic	Event Terms*
chlorpromazine	glycosuria, hyperglycemia
clozapine	*precaution*: hyperglycemia; *post-introduction reports*: hyperglycemia
haloperidol	hyperglycemia
quetiapine	*infrequent*: diabetes mellitus, hyperglycemia; *rare*: glycosuria
perphenazine	glycosuria, hyperglycemia
risperidone	*infrequent*: diabetes mellitus; *post-introduction reports:* diabetes mellitus aggravated, diabetic ketoacidosis
thiothixene	glycosuria, hyperglycemia
Zyprexa	*infrequent*: diabetes mellitus, hyperglycemia, ketosis; *rare*: diabetic acidosis

*frequent defined as >1%; infrequent defined as 0.1 to 1%; rare defined as <0.1%

CLINICAL TRIAL EXPERIENCE

In the initial registration studies of Zyprexa, treatment-emergent adverse events were analyzed from the overall integrated safety database for Zyprexa-treated patients (N=2,500)[27]. For the purpose of this evaluation, reported events that may be related to glycemic control were mapped to the following COSTART standardized event terms: hyperglycemia, diabetes mellitus, acidosis, hypoglycemia, ketosis, endocrine disorder, and diabetic acidosis (Table 2).

TABLE 2. Incidence of Treatment-Emergent Adverse Events Related to Glycemic Control in Zyprexa-Treatment Groups

COSTART Term	Zyprexa (N=2,500)	
	n	%
Hyperglycemia	16	0.6
Diabetes mellitus	16	0.6
Acidosis	7	0.3
Hypoglycemia	4	0.2
Ketosis	3	0.1
Endocrine Disorder	1	0.04
Diabetic acidosis	1	0.04

Treatment-emergent adverse events related to glycemic control and reported as reasons for discontinuation in Zyprexa-treated patients were diabetes (N=1) and hypoglycemia (N=1). An analysis of the incidence of any low or high non-fasting blood glucose level that developed at any time during Zyprexa therapy is presented in Table 3 and Table 4. A low and high non-fasting blood glucose are defined as <45 mg/dL and >250 mg/dL, respectively.

TABLE 3. Incidence of Low Non-Fasting Blood Glucose Levels at Any Time During Zyprexa Therapy

Lab	Zyprexa (N=2,284)	
	n	%
Non-Fasting Glucose	292	12.8

TABLE 4. Incidence of High Non-Fasting Blood Glucose Levels at Any Time During Zyprexa Therapy

Lab	Zyprexa (N=2,392)	
	n	%
Non-Fasting Glucose	79	3.3

An analysis of the mean change from baseline to endpoint of non-fasting blood glucose levels in Zyprexa-treated patients is summarized below (Table 5).

TABLE 5. Non-fasting Blood Glucose, Mean Change from Baseline to Endpoint in Zyprexa-Treatment Groups

Lab	n	Units	Baseline		Endpoint		Change		Within Group
			Mean	SD	Mean	SD	Mean	SD	p-value
Non-Fasting Glucose	2415	mg/dL	96.30	29.34	100.80	36	4.32	33.84	<.001

POST-MARKETING EXPERIENCE: *(September 27, 1996 to September 30, 1998)*

In a review of the spontaneous safety database between September 27, 1996 and September 30, 1998[27], the following COSTART terms were used to capture reports potentially related to hyperglycemia: diabetes mellitus, diabetic coma, diabetic acidosis, hyperglycemia, and ketosis. The reports matching any or all of the above terms showed that hyperglycemia and related events were rarely reported (~0.01%). This is not an incidence but merely the frequency with which these events are reported to Eli Lilly and Company. As of September 30, 1998, the estimated worldwide patient exposure to Zyprexa was approximately 1.8 million. Of the cases reported in the stated time period, about 38% were known diabetics and another 40% had known risks or confounding factors that may have accounted for the event observed (see above). In the remaining 22% of the cases, there were insufficient clinical details to conduct a meaningful assessment.

CONCLUSION

Given the multiple factors which can destabilize glycemic control and the prevalence of diabetes especially among schizophrenics, definitive conclusions regarding the relationship between Zyprexa and hyperglycemia cannot be drawn at this time.

ZY 5021 489

We hope this information is responsive to your specific request. If you have any further questions, please contact us at 1-800-545-5979.

Very truly yours,

ELI LILLY AND COMPANY

Guy Ruble

Guy C. Ruble, Pharm.D.
Medical Information Administrator
U.S.M.D. Medical Information Services

Bruce J. Kinon, M.D.

Bruce J. Kinon, M.D.
Senior Clinical Research Physician
U.S. Medical Operations

Enc.

ZYPREXA, olanzapine, Lilly

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ZY 5021 490

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