

HYPERGLYCEMIA, WEIGHT GAIN AND OLANZAPINE

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SUMMARY

- **Registration Trials:** 1.7% of 2,500 patients, who received olanzapine, experienced treatment emergent hyperglycemia with non-fasting blood glucose greater than 250 mg/dL. Most studies were 6-8 weeks in duration. Studies of longer duration are needed to determine the true incidence as the mean time of onset of hyperglycemia was 16 weeks based on spontaneous reports, and weight gain plateau occurred after 38 weeks.
- **Retrospective Study.** Dr. Daniel Casey of Portland Veteran Health Science Center reviewed the charts of 136 patients who had taken olanzapine for four months or more. The average duration of treatment for these patients was 17 months. 50% of 136 patients experienced weight gain of 7 pounds or more after initiating olanzapine therapy. Seven of the 39 patients (18%) who had normal blood glucose levels at baseline developed treatment-emergent hyperglycemia.
- **Animal Study**

Two of 10 rhesus monkeys developed fasting hyperglycemia after switching to calorie-unrestricted diet and initiation of clozapine treatment. The average weight gain was 26%. The Hb A1c of all monkeys became elevated above the upper limit of normal.

- **Post-marketing spontaneous reports**

As compared to those who did not report hyperglycemia

- 1). Caucasians and Blacks who reported hyperglycemia were about twice as likely to be obese.
- 2). Median daily dose of olanzapine for those were the same as those who reported hyperglycemia, thus suggesting that this event was not dependent on the doses of olanzapine.

When all races were combined, obese patients were 2.7 times more likely to report hyperglycemia than those who were not. Obesity posed a greater risk for developing hyperglycemia in Blacks than in Caucasians. Blacks were 4.1 times more likely, and Caucasians were 2.5 times more likely to report hyperglycemia if they were obese than those who were not.

need verification with later data.

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Duration of therapy at the time of diagnosis of hyperglycemia

Among patients with treatment emergent hyperglycemia with known duration of therapy, the Mean duration of olanzapine therapy at time of diagnosis of hyperglycemia was 116 days, and the Median duration was 82 days (Range of duration: 1-540 days).

- **Post-marketing reporting rates of hyperglycemia** (Olanzapine versus risperidone)
90 per 100,000 for olanzapine, and 74 per 100,000 for risperidone.

- **Obesity**
Both epidemiological studies in human and animal study suggest that obesity was a risk factor for development of hyperglycemia after exposure to atypical antipsychotropic drugs.

- **Important questions**
 - 1). Does prevention of weight gain associated with olanzapine therapy will prevent the development of hyperglycemia in humans or in rhesus monkeys?
 - 2). The incidence of hyperglycemia in the general population upon long term exposure to olanzapine?
 - 3). What are the effects of olanzapine on insulin production and insulin sensitivity in humans?

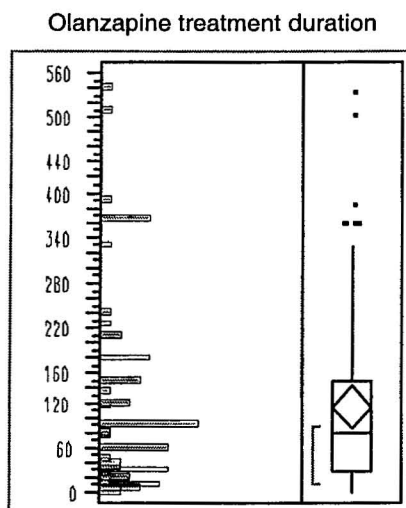
I) Prevalence of diabetes

7.8% of general population and 24.5% of schizophrenics (3 times higher) developed diabetes

II) Post-marketing Reports

A) Duration of olanzapine treatment at the time of diagnosis of hyperglycemia (Reports through September 1998)

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



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

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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

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

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

B) **Confounding factors** (168 cases as of 6/30/98; reporting rate was 0.01% among 1.6 million patients who were exposed to olanzapine reported hyperglycemia)

1) 38% (63) with known history of diabetes- 15 of 63 patients with baseline blood sugar. Mean baseline glucose of 135 m/dL, and mean peak of 441 mg/dL.

- 2) 40% (67) without known history of hyperglycemia
 - (a) 30% had confounding factor(s) - pancreatic disorder, binges with high concentrated sugar beverages, lithium therapy
 - (b) 70% had risk factors- obesity, recent weight gain, family history, heavy alcohol intake
 - (c) Mean age 38 and median age 40
- 3) 22% with insufficient information to evaluate

C) **Glucose levels** (Reports through August 1999)

- 1) 62% with blood glucose level unknown or less than 600 mg/dL; 38% with level >600 mg/dL.

D) **Age, Gender and Race Distribution** (Reports through Feb. 1999)

- 1) 237 reports contain one or more of the following query terms (diabetic ketosis, diabetes mellitus, diabetic coma or hyperglycemia)
- 2) **Age:** median 40 years old
- 3) **Gender:** 57% of patients who reported hyperglycemia were male and 53% of patients who reported any type of adverse events were male.

4) **Race:**

Among hyperglycemic reports that contain information on race, 33% were Blacks. Among reports of any type of adverse events, only 9.8% were Blacks. Thus, Blacks were over-represented among patients who reported hyperglycemia as compared to their representation among reports of any type of adverse events (33% versus 9.8%; $p < 0.000001$).

In the general population, Blacks are twice more likely to develop diabetes than Caucasians. Taking this into account, Blacks were still 66% higher risk than expected as compared to Caucasians when they were exposed to olanzapine.

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5) Glucose levels

The average was 567 mg/dL and the median was 479 mg/dL and the highest was 1700 mg/dL.

6) Duration of exposure to olanzapine at the time of diagnosis of hyperglycemia

Only patients without known history of diabetes were used for this analysis.

Mean duration: 116 days

Median duration: 82 days

Range of duration: 1-540 days

11% of the 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**.

7) Reversibility of hyperglycemia

Among reports where there were sufficient follow up information on the evolution of patients' hyperglycemic state, at least 23% of patients' hyperglycemia resolved (required no hypoglycemic drugs) upon the discontinuation of olanzapine. These include patients whose blood glucose levels were greater than 600 mg/dL and required insulin for therapeutic intervention at the time of the diagnosis of hyperglycemia. The readily reversible of hyperglycemia

8) Reporting rate

About 2.2 million patients were exposed to olanzapine as of Feb 1999. The reporting rate among is 1.1 in 10,000 patients exposed to olanzapine.

9) Obesity and Hyperglycemia

According to WHO, people with body mass index greater than or equal to 30 are considered obese. 1976 reports out of 8681 olanzapine reports received by Lilly as of 2/28/99 contained information on both height and weight to permit determination of BMI. Of these, 1852 contain credible information on BMI (weight <272 kg and height between 1.2 to 2.1 meter for adults).

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BMI	Reporting of Hyperglycemia		Total
	Yes (%)	No	
BMI ≥30	50 (9.7%)	463	513
BMI <30	48 (3.6%)	1291	1339
Total	98 (5.3%)	1754	1852

a). **Comparison between those who reported hyperglycemia and those who did not report such event**

98 of these 1852 cases reported hyperglycemia and 1754 did not. The mean BMI of "normoglycemic" group was 27.3 as compared to 33.1 for the hyperglycemic group ($p < 0.0001$). Thus patients who reported hyperglycemia had significantly greater BMI as a group.

Mean BMI of hyperglycemic group = 33.1

Mean BMI of "normoglycemic" group = 27.3

$P < 0.0001$ (2 tailed Chi Square test)

Reporting rate of hyperglycemia among obese patients = $50/513 = 9.7\%$

Reporting rate of hyperglycemia among non-obese patients = $48/1339 = 3.6\%$

$P < 0.00001$ (2 tailed Chi Square test)

About half of the patients who reported hyperglycemia but were not obese had either pre-existing history of diabetes, pancreatitis or weight gain of 30 pounds or more.

Obesity or weight gain of 30 pounds or more were risk factors for developing hyperglycemia. Obese patients were 2.7 times more likely to report hyperglycemia than those who were not.

Distribution of patients by race and gender in olanzapine Clintrace Database regardless of glycemic control state (i.e. all patients with BMI regardless of the adverse events that were reported)

	# of patients with known BMI	# obese (%)	% Female
Black	119	38.6%	44.5%
Caucasians	1095	14.9%	50.5%

Distribution of hyperglycemic patients by race and gender

	# of patients with known BMI	# obese (%)	% Female
Black	25	18 (72%)	44.5%
Caucasians	50	25 (50 %)	54%

A greater percentage of Blacks was obese as compared to Caucasians. Comparison with profile of patients who reported any type of adverse events in Clintrace olanzapine database, there was no gender effect on hyperglycemia among Blacks or Caucasians, and obesity was over-represented among patients who reported hyperglycemia. This suggests strongly that obesity is a risk factor for hyperglycemia.

Distribution of patients who did not report hyperglycemia by race

	# of patients with known BMI	# obese (%)	% Females
Black	94	28 (30%)	44.7%
Caucasians	1,048	282 (27%)	50.5%
Asians	19	5 (26%)	53%

Percentages of patients who were obese and who did not report hyperglycemia were comparable across different races.

Blacks who reported hyperglycemia were 2.2 times as likely to be obese than those who did not report such event.

Caucasians who reported hyperglycemia were 1.9 times as likely to be obese than those who did not report such event.

Frequency of reporting of hyperglycemia by BMI and race

	BMI	# of patients regardless of ADE reported	# patients who reported hyperglycemia	# obese (%)
Black	≥30	46	18	39.1%
	<30	73	7	9.6%
Caucasians	≥30	307	25	8.1%
	<30	791	25	3.2%

Obese Blacks were 4.1 times more likely to report hyperglycemia than those who were not obese.

Obese Caucasians were 2.5 times more likely to report hyperglycemia than those who were not obese.

Obesity is a greater risk for developing hyperglycemia in Blacks than in Caucasians. P value (2 tailed Chi Square test) <0.0001.

III) Clinical trials

A) Hyperglycemia

B) 2,415 patients with non-fasting blood glucose

- 1) Mean baseline glucose level before treatment was 96.3 mg/dL and 100.80 after treatment with olanzapine (p value <0.001).
- 2) The incidence of treatment emergent hyperglycemia among 2500 patients studied (initial registration studies of Zyprexa) was 1.7%, where high non-fasting hyperglycemia was defined as blood glucose > 250 mg/dL. As these trials are mainly short term studies, the actual incidence had patients been exposed to olanzapine for longer period would be higher.

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C) Weight Gain

Bruce Kinon had analyzed data from 70 olanzapine clinical trials, and found that the mean weight gain of patients was 6.5 kg. Weight plateau after 38 weeks of olanzapine. About 55% of patients had weight gain of over 5 kg after 1 year of olanzapine treatment. 16% had weight gain of 30 kg or more.

Upon analysis of the largest olanzapine clinical trial, he found that increased appetite, good clinical response and low baseline BMI to be the best predictors of weight gain. Patients who, at baseline were considered underweight, experienced the greatest mean weight gain. In trials with risperidone, both olanzapine and risperidone treated patients experienced statistically significant weight gain from baseline to endpoint. Olanzapine patients experienced statistically significant greater weight gain (1.8 kg over 28 weeks) than risperidone treated patients.

D) Dr. Daniel Casey's Post Hoc Analysis of 136 patients in the Portland VA Healthscience Center

Age: mean= 58; range= 28-83

Gender: 126 M: 10F

Olanzapine Dose: 11.8 (2.5-30) mg per day

Treatment duration: 1.39 year (4-32 months)

1) Fasting Glucose

2) 60 patients had fasting glucose levels before and after olanzapine therapy- 39 had normal fasting glucose levels, of these 7 (18%) had an increase in their fasting glucose levels ; mean fasting glucose levels was 100 mg/dL before olanzapine and 139 mg/dL (range of 125-260 mg/dL) during olanzapine therapy. Based on the new diagnostic criteria of ADA, diabetes mellitus is said to be diagnosed if a patient's fasting blood glucose is \geq 126 mg/dL.

3) Weight Gain

50% had 7 pounds or greater increase in weight. Average increase of 9.7% in body mass index.

IV) Study in rhesus monkey (Dr. Daniel Casey; Clozapine, an atypical antipsychotropic drug structurally related to olanzapine)

Both clozapine and olanzapine bind to dopamine D, serotonin 5HT, cholinergic, histamine and adrenergic receptors. The diet of 10 monkeys was switched from their normally restrict calorie to ad lib. After stabilization of their weight in 4-6 months, clozapine was administered. The doses were titrated to 5 mg/kg over a 13 weeks period, and clozapine was continued for 26 more weeks.

RESULTS

1. Weight Gain

Though the calorie intake per kg of body weight was stable over the entire study, there was further weight gain when the dose of clozapine was maintained at 5 mg/kg after their weight was stabilized initially after switching to Ad Lib feeding.

2. Glycemic Control

The Hg A1c of all monkeys became abnormal. Two with treatment emergent fasting hyperglycemia. Two developed fasting hyperinsulinemia.

This raises the possibility that olanzapine might cause hyperglycemia by increasing the resistance to insulin.

V) DISCUSSIONS

Both postmarketing reports, retrospective study in patients in veteran hospital in Oregon and animal studies suggest an association between obesity and treatment-emergent hyperglycemia in patients treated with atypical antipsychotics. Obesity is over-represented among olanzapine who reported hyperglycemia as compared to those who reported other side effects. This, however, does not prove that obesity was the cause of hyperglycemia. An increase in appetite was noted in patients who took olanzapine, suggesting a reset satiety threshold might account for the weight gain. It remains to be determined whether a control in caloric intake needed to prevent weight gain will also prevent the onset of hyperglycemia. If so, one can conclude that hyperglycemia was secondary to obesity. Even if that causal relationship was established, it does not explain why some patients who experienced treatment emergent hyperglycemia were not obese at the time of this event. The percentage

of increase in body mass at baseline in this subset of patients will be useful to determine the threshold of weight gain that heralded impaired glycemic control.

Dr. Casey found the incidence of treatment-emergent hyperglycemia be 18%. However, the patients studied were primarily older males. Thus, the incidence among the general population of patients who took olanzapine remains to be determined. In addition, it is useful to know the incidence of treatment emergent hyperglycemia by different body mass index categories. In HGAJ trial, patients who were not obese had the greatest increase in body weight. It would of interest to know whether non-obese patients at baseline had a disproportional increase in risk of developing hyperglycemia.

VI) Proposed Studies

A) Exploration of GPRD database

- 1) Compare the incidence of treatment emergent hyperglycemia among patients who took olanzapine and those who took risperidone and who took quetiapine?
- 2) Determine the absolute and percentage weight gain in patients who had taken olanzapine for 22 weeks or more.
- 3) Determine the incidence of treatment emergent hyperglycemia among olanzapine patients of different weight classes (BMI categories), different percentage weight gains, and of different races. Compare these rates with matched control of non-schizophrenic patients if possible.

- 4) What are the average, median and range of the duration of olanzapine therapy of all patients in the database regardless of whether they developed hyperglycemia? What are they at the time of diagnosis of hyperglycemia?
- 5) What are the characteristics of patients who developed hyperglycemia after the initiation of olanzapine?
- 6) Any risk factors of hyperglycemia: family history of diabetes, obesity, weight gain during olanzapine therapy, pancreatitis and alcohol abuse?
- 7) What are the demographic characteristics of these patients?
- 8) What was the average dose of hyperglycemic patients as compared to all olanzapine patients regardless of whether they experienced hyperglycemia? Was there a dose dependency for hyperglycemia?
- 9) What are the hazard rates of various factors for hyperglycemia- obesity, race, weight gain, dose, gender, duration of olanzapine therapy, family history of diabetes, alcoholism?

**B) STUDIES TO DETERMINE THE ROLE OF WEIGHT GAIN ON TREATMENT
EMERGENT HYPERGLYCEMIA**

The ideal study method is clinical trial. The drawbacks are difficulty in controlling weight gain and costs of study.

Study with rhesus monkeys is an alternate solution which offer answer at a reduced cost, and reliable weight control through caloric restriction. However, the drawback is that it requires extrapolation of findings to humans.

C) STUDIES TO DETERMINE THE EFFECT OF OLANZAPINE ON INSULIN SENSITIVITY

Charles already has a plan to study this in humans.