OLANZAPINE - BLOOD GLUCOSE CHANGES

SUMMARY

OLANZAPINE AND GLYCEMIA

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.

- Various psychotropic medications, including olanzapine, have been temporally associated with treatment-emergent diabetes mellitus and related disorders in published reports, product labeling, and other reports. Information from controlled trials is needed because anecdotal reports are of little use in estimating the frequency of such 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 small or moderate mean random glucose changes, a second analysis explored the estimated likelihood of an individual experiencing increase at or above any of four potentially important random glucose 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 or 140 mg/dL thresholds than patients treated with olanzapine.

- Clinical and research 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 increase the risk for a particular individual (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, does not demonstrate clinically important increase of risk of treatment-emergent glucose elevations with olanzapine compared to other psychotropic medications. However, available knowledge 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]. Amore 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[3]. 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 EVENTS - 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 2,500 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].

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.

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.

ACTIVE COMPARATOR OLANZAPINE CLINICAL TRIAL DATABASE

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). 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]. 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 relatively low. However, in populations with increased risk for diabetes, a number of reports have concluded that random capillary glucose measures are useful for screening[9]. 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[10]. 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.

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 3.2mg/dL to 4.6mg/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[5]

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 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 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.

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

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 with symptoms on two occasions as diagnostic of diabetes.

Table 4 reviews the potential clinical significance of several random blood glucose thresholds. These thresholds are derived from the recommendations of the American Diabetes Association and were used in analyses reported below[11].

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 (fingerstick) 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.

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 200mg/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.

Table 5 presents the calculated likelihood of olanzapine-treated patients exceeding a

particular threshold divided by the likelihood on the comparator agent. For example, at the 126 mg/dL threshold, the risk of an event was 0.88 times as likely during treatment with olanzapine as with haloperidol, and the 95% confidence interval for that hazard ratio was 0.67 to 1.17.

As another example, the likelihood of a glucose event at or above the 140 mg/dl threshold was 0.37 times as likely during treatment with olanzapine as with clozapine, implying that the risk of glucose elevation at or above that threshold was approximately three-times greater with clozapine compared to olanzapine.

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.

TABLE 5: HAZARD RATIOS* FOR EXCEEDING GLYCEMIA THRESHOLDS FROM COMPARATIVE STUDIES IN SCHIZOPHRENIA**

DATABASE	THRESHOLD (mg/dL)	HAZARD RATIO For Olanzapine	CONFIDENCE INTERVAL	p-value
Haloperidol-controlled	126	0.88	0.67 - 1.17	0.38
	140	0.92	0.62 - 1.37	0.69
	160	1.28	0.70 - 2.33	0.42
	200	2.32	0.69 - 7.81	0.18
Risperidone-controlled	126	0.99	0.50 - 1.96	0.99
	140	2.30	0.82 - 6.45	0.11
	160	1.08	0.17 - 6.91	0.93
	200	1.76	0.11 -28.88	0.69
Clozapine-controlled	126	0.41	0.21 - 0.81	0.01
	140	0.37	0.14 - 0.95	0.04
	160	0.34	0.09 - 1.32	0.12
	200	0.30	0.03 - 3.12	0.31

*Hazard ratio=estimated likelihood on olanzapine divided by estimated likelihood on comparator
**Analysis does not control for BMI during treatment

GLUCOSE CHANGES AND BODY WEIGHT

It is interesting to note that no significant difference in glycemic threshold emerged with olanzapine-treated patients compared to a treatment such as haloperidol, which is temporally associated with less weight gain than olanzapine. In the clinical trail 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 treatments. Across treatments, many of the patients with values above the specified thresholds did not have substantial weight gain (e.g., increase by 1 or more on BMI). In the risperidone and haloperidol comparisons, even among those patients experiencing a weight increase of 10% or more during olanzapine treatment, over 95% had no glucose elevation to 160 mg/dL or more. This is finding is not surprising, given what is known about the relationship between diabetes and obesity, which is only one of the many factors

contributing to the risk of diabetes[5].

STRENGTHS AND LIMITATIONS OF OLANZAPINE DATABASE ANALYSIS

Any research of clinical 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) 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 (ie. due to age, ethnicity, or concurrent medical conditions).

COMPARISON WITH PREVIOUS CLINICAL TRIAL GLYCEMIA ANALYSES[12]

The present analyses are an elaboration of an earlier analysis that explored the relative risk of developing sustained, possibly clinically significant hyperglycemia during treatment with olanzapine compared with haloperidol, risperidone, and clozapine[12]. That analysis identified patterns of random glucose elevations (e.g., persistent, uncertain, transient or probable error) above thresholds of 160 and 200 mg/dL. Consistent with the present analysis, using Kaplan-Meier survival curves the earlier analysis found no significant difference among patients treated with olanzapine and haloperidol or risperidone in estimated time to elevation at either threshold. At the 160mg/dL threshold, patients treated with clozapine experienced significantly shorter time to elevation in the six-month Kaplan-Meier estimate compared to patients treated with olanzapine; the difference was not significant at the 200mg/dL threshold.

Interestingly, this first analysis yielded these similar conclusions to the current analysis, at least in respect to the haloperidol and risperidone categorical comparisons, despite substantial methodological differences. In the earlier analysis, clinical trials of schizophrenia, bipolar disorder, Parkinson's disease, and dementia were included, whereas the current analysis achieved greater diagnostic homogeneity by including only clinical trials in schizophrenia spectrum disorders. Patients were excluded from the first analysis if they had known hyperglycemia/diabetes or baseline random glucose >140 mg/dL. In contrast, the second analysis was probably more sensitive because all patients entered in the trials were included in the glucose analysis, with the only exception being those who had known diabetes or were taking antidiabetic medications at baseline.

POST-MARKETING EXPERIENCE WITH OLANZAPINE

Spontaneous Adverse Event Database

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 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 hyperglycemia: 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 hyperglycemia 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 hyperglycemia 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. Reports that contained information on dechallenge and rechallenge were reviewed. There were 34 dechallenges, 6 of which were negative, and 28 of which were positive. Of those 28 positive dechallenges, there were 2 positive rechallenges, 2 negative rechallenges, and 2 rechallenges with unknown outcome.

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[13]. Further, the estimated prevalence of diabetes among adults worldwide in 1997 was 2.5%[14]. Studies from the late 1990's also suggest that the prevalence of diabetes continues to increase[15].

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[16]. Other variable factors have included dyslipidemia, lack of exercise, hypertension, and obesity[11, 16, 17]. In a two-decade epidemiological study, the incidence of diabetes approximately 1%/year greater among those with the greatest weight increase (≥20kg) compared with the lowest-risk group[16]. However, adults with normal body mass index can also develop diabetes and clearly not all obese adults will not develop diabetes[16, 18].

Though not well established, other factors such as alcoholism, diet, and hyperprolactinemia have been implicated as diabetes risk factors[16, 17, 19]. As discussed below, one potentially very important factor is presence of a serious psychiatric illness.

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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. In every report, the prevalence of diabetes was higher than the non-mentally ill reference groups. Studies in populations with schizophrenia have shown a prevalence of elevated blood glucose levels ranging from 2.5 to 24.5%[20-23], 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. It is also possible that other factors may be associated with an increased prevalence of type 2 diabetes in patients with mental illness, such as a behavioral or lifestyle issue, or an underlying genetic vulnerability to diabetes that may or may not be shared with the psychiatric disorder itself.

PSYCHOTROPICS AND HYPERGLYCEMIA AND/OR DIABETES

While it seems 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 whether some or all can be attributed 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[24-26]. Several reports have been unable to demonstrate a definitive association between diabetes and the use of psychotropics[20, 22, 27, 28], 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[21] 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[27, 29, 30], loxapine[31], and phenothiazines in general[29]. 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[32].

CASE REPORTS OF HYPERGLYCEMIA/DIABETES WITH ATYPICAL ANTIPSYCHOTICS

Of the atypical antipsychotics, case reports demonstrating a temporal association with hyperglycemia and/or diabetes have been reported for clozapine[33-51], olanzapine[38,52-60], risperidone[61-63], and quetiapine[64]. These case reports were identified by searching the medical literature using the following databases: Medline, Derwent Drug File, Biosis Previews, SciSearch, PsycInfo, Embase through February 2001. Based on case reports, many of the patients that may develop hyperglycemia 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

GLUCOSE-TOLERANCE TESTING AND OTHER LABORATORY-BASED REPORTS

To date, preclinical trials, studies of insulin levels, and studies of glucose-tolerance testing 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.

In a recent article, Melkersson and colleagues measured glucose and a variety of metabolic factors in 14 patients treated with olanzapine[65]. 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, 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.

Two recent 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[66]. 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 75gm 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, also was seriously flawed. For unclear reasons, 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[67]. A standard GTT consists of 75 grams of glucose with measurements at baseline, 30,60, and 120 minutes. The interpretation of

glucose values at other time points is inappropriate in assessing glucose homeostasis. Apparently subjects on established pharmacotherapy were enrolled, precluding the evaluation pre-treatment glycemic indices. In the study by Newcomer et al, 31 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 3 patients treated with olanzapine in this non-randomized, cross-sectional study have no clear clinical significance. Again, great caution is needed in interpreting the results from this very small and methodologically limited study.

CONCLUSION

Anecdotal reports 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 4.6mg/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.

Preclinical research and study of other parameters such as insulin levels and glucose tolerance testing may be informative. Unfortunately, available studies are limited and have serious 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, and previous history of glucose intolerance.

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 EPS, TD, QTc, prolactin, weight gain, cognition, etc.) that must be appropriately balanced against expected efficacy when selecting appropriate pharmacotherapy intervention for

psychiatric disorders.

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Alan Breier

03/30/01 03:23 PM

To: James G Kotsanos/AM/LLY@Lilly, Mauricio F Tohen/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly
cc: Alan Breier/AM/LLY@Lilly, Michael D Clayman/AM/LLY@Lilly, James A Harper/AM/LLY@Lilly, John C Lechleiter/AM/LLY@Lilly, Gerhard Mayr/AM/LLY@Lilly, Michael MD McDonald/AM/LLY@Lilly, Albertus VanDenBergh/EMA/LLY@Lilly
Subject: action team for quick medical response to customers with zyprexa safety questions

Given the fundamental importance of Zyprexa to Eli Lilly and its broad global use with over 6 million exposures, it is critical our customers are receiving prompt *Answers That Matter* about Zyprexa's safety. Bert Vandenberg, Mike McDonald, Michael Clayman, Jim Harper and I met today to insure customer's questions and concerns about safety issues related to Zyprexa were responded to quickly and, when appropriate, with direct contact with affiliate medical. Our current system is not broken and we believe we can build improvements upon what is already in place. In addition, some affiliates manage the vital link between customers and affiliate medical superbly, while others could improve. There are no alarming or new safety concerns about Zyprexa prompting this focus. In fact, Zyprexa's safety profile remains best in class. However, we felt that this issue was so significant that it required elevation in importance and the need to insure *all* affiliates are rapidly responding to their customers regarding Zyprexa safety.

We have proposed an action team be formed and to meet this Monday to delineate specific action steps, roll-out appropriate communications and to track implementation. We proposed the following membership: Paula Trapaez, chair, (Medical Director, US Neuroscience), Mauricio Tohen (Medical Director, ZPT), Jim Kasantos (pharmacovigilance), and a marketing designate from Jim Harper' group. Global medical is responsible for the affiliate CRP response link to customers; Zyprexa Product Team is responsible for disseminating up-to-date safety data and affiliate CRP training in zyprexa safety issues; Global marketing is responsible for sales reps' training and linkage to affiliate medical; and pharmocovigilance is responsible for global adverse events reporting.

We greatly appreciate your attention and rapid response to this critically important issue.

ZY 2196 182

Cindy Coe Taylor
04/12/01 01:42 PM

To: Alan Breier/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, Mark L Heiman/AM/LLY@Lilly, Margaret O Sowell NONLILLY/AM/LLY@Lilly
cc:
Subject: Weight gain/glycemia review outline revised from Tuesday's meeting

All,

Attached is the revised outline. I've tried to incorporate the points from the discussion on Tuesday. Note also that I have reorganized the material somewhat so that (hopefully!) it will tell a nice flowing story with the results of one experiment (or one part of an experiment) providing the rationale for the next experiment (even if this is not exactly how it happened!). Also, instead of providing all of the background material up front in the introduction, it seemed to make more sense to provide background where it was relevant to the particular experiment. I would welcome any thoughts on whether or not the hypotheses that I have proposed for each experiment are on track and if you agree or not with this organization.

Please review the outline and let me know as soon as possible if you have any comments or suggestions for revision. I will begin working on the draft manuscript and will incorporate the additional missing data as it comes available (Mark, if the data are unavailable at this time, it would be extremely helpful if you could provide some methods clarifications and general results/conclusions on the outline).

Thanks much,
Cindy

[redacted]
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