ATYPICAL ANTIPSYCHOTICS
ISSUES MANAGEMENT

HYPERGLYCEMIA / DIABETES CONCERNS

COMPETITIVE LITERATURE / POSTERS REVIEW

Confidential Information
For Lilly Internal Use Only

CONFIDENTIAL: Internal Lilly Use Only
Document Owner: Patrick Toalson
Last Modified: November 8, 2001
# Table of Contents

DIABETES PREVALENCE IN SCHIZOPHRENIA ........................................... 4

RETROSPECTIVE DATABASE ANALYSES .................................................. 5

PREVALENCE OF DIABETES DURING EXTENDED CLOZAPINE AND OLANZAPINE TREATMENT .......................................................... 5
Casey DE ................................................................................................. 5

HYPERGLYCEMIA IN SCHIZOPHRENIC PATIENTS TREATED WITH OLANZAPINE AND CLOZAPINE ................................................. 6
Smith RC, Lindenmayer JP, Khanadat A Parker B, Singh A .................................................................................................................. 6

DIABETIC KETOACIDOSIS IN PATIENTS WITH SCHIZOPHRENIA DISORDERS ................................................................. 7
Caglieri E, Henderson DC, Nathan DM ............................................................................................................................................. 7

LITERATURE REVIEW OF HYPERGLYCEMIA AND DIABETIC KETOACIDOSIS (DKA) WITH ATYPICAL NEUROLEPTICS ......................... 8
Schwarz ME, Aladjem AD ........................................................................ 8

A RETROSPECTIVE COMPARISON OF LIPID, GLUCOSE, AND WEIGHT CHANGES AT ONE YEAR BETWEEN OLANZAPINE AND RISPERIDONE TREATED PATIENTS ............................................ 8
Meyer J .................................................................................................... 8

GLUCOSE INTOLERANCE WITH ATYPICAL ANTIPSYCHOTICS .......................................................... 10
Wilson D, DeSouza L, Sarkar W, Newton MA, Hammond C .............................................................................................................. 10

WEIGHT GAIN, DIABETES MELLITUS AND THE PHARMACOLOGY OF SCHIZOPHRENIA .................................................. 11
Singer B, Buckley PF, Friedman L, Massani E, Parnes C .................................................................................................................. 11

USE OF NOVEL ANTIPSYCHOTIC MEDICATIONS IN DIABETES: A RETROSPECTIVE REVIEW ................................................................. 12
Yu BP, Maguire GA, Chong, YS ................................................................ 12

NOVEL ANTIPSYCHOTICS: HYPERGLYCEMIA, HYPERLIPIDEMIA, AND EKG CHANGES IN THE "REAL WORLD" .............................................. 12
Gupta S, Frank BL, Steinmeyer C, Lockwood C ........................................ 12

ANTIPSYCHOTIC MEDICATION: IMPACT ON CORONARY ARTERY DISEASE RISK FACTORS ................................................................. 13
Wirshing D, Wirshing, WC, Boyd JA, Meng LR ......................................... 13

RANDOMIZED CONTROLLED STUDIES .................................................. 15

INSULIN RESISTANCE IN OLANZAPINE AND ZIPRASIDONE TREATED PATIENTS: RESULTS OF A DOUBLE BLIND CONTROLLED 6-WEEK TRIAL .......................................................... 15

CROSS SECTIONAL INSULIN SENSITIVITY / CHALLENGE STUDIES ............................................................... 17

GLUCOSE METABOLISM DURING ANTIPSYCHOTIC TREATMENT IN SCHIZOPHRENIA ............................................................. 17
Newcomer JW, Facetola R, Haupt DW, Melson AK, Schweiger JA, Cooper BP, Selke G ...................................................................................... 17

ATYPICAL ANTIPSYCHOTIC AGENTS AND GLUCOSE METABOLISM: BERGMAN'S MINIMAL MODEL ANALYSIS ................................. 19
Henderson DC ......................................................................................... 19

ANTIPSYCHOTIC MEDICATION AND INSULIN RESISTANCE .................. 20
Cohn TA, Remington GA, Leiter L, Kameh H ............................................ 20

GLUCOSE METABOLISM AND THE TREATMENT OF SCHIZOPHRENIA: A COMPLEX RELATIONSHIP ...................................................... 21
Goldman M, Milner KK, Shriberg RF .......................................................... 21

EPIDEMIOLOGICAL STUDIES ............................................................. 23

INTRODUCTION ....................................................................................... 23

ASSOCIATION OF DIABETES MELLITUS WITH ATYPICAL NEUROLEPTICS ............................................................ 24
Sernyak MJ .............................................................................................. 24

ASSOCIATION OF NEW-ONSET DIABETES AND ANTIPSYCHOTICS: FINDINGS FROM A LARGE HEALTH PLAN DATABASE .......... 25

CONFIDENTIAL: Internal Lilly Use Only

Document Owner: Patrick Toalson
Last Modified: November 8, 2001

ZYPREXA MDL 1596 Confidential-Subject to Protective Order
ZYPREXA MDL Plaintiffs' Exhibit No.03908

ZY1 00518226
Diabetes Prevalence in Schizophrenia
Retrospective Database Analyses

Prevalence of Diabetes During Extended Clozapine and Olanzapine Treatment

Casey DE

Introduction/Methods: Retrospective chart review at the Portland VA of patients receiving extended treatment of clozapine over 1-5 years or olanzapine over 1-3 years

Results:
- Diabetes rates for Clozapine were:
  1 year = 14.7% (5 of 34 patients)
  3 year = 18.5% (5 of 27 patients)
  5 year = 23.1% (3 of 13 patients)
- Diabetes rates for Olanzapine were:
  1 year = 26.7% (32 of 120 patients)
  2 year = 24.4% (20 of 82 patients)
  3 year = 35% (7 of 20 patients)
- Clozapine patients tended to gain weight through out the 5 year study period where as Olanzapine patients weight gained stabilized at the 1 year point with no further weight gain observed beyond 1 year.
- In both treatment groups increases in weight and BMI were similar for those with and without diabetes.

Conclusion: These data confirm that diabetes is highly prevalent in patients taking clozapine and olanzapine and that prevalence tends to increase with extended treatment.

Reviewer’s Comments:
- This is a pure retrospective examination of patient data, there are no controls for baseline diabetes rates, pre-existing patient risk factors. What selection biases may be present in determining how physicians decided which antipsychotic to use for a given patient? What is the baseline rate of diabetes in the mentally ill population within this particular VA system?
- The diabetes rates seen here are higher than any other study, suggesting something is different in their patient population. Do they have a higher than normal minority population?
- No data is given as to whether these diagnoses were made via fasting blood glucose or random glucose values. This could have a significant impact upon the high rates observed.
- It is unclear from the abstract what the total N is for each treatment group. For instance are there 34 total Clozapine patients examined or is it 74 (34+27+13)? They had 5 of 34 clozapine patients exhibit diabetes at year 1 and 5 of 27 at year 3. Are these the same 5 patients or 5 new ones (how much duplication of patients is being counted)? He would suggest that his prevalence is going up when it appears that he may be just double counting existing patients. Are the 7 Olanzapine patients at year 3 new cases or are they a subset of the 32 diabetics in year 1? This was unclear from both his poster and the abstract.
- Based upon the data presented it is not possible to establish that there is a causal link as is suggested in the authors conclusions.

Where Presented: ACNP Annual Meeting, Dec 2000, San Juan PR.
Hyperglycemia in Schizophrenic Patients Treated with Olanzapine and Clozapine

Smith RC, Lindenmayer JP, Khandat A Parker B, Singh A.

Introduction: There are case reports of hyperglycemia in patients receiving olanzapine, but no published larger series to begin to provide prevalence estimates.

Methods: This study examined glucose levels in 51 schizophrenic patients who participated in research studies, and extended these findings with a chart study sample.

Results: Three of 55 patients (5.5%) showed persistent, clinically significant, glucose elevation of glucose values over baseline during treatment with olanzapine, and five patients showed a transient elevation in glucose > 140 mg/dl, which returned to normal values during continued treatment with olanzapine. Patients had statistically significant higher maximum glucose values during treatment with olanzapine compared with pre-olanzapine baseline. Glucose increases were not related to olanzapine dose or weight change. Blacks and Hispanics tended to show an increase in maximum glucose on olanzapine, whereas whites did not. In the routinely treated patient study (i.e. chart review) rates of hyperglycemia were also low. Mean glucose levels in olanzapine and clozapine treated patients were all within normal limits and below 100 mg/dl. 4% of olanzapine patients and 2% of clozapine patients had mean glucose levels ≥ 140mg/dl. 8.1% of patients treated with olanzapine and 10% of patients treated with clozapine had at least borderline or very mildly elevated glucose levels (i.e. >110 mg/dl). Mean cholesterol and triglyceride level in clozapine and olanzapine patients were within the normal range. Rates for elevated triglycerides were much higher, 17% in the olanzapine patients and 26% in the clozapine patients.

Conclusions: The rates for hyperglycemia in our olanzapine patients are not higher than the rates of diabetes in epidemiological surveys in U.S. adults (7.8%). However, elevated triglyceride levels may be a more important prevalent abnormality.

Reviewer's Comments:

- This study examined glucose levels in 51 schizophrenic patients participating in a clinical study of treatment refractory schizophrenia with Olanzapine. The authors supplemented the findings from the clinical study by conducting a retrospective chart review of 80 patients on either olanzapine or clozapine.
- In the research study sample they state that 3 of 55 patients (5.5%) on Olanzapine showed a persistent, clinically significant, elevation in glucose over baseline and 5 patients showed a transient elevation (glucose value over 140) which returned to normal levels during continued olanzapine treatment. Two of the three with persistent glucose elevation had a personal or family history of diabetes.
- Patients had statistically significant higher maximum glucose values during treatment with olanzapine compared to baseline but these increases were not within a clinically significant range. Increases in glucose were not related to Olanzapine dose or weight gain.
- Blacks and Hispanics tended to show increases in maximum glucose values where as whites did not. Correlates with known risk factors of ethnicity.
- A sub-sample analysis showed no difference over 8 weeks of treatment in glucose increases between olanzapine and haloperidol patients.
- In the chart review patient population, mean glucose levels within both the olanzapine and clozapine groups were within normal ranges and hyperglycemia rates were low.
- The authors use cutoff points for determining hyperglycemia based upon fasting glucose values, but were most likely non-fasting samples. They don't say how they obtained glucose levels (random or fasting). Clinically insignificant increases in mean glucose may reflect random samples + increased appetite.
• Mean cholesterol and triglyceride levels were within the normal range. However, they focus on the significance of the elevation in TGs. They don't specify methodology but very likely these are random samples (a chart review); likely they are counting abnormalities based on fasting triglyceride cut-offs.

**Where Presented:** ACNP Annual Meeting, Dec 2000, San Juan PR.; APA Annual Meeting, May 2001, New Orleans LA.

# Diabetic Ketoacidosis in Patients with Schizophrenia Disorders

*Cagliero E, Henderson DC, Nathan DM.*

**Introduction:** Use of atypical antipsychotic agents has been linked to increased incidence of diabetes mellitus in patients with schizophrenia, and cases of diabetic ketoacidosis (DKA) have been described in such patients.

**Methods:** We identified patients with a diagnosis of schizophrenic disorders, diabetes, and DKA attending a large urban teaching hospital between 1/95 and 1/01.

**Results:** The prevalence of diabetes in 3,753 schizophrenic patients was 11.2%, compared with 4.5% in the general hospital population (n = 642,823), confirming the high frequency of diabetes in these patients. Fifteen patients with schizophrenic disorders had DKA, and chart review showed that six developed DKA without a prior diagnosis of diabetes. The incidence of DKA in the schizophrenic patients without a prior diagnosis of diabetes, all of whom were on atypical antipsychotic agents (four on olanzapine, one on clozapine, and one on clozapine and risperidone) was 10.6/10,000 patient year, nearly ten-fold higher than that reported in a non-diabetic population (1.4/10,000). Their age was 37 ± 8 years (mean ± SD), body mass index (BMI) was 30.2 ± 5.4, four were males, four were Caucasian, one African American, and two Hispanic. At the time of presentation with DKA mean glucose was 812 ± 350 mg/dL, pH 7.23 ± 0.24, bicarbonate 14.5 ± 5.96 mmol/L, and hemoglobin Alc (HbAlc) 12.25 ± 1.29%. After 2.2 ± 1.5 years of follow-up, only one patient required long-term insulin therapy, excluding the diagnosis of type 1 diabetes for most, and HbA1c decreased to 7.72 ± 1.84.

**Conclusion:** Patients with schizophrenic disorders have a very high incidence of DKA. The cases were observed only in patients treated with atypical antipsychotic agents, supporting a link between the use of these drugs and severe abnormalities of glucose metabolism.

**Reviewer's Comments:**

- Significant limitation to evaluation of this abstract is an overall lack of information regarding expected rates of DKA in the schizophrenic population, here 15 had DKA (3.6% of the diabetics) for an incidence of 10.6/10,000 patient years. DKA rate appears at least double the rate usually seen in DM, but there is a dearth of "normal" information for DKA in schizophrenia—i.e., more likely to see such results if patients are not well-monitored, not identifying or communicating early symptoms well, or having comorbid stressors, eg infection, substance abuse, acute psychosis.

Literature Review of Hyperglycemia and Diabetic Ketoacidosis (DKA) with Atypical Neuroleptics

Schwarz ME, Aladjem AD.

Introduction: There has been little research published on an association of atypical neuroleptics with diabetes and diabetic ketoacidosis (DKA). Methods: This abstract reviews 26 case reports of new-onset diabetes after antipsychotic treatment initiation. Although the number of case reports is few, these reports are worrisome, since the use of atypical antipsychotics has become the first line of treatment for schizophrenia. Results: There have been 14 case reports of diabetes, DKA, or worsening diabetic blood glucose control after initiation of olanzapine. Five (36%) of these patients developed DKA, and 79% required discontinuation of their antipsychotic. Of those who discontinued treatment, 18% required long-term insulin, and 18% required long-term oral hyperglycemia treatment. There also have been 12 case reports of diabetes, DKA, or worsening glucose control after the initiation of clozapine. Six (50%) of the patients developed DKA, and 42% required discontinuation of their antipsychotic. Of those who discontinued treatment, one patient required long-term insulin, and two required long-term oral hyperglycemic treatment. Further review of the literature found one report each of associated increases in blood glucose with thioridazine, loxapine, and quetiapine. In each case, blood glucose levels normalized after medication discontinuation. No cases of diabetes associated with risperidone were found. Conclusion: These cases of diabetes and DKA should be significant enough to stimulate further research into an association of secondary diabetes with atypical neuroleptics, specifically olanzapine and clozapine. Clinicians should keep this in mind when starting these neuroleptics, since diabetes and DKA can involve serious morbidity and mortality.

Reviewer’s Comments:
- Review lacks consideration of patient or family history of diabetes discussion.
- Incomplete analysis, lacks inclusion of data on risperidone.

A Retrospective Comparison of Lipid, Glucose, and Weight Changes at One Year between Olanzapine and Risperidone Treated Patients

Meyer J

Introduction: Metabolic side effects are increasingly noted during therapy with novel antipsychotics, but there is a dearth of comprehensive data in this area about risperidone and olanzapine. Methods: A retrospective study was performed at Oregon State Hospital examining changes in fasting triglycerides, glucose, cholesterol, and weight parameters during the first year of therapy with either risperidone or olanzapine. Results: Among those < 60 years old, olanzapine patients (n = 37) experienced significantly greater increases in all metabolic parameters than the risperidone group (n = 39), except for weight variables: fasting triglycerides +104.8 mg/dL [olanz] vs. +31.7 mg/dL [risp] (p=0.037); cholesterol +30.7 mg/dL [olanz] vs. +7.18 mg/dL [risp] (p=0.004); glucose +10.78 mg/dL [olanz] vs. +0.743 mg/dL [risp] (p=0.03). Age < 60 years and concurrent use of lithium or valproate were associated with greater weight gain in both drug groups, but this difference was statistically

CONFIDENTIAL: Internal Lilly Use Only

Document Owner: Patrick Toalson
Last Modified: November 8, 2001
significant only for the olanzapine cohort. Neither weight change nor use of lithium or valproate was significantly associated with increases in glucose or lipids among those < 60 years old for either drug. 

**Conclusion:** Olanzapine therapy is associated with significantly greater increases in fasting glucose, triglycerides and cholesterol after one year of treatment for nongeriatric adult patients than risperidone.

**Reviewer's Comments:**
- This was a Janssen sponsored retrospective non-randomized inpatient chart review of 330 patients (n=175 olanzapine, n=155 risperidone) examining changes in fasting triglycerides, glucose, cholesterol and weight during the first year of therapy for patients on risperidone or olanzapine. Patients had to have been over 18 yo, have a baseline weight measurement within 3 weeks of therapy initiation and a fasting triglyceride, cholesterol and glucose measurement within 3 months of therapy initiation along with final measurements at 1 year to be included. This resulted in 47 patients in each therapy group being included into the study.

- Anyone receiving an 2nd atypical antipsychotic for >4 weeks at any time during the 1st year of therapy was excluded from analysis. Concurrent use of Li or Valproate was allowed and noted if given for 2 months.

- Note that only when you take out the geriatric patients (>60 yo) do you achieve statistical significance over risperidone, when the geriatric group is the one you would suspect to be at highest risk for type 2 diabetes and hyperglycemia and have the greatest impact on significance. It also should be noted that even though the increase in glucose levels achieves significance versus baseline, no patient reached a blood glucose level which met ADA criteria for being newly diagnosed as diabetic. Also the average blood glucose level at 1 year for all patients and the non-geriatric (<60 yo) groups for both olanzapine and risperidone are below the ADA 110 mg/dl level for impaired glucose tolerance and within normal levels.

- Though not acknowledged in the report, author reports that there were no cases of clinically significant glucose elevation, and therefore drills much deeper to find laboratory contrasts in patient subsets.

- It is a two point snapshot – baseline and one year
  - Therefore this is an unusual group – hospitalized for at least one year and on olanzapine and risperidone throughout the year.
  - No information on patients who start meds but do not meet these longevity criteria, for example, might it be more likely on olanzapine than risperidone that a patient is continued on treatment despite weight-related adverse event?
  - Almost ¾ of subjects do not have full data available and are excluded, no telling what bias this introduces
  - Of course, likelihood of having lab work done should go up if medical issues are suspected, presumably pushing both groups toward more abnormalities.
  - No control for the other things that can happen in a year, eg prescription of other psychotropics or hypoglycemic agents
  - As this was not a prospective study, must rely on standards of the state hospital in assuring that blood work is fasting. Normally such standards are lax, and Dr. Meyer admits that many tests likely are non-fasting (though poster does not acknowledge this). We anticipate this will disadvantage olanzapine (appetite – more likely to eat in proximity to blood work) and this especially would impact triglycerides and glucose.

- As with most retrospective studies and case reports, this non-randomized comparison cannot discriminate differences related to the treatment versus differences in the patients receiving one drug or the other.
This poster appears to include patients irrespective of diagnosis. It does not comment on whether diagnoses differed between olanzapine and risperidone. Even if they did not differ, non-randomized design will always carry a bias for differential assignment to treatment, eg based on clinical severity. No adequate justification of focus on one subgroup (age < 60), presumably post-hoc. Patients on olanzapine are relatively more likely to receive concomitant lithium or divalproex. In fact, comparison of those on olanzapine alone to risperidone alone shows more marginal difference in metabolic parameters, of doubtful statistical significance (p not mentioned).

- Total cholesterol change magnitude is not much different from anticipated VLDL increase secondary to TG increase.
- Compared to findings of larger, better, and randomized Lilly studies, this trial finds bigger weight gain differential, and strikingly larger glucose differential. These go away if one looks at those on risperidone or olanzapine without concomitant lithium or divalproex. This illustrates well how misleading a non-randomized non-prospective small comparison can be.
- They report that metabolic changes are not significantly correlated with weight change, discrepant from what we would expect at least in the case of triglycerides.


---

**Glucose Intolerance with Atypical Antipsychotics**

Wilson D, DeSouza L, Sarkar W, Newton MA, Hammond C.

**Introduction:** To evaluate the risk of new-onset diabetes and ketoacidosis in patients treated with atypical antipsychotics.

**Method:** Our initial case series is augmented by an interim analysis of statewide data maintained by the Ohio Department of Mental Health (ODMH). Records of patients treated with an atypical antipsychotic and also evaluated or treated for diabetes mellitus are being systematically examined.

**Results:** The case series was obtained by a collation of blood glucose levels, glucose tolerance, or other evaluations of diabetes conducted in 14 of the 126 patients treated with atypical antipsychotics at the state hospital in Cincinnati. In 11 of the 14 patients, new-onset, acute, and marked glucose intolerance developed after treatment with clozapine, olanzapine, or quetiapine. Of these, six patients required insulin therapy (four only transiently) and five patients developed diabetic ketoacidosis. Additional interim data are accruing from analysis of similar information for patients treated with any atypical antipsychotic at ODMH inpatient facilities from 1994.

**Conclusion:** Certain atypical antipsychotics are associated with new-onset glucose intolerance that can result in ketoacidosis. Monitoring patients taking atypical antipsychotics for changes in blood glucose levels may be indicated. Preliminary analysis of a larger database appears to confirm these risks. More systematic study data are needed.

**Reviewer's Comments:**
- Overview: A state hospital chart review with questionable fairness and dubious conclusions of elevated diabetes risk on Olanzapine.
- Interim data analysis of the ODMH statewide database indicates that the overall rate of diabetes among 2,542 patients treated with Olanzapine during 1998-99 was 10.9% (278 cases)

**CONFIDENTIAL: Internal Lilly Use Only**

Document Owner: Patrick Toalson
Last Modified: November 8, 2001

ZY 8608 1212

Zyprexa MDL 1596 Confidential-Subject to Protective Order
Zyprexa MDL Plaintiffs' Exhibit No.03908

ZY1 00518234
with 127 or 5% being "new onset"). They state that data for risperidone, clozapine and quetiapine have yet to be validated. This poster has been presented numerous times over the past 2 years with this same lack of reporting the data on atypicals other than Olanzapine. According to the author, Risperidone was not complete because of the need for "painstaking hand chart review to clarify ambiguities and eliminate false positives".

- Author concludes that his findings indicate that Clozapine, Olanzapine and Quetiapine are "diabetogenic". He also states that best practice guidelines should be changed to include routine blood glucose monitoring for at least some atypical antipsychotics. In detailed review of "ketoacidosis" author mentions that one patient was on risperidone, entirely omitted from all the other discussions of which drugs are "diabetogenic".

- When pressed the author has commented that based upon his examination of the data it appears that the rate for Risperidone is no different than for Olanzapine.


---

**Weight Gain, Diabetes Mellitus and the Pharmacology of Schizophrenia**

*Singer B, Buckley PF, Friedman L, Massanyi EZ, Pamies C*

This poster had some interesting data on weight gain and diabetes. It looked at weight gain in 55 male patients and showed that weight gain was greatest for Olanzapine versus Clozapine, Quetiapine and Risperidone. However on the graphic they showed that the baseline BMI for the Olanzapine group was ~27.5, increased to ~30 at the third month of treatment but then decreased back to ~27.5 by month 5 and remained at this level through month 7 (no explanation for why weight normalized or if interventions took place to achieve this). The diabetes evaluation was a retrospective analysis of a state hospital from July 1992 through May 1999. They identified 56 antipsychotic treated patients (didn't state out of how many patients reviewed) who developed diabetes during this time period. Of this group there were 34 males and 22 females. Thirty four patients were treated with atypicals and 22 with typical agents. Of the atypical treated group, 11 had diabetes mellitus onset while taking the atypical drug and the other 23 had onset of diabetes prior to atypical usage. The break out of atypical usage was:

- Clozapine N = 4 with an onset of diabetes ranging from 3 months to 9 months after starting clozapine
- Risperidone N = 4 with an onset of diabetes ranging from 3 weeks to 11 months after starting risperidone
- Quetiapine N = 1 onset of 6.5 months after starting therapy with quetiapine
- Olanzapine N = 2 onset of 8 months to 10 months after starting olanzapine

**Where Presented:** International Congress on Schizophrenia Research, April 2001, Whistler British Columbia, Canada.
USE OF NOVEL ANTI PSYCHOTIC MEDICATIONS IN DIABETES: A RETROSPECTIVE REVIEW

Yu BP, Maguire GA, Chong, YS

Introduction: Novel antipsychotic medications have been reported through isolated case reports to lead to glucose intolerance and possible induction of diabetes mellitus. However, new research has revealed that no one antipsychotic medication has an increased risk over any other. Also, little is known of the effects of these medications on individuals with known diabetes mellitus. Methods: Twenty-one subjects (aged 23 to 86, 14 female, seven male) with diabetes mellitus and comorbid psychotic disorders were reviewed in regard to the effects on fasting glucose levels associated with treatment with novel antipsychotic medications. In this retrospective analysis, patient charts were reviewed for fasting glucose levels and time course of antipsychotic medication.

Results: Ten subjects received olanzapine (doses from 2.5mg to 30mg), nine subjects received risperidone (doses from 0.25mg to 8mg), and two subjects received quetiapine (doses from 25mg to 800mg) with a mean duration of therapy of 24.6 days. Analysis revealed no worsening of fasting blood glucose associated with any one agent. Of note, olanzapine was associated with a reduction of fasting blood glucose and favorable modification of diabetes medication treatment in four of the 10 cases analyzed.

Reviewer’s Comments:
- Retrospective analysis having standard limitations

Where Presented: Institute of Psychiatric Services Meeting, October 2001, Orlando FL.

NOVEL ANTIPSYCHOTICS: HYPERGLYCEMIA, HYPERLIPIDEMIA, AND EKG CHANGES IN THE “REAL WORLD”

Gupta S, Frank BL, Steinmeyer C, Lockwood C

Objective: To study the differences between groups of patients treated with conventional antipsychotics and various atypical agents with regard to hyperglycemia, hyperlipidemia, and EKG abnormalities.

Methods: The sample (n=162) was divided into groups of patients on conventional agents (n=41), risperidone (n=35), olanzapine (n=73), quetiapine (n=13). The patients had a variety of diagnoses, including schizophrenia, schizoaffective disorder, bipolar disorder, major depression with psychosis, and psychotic disorder not otherwise specified. The majority of the patients (71%) were in the schizophrenia spectrum. The sample included inpatients, those from a continuing day treatment program, hospital outpatient clinic, as well as office practice. Fasting blood glucose and fasting lipid profile values were obtained from the chart. The EKGs were reviewed for rhythm abnormalities as well as the duration of the QT/QTc interval.

Results: A one-way analysis of variance revealed no significance between group differences with regard to hyperglycemia, lipid abnormalities, EKG changes.

Conclusion: There is a need for a prospective study to assess the potential concerns of hyperglycemia, hyperlipidemia, and EKG changes with the atypical agents.

Reviewer’s Comments:
CONFIDENTIAL: Internal Lilly Use Only

Document Owner: Patrick Toalson
Last Modified: November 8, 2001
Where Presented: Institute of Psychiatric Services Meeting, October 2001, Orlando FL.

ANTIPSYCHOTIC MEDICATION: IMPACT ON CORONARY ARTERY DISEASE RISK FACTORS

Wirshing D, Wirshing, WC, Boyd JA, Meng LR

Introduction: Novel antipsychotic medications such as clozapine (CLOZ), and olanzapine (OLZ) have been linked to increases in weight and dysregulation of glucose control. Because of these side effects we retrospectively examined the records of subjects in our hospital to see if there were perturbations in weight gain, glucose, cholesterol, and triglycerides—risk factors for coronary artery disease.

Method: This pilot study is a retrospective chart review of patients on one or more of the following medications: CLOZ (N = 39), OLZ (N = 39), risperidone (N = 45), quetiapine (QUE) (N = 13), haloperidol (N = 41), or fluphenazine (N = 38). Medication records of patients who have received refills of any these medications were generated from pharmacy records. Weight gain, glucose, cholesterol, and triglyceride data were obtained. Patients were included in the study if they had record of two or more blood glucose levels, and/or a cholesterol panel, with at least one record before initiation of the target medications and one lab record one or more weeks after initiation of the target medication.

Results: CLOZ, OLZ, and QUE treated subjects all had statistically significant increases in weight. All medication groups were overweight (BMI > 25). From the available data we found that there were statistically significant differences in total cholesterol (F = 2.4, p = .04, df = 5, 151) and triglyceride levels (F = 4.7, p = .0006, df = 5, 125) among the antipsychotic groups. CLOZ, OLZ, and QUE treated subjects had statistically significant increased glucose levels. CLOZ and OLZ treated subjects had significant increases in triglyceride levels, whereas QUE treated subjects had decreases in triglycerides.

Conclusions: The novel antipsychotics offer a favorable EPS profile but have their own troublesome side effects. Weight gain, glucose elevation, and dyslipidemias may be linked phenomena. The novel antipsychotics differ in their effects on these factors. Clinicians need to be aware of these potential side effects and intervene to prevent these risk factors for coronary artery disease.

Reviewer’s Comments:
- Authors acknowledge in the poster that it is unknown if lab values are fasting and that they are unable to determine if the changes occurred independent of weight gain. These two facts make it difficult to evaluate the validity of the causality of the findings.
- The poster would lead one to believe that OLZ and CLOZ have a significant relationship to diabetes, however, Dr Wirshing has stated in discussions with her around this data that her belief is that all of the atypicals had equivalent rates of associated diabetes.
- The poster contains a table which outlines the percentage of patients reaching various metabolic thresholds determined to be clinically significant by the authors after the patients started medication:
  1. Percentage of patients with BG > 126: CLOZ 40%, OLZ 35.7%, RISP 30.8% HAL 25% (non statistically significant).
2. Percentage of patients with BG > 200: CLOZ 11.4%, OLZ 14.3%, RISP 10.3%, HAL 0% (non statistically significant).
3. Total Cholesterol > 200: CLOZ 43.3%, OLZ 30.8%, RISP 17.2%, HAL 26.7% (non statistically significant).
4. Triglycerides > 200: CLOZ 48.2%, OLZ 29.4%, RISP 25%, HAL 3.7% (non statistically significant, except for CLOZ at p=0.002).

Randomized Controlled Studies

Insulin Resistance in Olanzapine and Ziprasidone Treated Patients: Results of a Double Blind Controlled 6-Week Trial

Glick ID, Romano SJ, Simpson G, Horne RL, Weiden P, Piggott T, Bari M

Objective: To determine the effects of Ziprasidone (ZIP) and Olanzapine (OLZ) on weight, lipids, and metabolic parameters associated with insulin resistance (IR) in schizophrenic patients.

Methods: In a double-blind trial, 269 acute inpatients were randomized to ZIP or OLZ for 6 weeks. Fasting insulin, glucose, total cholesterol, and triglycerides were measured pre-randomization and at last visit. An IR index (HOMA IR = [Ins x Glu]/22.5) was calculated.

Results: From baseline, patients treated with OLZ had weight gain of 7.2 lb (p<0.001) and increases in fasting insulin of 36% (p<0.001) and in HOMA IR (log) of 11% (p<0.001). No significant difference was observed in fasting glucose. Total cholesterol and triglycerides increased 9% and 20%, respectively, with OLZ (both p<0.001). In contrast, ZIP did not significantly alter any of these parameters, and all but glucose and HOMA IR were statistically separable (p<0.05).

Conclusions: Ziprasidone was not associated with worsening of studied metabolic parameters. By contrast, within only 6 weeks of treatment, weight, fasting insulin, IR, total cholesterol, and triglycerides rose significantly with OLZ compared with ZIP. This suggests that OLZ worsens IR, which may predispose patients to type 2 diabetes mellitus.

Reviewer’s Comments:

- Overall this is a better designed study than most we have seen. Randomized treatment assignment is a very big advantage over the various retrospective and cross sectional reports.

- Only 2 blood draws were done for each patient (baseline and at 6 week study endpoint). They report all lab work as being in a fasting state. These patients started in the study during a 1-3 day inpatient visit, therefore the baseline data is likely to be fasting. However, the patients were not in an inpatient setting for the remaining 6 weeks of the study. In talking with the study authors at APA, they contend that they requested patients to be fasting when endpoint (6 week) blood draws were taken, however they can not be assured that all patients were truly fasting. This is critically important since fasting values are critical for accurate calculations in HOMA IR. What is the likelihood that OLZ patients had recently snacked given known increases in appetite and carbohydrate cravings?

- They used a measurement called HOMA IR which is a insulin resistance statistic calculated as Fasting Insulin X Fasting Glucose/22.5. Although the HOMA IR numerically increased for olanzapine it was non-significant compared to ziprasidone after adjustment for baseline values.

- Labs measured included weight, measures of insulin resistance (fasting insulin, plasma glucose), lipid profile (triglycerides, total cholesterol, LDL and HDL), blood pressure, uric acid and c-peptide.

- Poster reports all results as median values versus mean values, which may indicate that a small number of outliers are the drivers of any significant differences observed.

- Key result is no difference in fasting glucose change between olanzapine and ziprasidone.
  - Confirms risperidone/olanzapine comparison in Allison study
  - Because no apparent difference at this clinically key level, drills down to laboratory tests that might imply some future difference in glycemic abnormalities
  - They also report no between-drug differences in blood pressure effects
• Patients on Olanzapine had a statistically significant higher median weight gain than Ziprasidone pts. (7.2 lbs versus 1.2 lbs). Insulin resistance differences reflect what we’d expect given differences in weight gain, so we need to scrutinize statement that this does not appear to be weight-related, eg is this a powering issue? \( P>0.18 \) shows a trend towards a possible relationship.

• A key question is whether changes in metabolic parameters observed over 6 weeks reflect what will happen over the long run – ie, after acute appetite/weight gain/nausea/efficacy issues stabilize.

• Cholesterol increase on olanzapine is a major discrepancy from that observed in our HGAIJ trial. Ours were non-fasting samples, but this should not have a great impact on cholesterol, otherwise its larger size and longer duration should trump this Pfizer report
  - This study does cite increase in LDL. Lipoprotein subfractionation historically was not done in Lilly trials.
  - Interestingly HDL increased insignificantly on both ziprasidone and olanzapine, suggestive that comparative LDL/HDL ratio changes may be more attractive than LDL alone.

• There was a statistically significant increase in median total cholesterol (OLZ 16, ZIP 0), triglyceride (OLZ 28, ZIP -3) and LDL (OLZ 10, ZIP -3) for Olanzapine patients. These changes were significant vs. baseline and also vs. Ziprasidone patients over the 6 weeks. However, all median values for both groups were still within the normal ranges.

• Even after triglyceride increases, median value on olanzapine is solidly within the normal range (at 158) and median increase of 27 on OLZ vs. 12 on ZIP is not as unfavorable as numbers we've seen in more confounded studies.

• Authors Conclusion - these changes in metabolic parameters are suggestive of worsening of insulin resistance in patients taking Olanzapine.

**Where Presented:** ACNP Annual Meeting, Dec 2000, San Juan PR (interim analysis); APA Annual Meeting, May 2001, New Orleans LA; Institute of Psychiatric Services, October 2001, Orlando FL.
Cross Sectional Insulin Sensitivity / Challenge Studies

Glucose Metabolism During Antipsychotic Treatment in Schizophrenia

Newcomer JW, Fucetola R, Haupt DW, Melson AK, Schweiger JA, Cooper BP, Selke G

Introduction: Hyperglycemia and type 2 diabetes mellitus are more common in schizophrenia than in the general population. Glucoregulatory abnormalities have additionally been associated with antipsychotic medications. Type 2 diabetes is characterized by disturbances in insulin action on skeletal muscle (glucose disposal), liver (glucose production), and adipose tissue (lipolysis). While increased adiposity can decrease insulin sensitivity and antipsychotics may increase adiposity, disease- and medication-related differences in glucose regulation might occur independent of differences in adiposity.

Methods: In an initial study, modified glucose tolerance tests were performed in schizophrenia patients receiving clozapine, olanzapine, risperidone or typical antipsychotics, and untreated healthy controls, excluding subjects with diabetes and matching groups for adiposity and age.

Results: Effects of treatment group on plasma glucose were significant at all time points. Homeostatic model assessment suggests effects on insulin resistance. Other methodological approaches are used to further resolve effects on beta cell function and various insulin actions.

Conclusion: Antipsychotic treatment of schizophrenia can be associated with adverse effects on glucose regulation, which can vary in severity independent of adiposity.

Reviewer's Comments:
- Dr. Newcomer uses a challenge procedure similar to an oral glucose tolerance test, yet with several non-standard features that limit interpretability (abbreviated 9 hour overnight fast; modified glucose challenge (50 grams) and shortened observation (75 minutes). Differential impact of meds can affect gastric emptying/glucose absorption, and alter subsequent glucose and insulin curves.
- They now report that they have data looking at glucose levels in 79 patients. Of these 79 patients, they have an N=31 who are healthy untreated controls, and an N=48 chronically ill schizophrenics (Clozapine N=9, Olanzapine N=12, Risperidone N=10, Typicals N=17).
- The data in this poster originally derives from brain glucose uptake studies looking at cognitive effects with significant limitations in extrapolating to serum glucose levels.
- Olanzapine and Clozapine groups had a significantly higher baseline blood glucose as well as glucose levels at 15, 30, 45, and 75 minute time points in comparison to untreated healthy controls and the typical antipsychotic treated group ($p<0.005$). Risperidone also had a significant increase in baseline blood glucose and glucose levels at all time points versus healthy untreated control group only ($p<0.005$).
- They calculated insulin resistance using the HOMA IR formula as well as a HOMA Beta Cell function statistic ($20 \times$ Fasting Ins / Fasting glucose – 3.5). Increases in HOMA IR for OLZ and CLOZ were significant versus typical antipsychotic group only ($p<0.05$ OLZ, $p<0.06$ CLOZ). No HOMA IR value actually reported. No significant difference between any group on HOMA Beta Cell statistic reported.
- There was no significant difference in HOMA IR or HOMA Beta for Risperidone versus typicals or healthy controls.

Poster Conclusions:
1. Olanzapine and Clozapine were associated with an elevated fasting plasma glucose level versus patients treated with typical antipsychotics and untreated healthy controls. Olanzapine and Clozapine were also associated with elevated plasma glucose and insulin levels following an oral glucose loading regimen versus both typicals and controls. Risperidone was associated with an increased plasma glucose level versus controls only. Risperidone was not associated with an increased plasma glucose level versus typicals.

2. Effects on glucose metabolism are not explained by differences in adiposity (BMI).

3. Effects sizes for increases in plasma glucose levels for Olanzapine and Clozapine versus typicals and untreated healthy controls ranges from 1.0 – 1.5 SD.

- The study is too limited and flawed for meaningful conclusions. Earlier presentations were based upon an N of 3 for OLZ and 5 RIS patients. Larger N’s now are presented, however the graphs that continue to be shown are identical to those when a smaller N was used. Questionable accuracy of data exists.

- Apparently subjects were on stabilized treatment; without random assignment there is likely a substantial difference between baseline patient characteristics, eg severity of illness, that will influence glucose and insulin findings.

**Where Presented:** International Congress on Schizophrenia Research, April 2001, Whistler British Columbia, Canada.

---

"Schizophrenia-Related Abnormalities in Glucose Regulation"

![Graph showing glucose metabolism](image)

**Figure 1a & 1b.** Mean plasma glucose (mg/dL ± SE) and insulin (μU/mL ± SE) before and after 50g oral dextrose in patients with schizophrenia (n = 10) and bipolar affective disorder (BPD, n = 10), and normal healthy controls (n = 10).


---

CONFIDENTIAL: Internal Lilly Use Only

Document Owner: Patrick Toalson

Last Modified: November 8, 2001
“Medication-Related Abnormalities in Glucose Regulation in Schizophrenia”

Oral 50 g dextrose challenge in patients with schizophrenia (n = 45) and healthy controls (n = 31), with treatment groups matched for age and body mass index (BMI)


ATYPICAL ANTIPSYCHOTIC AGENTS AND GLUCOSE METABOLISM: BERGMAN’S MINIMAL MODEL ANALYSIS

Henderson DC

Introduction: Recently, atypical antipsychotic agents have been linked to diabetic ketoacidosis and adult-onset diabetes mellitus in uncontrolled clinical reports.

Methods: The purpose of this study was to examine, in a cross-sectional design, the effect of the atypical antipsychotic agents, clozapine, olanzapine, and risperidone, in schizophrenia subjects, on glucose metabolism with a frequent sampled intravenous glucose tolerance test (FSIVGTT) using Bergman’s Minimal Model Analysis (MINMOD). The MINMOD allows for examination of insulin sensitivity (SI) and glucose effectiveness (SG). After fasting overnight, subjects were admitted to the GCRC at Massachusetts General Hospital and underwent a FSIVGTT. Data were analyzed using an analysis of variance comparing the values of the three treatment groups.

Results: Twenty-five subjects completed the study. There were no differences between the three groups for age, race, BMI, fasting glucose, fasting insulin, and insulin 20 minutes post glucose injection. There were significant differences between groups for glucose concentrations 20
minutes post glucose injection (p = 0.02) and for SI to (p = 0.0022). SI significantly differed between groups comparing clozapine (mean 2.44 ± 2.25 × 10 - 4* min-1 ml-1) to risperidone (mean 10.45 ± 7.00 × 10 - 4* min-1 ml-1) (p = 0.0007) and olanzapine (mean 4.257 ± 2.48 × 10 - 4* min-1 ml-1) to risperidone (p = .0051). Controlling for gender, differences between the three groups for SG were not significant (p = 0.15), although clozapine (mean 0.015 ± 0.005 min - 1) differed from risperidone (mean 0.021 ± 0.006 min - 1) (p = .067), and olanzapine (mean 0.016 ± 0.008 min - 1) differed from risperidone (p = .09) at trend levels.

Conclusions: Preliminary results suggest that the three groups differ significantly for insulin sensitivity, with clozapine and olanzapine associated with abnormally low insulin sensitivity. Larger sample sizes are needed to elucidate any effect on SG.

Reviewer’s Comments:
• Findings should be interpreted cautiously:
  - patients are not randomized to treatment, so patient-related differences that impact who gets on or stays on a particular treatment may contribute to findings
  - sample is too small for interpretation
  - recent weight gain is not specified – it could greatly impact findings

• The investigators recruited 25 patients of unspecified diagnosis for a cross-sectional IV glucose tolerance test. They were hospitalized overnight and after a 12-hour fast challenged with 0.3 mg/Kg IV glucose, and drew baseline and 20-minute glucose and insulin.

• A computer program calculated several variables called glucose effectiveness, insulin sensitivity index, and acute insulin response to glucose.

• 10 patients on clozapine are compared to 9 on olanzapine (all male) and 6 on risperidone (3 males). Glucose at 20 minutes increased by 115 mg/dl on clozapine, 93 on OLZ and 81 on RIS. Insulin increases were clozapine 25, OLZ 34, and RIS 15. Comparing olanzapine and risperidone the only significant difference is on the calculated insulin sensitivity index, though the author reports that 7/9 on OLZ were abnormal on this index vs 1/6 on RIS; 6/9 had abnormal glucose effectiveness on OLZ vs. 1/6 on RIS

• Fasting glucose was 99 on OLZ, 98 on CLOZ, and 93 on RIS. While these are not statistically significant they suggest important baseline differences between patients. While we don’t know whether this reflects between treatment differences, it should predict worse response to challenge for those with higher baselines.

• Abnormal MINMOD is associated with higher diabetes risk, but ultimate clinical relevance of MINMOD calculations for psychiatric patients is unclear.


Antipsychotic Medication and Insulin Resistance

Cohn TA, Remington GA, Leiter L, Kameh H

Introduction: This report represents an interim analysis of data on 50 consecutive patients from an ongoing study addressing the issue of weight gain and related side effects of antipsychotic medication treatment.

Method: Patients were on a single antipsychotic medication for at least three months. Those on concomitant lithium or tricyclic anti-depressants were excluded. For the purpose of this analysis patients were divided into the following three medication groups: clozapine (10), olanzapine (11), and other (29). Homa’s index, a measure of insulin resistance was calculated using fasting
glucose and insulin data. Groups were compared for Homa’s index, fasting insulin, fasting triglyceride, body mass index (BMI), waist circumference, and blood pressure.

**Results:** The clozapine and olanzapine groups were similar on all the above variables. These two groups were combined and compared with patients on other antipsychotics. BMI was similar but significant differences were found in insulin resistance, fasting insulin levels, and triglycerides. Waist circumference and blood pressure followed the same trend.

**Conclusion:** These preliminary results suggest that antipsychotic treatment with both clozapine and olanzapine is associated with insulin resistance compared with other antipsychotics. This association is independent of BMI and may predispose these patients to the development of diabetes and coronary heart disease.

**Reviewer’s Comments:**
- Very little information is shared about the methodology, appears to be a non-randomized analysis. Claims to use fasting data, however unlikely to be accurate in collecting fasting data over a three month time period. Homa’s index calculations are very sensitive to fasting data for accuracy.
- Pooling of olanzapine and clozapine data represents an inappropriate and biased assumption.
- Findings of increased blood pressure are not consistent with Lilly’s large scale randomized data.


---

**GLUCOSE METABOLISM AND THE TREATMENT OF SCHIZOPHRENIA: A COMPLEX RELATIONSHIP**

*Goldman M, Milner KK, Shriberg RF*

**Introduction:** A complex relationship is emerging among atypical antipsychotics, abnormalities in glucose regulation, and obesity in schizophrenia.

**Methods:** We investigated these relationships in a cross-sectional study of 96 patients with schizophrenia or schizoaffective disorder at a community mental health center (mean age = 45.3 years; 39% female; 72% Caucasian; 22% African American).

**Results:** Sixteen patients were diagnosed with DM. Fasting plasma glucose (FPG), fasting plasma insulin (FPI), and cortisol levels were assessed in the remaining 80 subjects. FPG (ADA criteria, 1999) identified an additional case of DM (total DM = 17.9% versus about 7.8% in the general adult population) and nine cases of impaired fasting glucose (IFG; 9.5%). Forty-six percent of the sample met criteria for obesity (body mass index greater than or equal to 30) versus about 32% of the general population. In a multiple regression analysis to assess the effect of age, body mass index (BMI), duration on medication, and type of medication (atypical versus typical) on fasting plasma glucose, BMI was the strongest correlate of elevated FPG (beta = .43; p = .01).

After controlling for the other factors, there was little evidence for a differential effect of atypical compared with conventional agents on FPG (beta = .15; p = .46).

**Conclusion:** These data confirm an increase in the prevalence of DM in persons with schizophrenia and suggest that obesity may be the primary mechanism underlying the increase in impaired glucose regulation in schizophrenia.

**Reviewer’s Comments:**
Where Presented: Institute of Psychiatric Services Meeting, October 2001, Orlando FL.
Epidemiological Studies

Introduction

Pharmacoepidemiology studies are reviews of the claims databases of large insurers and other third party payers. These studies provide a real world estimate of the incidence of diabetes in patients receiving antipsychotics.

Epidemiological studies can provide useful information about large unselected patient populations. The large sample population allows analysis with sufficient statistical power to examine relatively rare events. Also, factors such as age, race, and gender can be analyzed in sub-populations with sufficient power to detect statistically significant differences. In addition, these studies may also be designed with less rigorous exclusion criteria than clinical trials, therefore, the results may be more easily generalizable.

Pharmacoepidemiology offers a reliable context for anecdotal case reports. Despite the desire by some to count case reports to estimate the relative risk of various medications, they simply cannot answer this question. One key problem is that they are not randomized so they do not account for important patient-related risk factors. (For example, if treatment refractory patients have higher baseline risk, then treatment related risk may falsely appear elevated in medications preferentially prescribed to the treatment refractory.) Pharmacoepidemiological studies may not address this either, but it is well handled by randomized clinical trials.

In terms of rates, case reports provide neither an accurate numerator nor denominator. Pharmacovigilance professionals assure us that a minority of side effects are ever reported, generally, published cases are likely to be a very small minority. What factors determine which cases are written up and published? For one, the author needs to view the event as likely medication-related, and preconceptions may be the deciding factor (i.e., when diabetes emerges, a clinician is likely to ascribe it to a medicine that he/she has been informed “causes diabetes” but not to one the clinician believes does not cause it). Epidemiology addresses these problems by identifying all patients taking the medication of interest (the denominator) and uses a uniform approach to identifying all treatment emergent cases (the numerator).

A useful pharmacoepidemiology analysis would include patients on only one antipsychotic, who had not been diagnosed with diabetes prior to the analysis period, and who has a readily identifiable diagnosis.

An understanding of the following terms is useful in understanding the limitations of the studies.

Incidence is the number of new events occurring in some time interval.

Prevalence is the relative frequency of cases in the population.

Relative risk is the ratio of the probability of the event occurring in one group (treated) to the probability of the same event occurring in another group (control or competitor). This is most useful if the event rates are low.

The odds of an event occurring are the probability of the event divided by the probability that the event does not occur. So, 3 to 1 odds means that the event is 3 times more likely to occur than
not occur (i.e. the probability that the event occurs is .75). If patients experience differing exposure times, the hazard rate and hazard ratio are often applied. These arise from "survival analysis", typically the proportional hazards model (also called Cox regression).

**Odds ratio** – This number describes the odds of developing diabetes. The odds ratio for the control group will be one and the odds ratio for the study groups will be the risk of developing diabetes relative to the control group. Odds ratio often does not control for factors such as age, gender and concomitant medications. Relative risk and odds ratios are most often used when all patients have the same exposure times and only a minority of the patients experience the event of interest.

The **hazard rate** is the instantaneous probability of an event given that it has not occurred to date.

**Hazard ratio** – The hazard ratio is the odds ratio adjusted for other variables that may affect the outcome. The hazard ratio for our purpose controls for age, gender and concomitant medications. The hazard ratio is then the ratio of the hazard rate in one group to the hazard rate in another group.


---

**Association of Diabetes Mellitus with Atypical Neuroleptics**

Sernyak MJ

**Introduction:** There have been reports of the development of both type I and type II diabetes following initiation of some of the atypical neuroleptics. These studies have consisted primarily of small series of patients.

**Methods:** All VA neuroleptic-treated outpatients with schizophrenia in the last quarter of fiscal year 1999 were included in this study. Patients who received clozapine, olanzapine, risperidone, or quetiapine comprised the atypical group. The frequency of diabetes mellitus across age groups and different atypical neuroleptics was examined using a multiple logistic regression analysis.

**Results:** 30,819 veterans were studied: 12,695 received typical neuroleptics (T), and 18,124 received atypical neuroleptics (A) (clozapine: 935 [5.2%]; olanzapine: 8,772 [48.4%]; quetiapine: 773 [4.3%]; or risperidone: 7,944 [43.8%]). A higher percentage of the A group compared with the T group in the under 40 (8.74% versus 6.21%, p = 0.007), 40–49 (15.89% versus 13.93%, p = 0.002), and 50–59 (22.73% versus 20.56%, p = 0.003) age groups were diagnosed with diabetes. By medication prescribed, risk of diabetes was also increased for clozapine (odds ratio [OR] = 1.251, 95% confidence interval [CI] = 1.070–1.462), olanzapine (OR = 1.107, CI = 1.038–1.180), and quetiapine (OR = 1.313, CI = 1.113–1.547) but not risperidone (OR = 1.049, CI = 0.982–1.120).

**Conclusions:** In this large group of patients with schizophrenia, atypical neuroleptic prescription was significantly more often associated with diabetes mellitus than typical neuroleptic prescription.

**Reviewer Comments:**

CONFIDENTIAL: Internal Lilly Use Only

Document Owner: Patrick Toalson
Last Modified: November 8, 2001
• Short term incidence study (3 month time frame) of a large sample size which adds credibility to the analysis.
• Authors state that data favors Risperidone over other atypical antipsychotics regarding odds ratio, however raw numbers are not out of line with those observed in other epidemiology studies (ie, Advance PCS, RAM-Q, Gianfrancesco).
• Unknown what factors were taken into consideration when multiple regression analysis calculated (age, gender, illness, BMI). Appears the odds ratio is versus typical AP prescription, or is it the general VA population? Unlikely that they corrected for differences in severity of illness between patients.


Association of New-Onset Diabetes and Antipsychotics: Findings from a Large Health Plan Database

Gianfrancesco F, Grogg AL, Mahmoud RA, Nasrallah HA

Background: Case series suggest that some antipsychotics may induce diabetes. This study measured the association of antipsychotic treatments with diabetes at a population level.

Methods: Claims data for psychosis patients (n = 7,933) within health plans encompassing 2.5 million lives were analyzed. Patients reporting pre-existing diabetes, either with diagnosis or claim for antidiabetic medication, up to eight months prior to observation were excluded. The frequency of newly reported diabetes in untreated patients and among patients treated with risperidone, olanzapine, clozapine, and high-and low-potency conventional was compared. Logistic regression models compared the odds of diabetes based on exposure to each of the antipsychotic categories and other explanatory variables.

Results: The odds of diabetes for risperidone patients was not significantly different from untreated patients (OR = 0.88, 95% CI = 0.37-2.07). Other antipsychotics had significantly higher odds of diabetes than untreated patients: olanzapine (OR = 3.10, 1.62-5.93); clozapine (OR = 7.44, 1.60-34.75); high-potency conventional (OR = 2.13, 1.10-4.13); and low-potency conventional (OR = 3.46, 1.52-7.79). The odds of developing diabetes with olanzapine, clozapine, and high-potency conventional differed significantly from risperidone (p < 0.05).

Conclusions: These data support case findings that some antipsychotics may increase the risk of developing diabetes. Risperidone was not associated with a higher risk of developing diabetes.

Reviewer Comments:
• This Janssen supported health plans database analysis generates the suggestion that is damaging to Zyprexa, but there are several flaws in the study, and the unmanipulated results actually suggest comparable rates. Claims data over a 2 year period (1996-97) were pooled from two distinctly different types of health plan databases from different parts of the US for this retrospective study. Were the populations comparable? Does this introduce biases and uncontrolled variables?
• Study examined data in 7,395 “psychotic” patients (n=4,334 who were taking an antipsychotic med, the remainder were “untreated”). The “untreated” control group is suspect, over 40% of “psychotic” patients were not prescribed any antipsychotic treatment. This does not match clinical practice and calls into question the quality of this dataset. The poster includes a number of analyses but is deficient in explanation and raw results, it’s small for an epidemiological study and though a study of ‘schizophrenia’, only 17% have schizophrenia.

CONFIDENTIAL: Internal Lilly Use Only
Document Owner: Patrick Toalson
Last Modified: November 8, 2001
• The analysis eliminated those patients with pre-existing diabetes diagnoses at 4 and 8 months prior to study time period from the study group. Diabetes identified via ICD-9 criteria or current antidiabetic medication usage.

• The authors do not provide much information based on patients, instead relying on “treatment episodes”. This means that individuals may be counted multiple times, e.g., if they came on and off drugs. This might be reasonable if we knew that medications posed a risk and if this risk were linear over time; in fact we wonder if either is true. This practice may have lowered apparent risk. If a subject did not develop diabetes (i.e. is not diabetes prone) he or she may be counted repeatedly, whereas if diabetes occurred, he or she could not be counted again. This may well have improved risperidone’s numbers. Dr. Gianfrancesco verbally reported that such patients were predominately in the risperidone group.

• The study is not clear regarding which cofactors are considered, but they are explicit that though a diagnosis was available, they did not control for it (the diagnoses were not available in the PCS study). If diabetes is more common in schizophrenia, or treatment refractory schizophrenia, this would disadvantage olanzapine, more so in that this study included only the first years of olanzapine availability, so that prescriptions would be more consistently “on label”.

• These are not identified as monotherapy patients as in the PCS analysis. Likely that multiple medications per patient were used throughout the study period.

• The authors are not forthcoming regarding actual rates of treatment emergent diabetes. Instead, they report only the calculated odds ratio and report these only “per month”. That is, in some way they divided the incidence by time of exposure (a reasonable approach only if occurrence is linear with time). Given that mean exposure was about a month longer on risperidone, this alone could more than account for the very small numerical risk advantage over olanzapine they report. For their overall analysis, no statistical test is reported for olanzapine vs risperidone, but the difference is very likely not significant. Odds Ratios from Table 2 of the poster: RIS 1.021, OLZ 1.082, CLOZ 1.079, High Potency Typicals 1.047, Low Potency Typicals 1.058

• The results section identified in this abstract are those Janssen is stressing in scientific meetings. Janssen is emphasizing a complex sub-analysis that amplifies olanzapine’s risk. As you will see below, it is difficult to understand the analysis. The primary analysis is in patients who had been followed in the database for at least four months prior to prescription of the antipsychotic of interest. For apparently arbitrary reasons, they looked at subsets of this group who had been in the database for at least 6 or at least 8 months, and chose to report only the latter. Again, there is a small olanzapine – risperidone difference, albeit a bit under that in the overall group. Then, remarkably, they “estimate” annual risk by raising monthly risk to the power of 12. This exponential maneuver amplifies a small olanzapine – risperidone difference to an estimated four-fold difference in risk. This seems to be the finding that Janssen would like to emphasize, rather than the primary objective from this study or from the much larger Caro study. We do not find this appropriate, given that this was a longitudinal study they could have used actual data to estimate risk, rather than this exponential approach. Secondly, this approach presupposes that risk is only drug related (although it is clear that patient predisposition is important) and is linear over time.

• It is worth pointing out that this finding is very out of line with the epidemiological studies including Caro. They estimate that risk on risperidone is lower than on no antipsychotic treatment at all; and that even this tortured analysis places the risk on olanzapine squarely within the range of conventional antipsychotic drugs and about half that of clozapine.

Key take away: Competitors may use selected manipulation of this dataset to support their argument that olanzapine has greatly elevated diabetes risk compared to risperidone. This is the
smallest and therefore the weakest of the current four pharmacoepidemiological studies, but overall results suggest comparable risk in olanzapine vs risperidone and all of their analysis suggests comparable rates on olanzapine vs conventional antipsychotics. We find their conclusion of lower risk on risperidone to be unjustified because it reflects a smaller subgroup and tortured, inappropriate analysis and biased study methodology. It conflicts with the overall results of this study or other available studies.


### The Risk of Developing Diabetes in Users of Atypical Antipsychotics

**Caro J, Ward A, Levinton C, Robinson K, Kopala L, Caro Research**

**Reviewer Comments:**

- Retrospective database analysis of the Quebec Medicare database to assess the risk of diabetes among patients being treated with Olanzapine versus Risperidone over a three year period from 1997-1999.
- One cohort consisted of patients who had at least one prescription for Olanzapine but not Clozapine during the study period (n=19,153) and the other cohort of patients receiving Risperidone but not Olanzapine or Clozapine (n=14,792). It can be reasoned that some of the Olanzapine patients simultaneously were taking Risperidone. Such patients likely had severe or treatment refractory psychosis and some information suggests that these patients are at an especially high diabetes risk. The fact that these investigators assigned patients taking both drugs to the Olanzapine group only reflects their pre-existing bias and may have inflated the risk for Olanzapine. We’ve seen in another study (Saklad, CPNP) higher rates of diabetes in pts on Olanzapine plus Risperidone compared to those on either alone.
- Exclusion criteria were any patient having an ICD-9 for diabetes (250.0 to 250.93) or an pre-existing prescription for insulin or an oral hypoglycemic agent. Patients were not necessarily neuroleptic free at baseline and apparently could be on multiple meds and still be included.
- New diabetes diagnoses (ICD-9 or diabetes prescription initiation) after antipsychotic initiation were tabulated over the three-year study period. There were 319 patients developing diabetes after being prescribed Olanzapine and 217 patients after beginning Risperidone. Logistic regression found risk ratio of 1.08 – ie, predict 108 cases on OLZ for every 100 on RIS, difference not significant.
- The authors state that there was a severe imbalance in age and gender between the two cohorts and conduct a Cox proportional hazards analysis which gives a "corrected ratio" of 1.2 for Olanzapine vs. Risperidone meaning Olanzapine patients had a 20% greater risk for developing diabetes. This risk ratio is borderline non-significant despite an N of 35,000.
- They also do a Cox proportional hazard analysis adjusting for age in women showing a risk ratio of 1.31, meaning that women had a 31% greater risk for diabetes on Olanzapine than Risperidone. (What they don’t state but show in a graphic is that men had a lowered risk on Olanzapine vs. Risperidone). Incidentally, women have a higher risk for diabetes than men in the normal population also.
- The Cox proportional hazard ratios controlled for age and gender, but not for concomitant medications, differential rates of treatment discontinuation, difference in treatment setting, diagnosis, severity of illness or time of exposure.
Calculated 3-year incidence of new onset diabetes based upon data in the ACNP 2000 abstract is 1.7% on OLZ (319/19,153) vs. 1.5% on RIS (217/14,792). The annual one year incidence of newly diagnosed diabetes in the normal US population is ~0.4% per year, or over 3 years a rate of ~1.2%. So in this rather large database analysis they found that the incidence of new diabetes cases for patients on Olanzapine and Risperidone are both just slightly higher than the expected incidence in a normally healthy population and likely below a mentally ill population incidence.

One weakness of this study in contrast to the AdvancePCS study is its failure to include consideration of all 4 atypical antipsychotic drugs as well as typical antipsychotics and a control group. The relative consistency across groups in the PCS study tends to validate the impression of comparable risk. The Caro study does not offer such reassuringly, nor does it give perspective on whether rates on Risperidone are similar are much higher/lower than typical drugs or the general population.

Timeframe of the study is a positive, preceded time of clinical focus on diabetes as an issue.

The key take away from the Caro study is that though numerically Risperidone risk looks better than Olanzapine. Overall rates were of similar magnitude on the two drugs.

Where presented: ACNP Annual Meeting, Dec 2000, San Juan PR

Prevalence of Diabetes in Schizophrenia Patients Treated with Antipsychotics

Casey DE, Danielson EM, Fishman NB.

Introduction: Patients with schizophrenia are often described as being at greater risk for diabetes mellitus (DM) than the general population. This has been attributed, in part, to higher rates of obesity and higher body mass indices (BMI). With the wide adoption of atypical antipsychotics, and the potential for substantial additional weight gain that is associated with certain agents, the rate of weight-induced DM may be higher than previously observed. Additionally, early evidence suggests that some antipsychotics may produce adverse effects on glucose metabolism even in the absence of weight gain. Surprisingly little is known about the actual prevalence of DM with either typical or atypical antipsychotics in various populations.

Methods: To address this issue, the prevalence of DM was determined by reviewing the clinical records of patients with the diagnosis of schizophrenia at the Portland, Oregon VA Medical Center to identify those with a concurrent diagnosis of DM. Drug treatment records were also reviewed to determine which antipsychotic medicines patients were taking at the time of the survey. The DM prevalence and mean ages of schizophrenia patients treated with an antipsychotic are presented.

Results: For the typical antipsychotic agents: haloperidol, N = 3/47 (6.4%), age = 66.3 years; perphenazine, N = 3/42 (7.1%), age = 45.7 years; chlorpromazine, N = 2/18 (11.1%), age = 46.0 years; thioridazine, N = 4/20 (20%), age = 61.0 years. For the atypical antipsychotic agents: risperidone, N = 6/73 (8.2%), age = 57.2 years; quetiapine, N = 2/16 (12.5%), age = 47.5 years; clozapine, N = 5/31 (16.1%), age = 58.8 years; olanzapine, N = 33/194 (17.0%), age = 57.9 years. These results compare with the rates in the general population of 3.9% for 40–49 year olds, 6% for 50–59 year olds, and 12.6% for 60–69 year olds.

Conclusions: Agents that are traditionally associated with higher amounts of weight gain, such as the typical agents of chlorpromazine and thioridazine as well as the atypical agents quetiapine, clozapine, and olanzapine are associated with a higher than average prevalence of diabetes. The clinical consequences of these findings will be discussed.
Reviewer’s Comments:
- Overall this is a small prevalence study (N=441) derived from a cross sectional review of patient records, larger studies have shown more comparable rates of diabetes.
- No consideration is given in this analysis for differences in treatment groups such a severity of illness, length of time on medication, prior antipsychotic usage or current use of concomitant meds at time of diabetes diagnosis, baseline BMI or changes in BMI, gender, ethnic background, family history or diagnosis of diabetes prior to antipsychotic initiation.


Atypical Antipsychotics and Concomitant Antidiabetic Use

Saklad SR

Introduction: The Atypical Antipsychotics (AA) have been implicated in causing decreased glucose tolerance. Routine monitoring of inpatients at a large state hospital and subsequent diagnosis and treatment of Type II Diabetes Mellitus (DM) with oral antidiabetic agents may differ depending upon which AA has been prescribed, dosing, and patient demographics. This provides a "Real World" measure of the actual change in glucose tolerance.

Methods: Review of the San Antonio State Hospital pharmacy distribution system (Pharmakon 2000) and Texas Department of Mental Health and Mental Retardation statewide client tracking system (CARE). This analysis looked at 58,176 treatment episodes in 2862 patients with 56% having a primary diagnosis of schizophrenia.

Results:

![Graph showing DM Type 2 Diagnosis and Temporally Implicated AA Does Not Predict Antidiabetic Use]

Chi Square = 5.117, DF = 5, p = 0.4018

CONFIDENTIAL: Internal Lilly Use Only

Document Owner: Patrick Toalson
Last Modified: November 8, 2001
**Antidiabetic Use & AA Use**

Chi Square = 30.037, DF = 14, p = 0.0075

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>CO</th>
<th>CQ</th>
<th>CR</th>
<th>CRQ</th>
<th>CR</th>
<th>O</th>
<th>Q</th>
<th>R</th>
<th>RO</th>
<th>RQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>19</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>124</td>
<td>26</td>
<td>197</td>
<td>41</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>423</td>
<td>90</td>
<td>20</td>
<td>126</td>
<td>54</td>
<td>17</td>
<td>237</td>
<td>396</td>
<td>339</td>
<td>534</td>
<td>109</td>
</tr>
</tbody>
</table>


**USE OF ATYPICAL ANTIPSYCHOTICS AND THE INCIDENCE OF DIABETES**

*Lage MJ, Kemner J*

**Objective:** Compare the incidence of diabetes between patients initiating treatment with typical or atypical antipsychotics.

**Methods:** Retrospective analysis of the IMS Lifelink™ claims database identified 6,758 enrollees with the following characteristics: (1) age 18–65; (2) initiated on typical (n = 3,381), or atypical (n = 3,377) between October 1996 and December 1998; (3) no use of antipsychotics for six months prior-initiation; (4) not classified as diabetic (i.e., no diagnosis of diabetes or receipt of any diabetic medication for one year prior to initiation). Logistic regressions were used to estimate odds ratios (OR) of a diagnosis of diabetes or use of any diabetic medication in the one year post-initiation, controlling for age, gender, and regional differences.

**Results:** Higher probability of becoming diabetic was not evident following initiation on atypicals (mean duration of therapy = 135 days) compared with typicals (mean duration of therapy = 84 days) (OR = 1.032, p=0.825) or initiation on olanzapine (OLZ) or risperidone (RIS) compared with typicals (OR=0.977, 1.170; p=0.899, 0.35, respectively. The probability of developing diabetes was less in patients treated with OLZ (mean dose 9.01 mg/day) than in patients treated with RIS (mean dose 2.37 mg/day) (OR=0.834; p=0.277), although the difference was not statistically significant.
Conclusion: The probability of developing diabetes was no more likely following treatment with atypicals than typicals. Within atypical use, the probability of developing diabetes was less during treatment with OLZ than with RIS, although the difference was not statistically significant.

Reviewer’s Comments:

Where Presented: Institute of Psychiatric Services Meeting, October 2001, Orlando FL.
Published Manuscripts

"The Effects of Ziprasidone on Plasma Lipids and Glucose" - George Simpson MD, et al

- A Pfizer supported study retrospectively looking at lab parameters collected on 37 outpatients during a 6 week Ziprasidone switching study. All lab parameters were non-fasting measurements. Patients were switched from olanzapine, risperidone or typical agents.
- No changes were noted in BMI from baseline to endpoint, all weights were converted to BMI. No weight data given, BMI measurements may have been used and reported to cause the data to appear more favorable?
- Glucose levels did not significantly change during the 6 weeks.
- Cholesterol and triglyceride levels decreased significantly from baseline to endpoint. Baseline levels were borderline for being above the normal range prior to switching to Ziprasidone in these patients.
- Authors conclusions: Ziprasidone appears to be the only weight change neutral atypical and capable of lowering plasma lipid levels. They go on to say that Ziprasidone may have a potential beneficial effect on hyperlipidemias in the schizophrenic population and reduce corresponding cardiac risk. However, they do mention briefly concerns over QTc prolongation being a potential issue.

Comments: Straightforward lab analysis data. May be biased due to lack of non-fasting status and collection of blood at different times of the day. The authors cite a lack of a placebo group, small sample size and short trial duration as possible design flaws which interfere with drawing inferences from secondary lab data such as this.
Triglyceride / Cholesterol Issues

Olanzapine seems to be associated with triglyceride increase, and most likely this is secondary to increased appetite and weight. Cholesterol is less of an issue for OLZ, if an issue at all; though Pfizer I believe is arguing that ziprasidone has a favorable impact.

Triglyceride is a factor in long-term cardiovascular risk, there remains some debate about its relative importance vis a vis other important factors. To my view it is not an important consideration in acute treatment decisions. In terms of longer-term management, I doubt that there should be any differences based on which psychotropic a patient is taking. Standard recommendation for all adult Americans is periodic screening of lipids. If they are abnormal, they can be managed effectively, and again danger is long-term risk more than any immediate cardiovascular effect. Patient-specific factors could influence more frequent monitoring/closer attention, and obesity could certainly be a reason to screen more often, as well as others such as smoking or family cardiac history.

I take strong exception to the assertion that long-term OLZ prescription is malpractice. Because of its excellent efficacy it usually is good practice. Perhaps some would like clinicians to lose sight of the fact that the core reason for prescribing these drugs is beneficial effects; good clinical practice includes ongoing monitoring on an individual level of actual benefits achieved versus actual side effects encountered and known drug-specific risks. In most cases this should be favorable for olanzapine, especially as a manageable and long-term consideration like triglyceride should seldom tip the balance.

Proactively education on this issue could help pts and clinicians; further, any successful management of weight will decrease saliency of lipids.

Robert PS - here is some data background:

I believe that on average, across the general population, obesity is associated with relatively higher triglyceride and lower HDL. Especially in the case of HDL other variables, eg genetic predisposition may be more important determinants. Therefore, such general statements may or may not apply to individual patients. Nevertheless I do not think that we could or would want to refute the assertion that weight gain increases the likelihood of lipid changes that in the long term increase cardiovascular risk.

In terms of olanzapine-specific information, as you know we are proposing modifying our label to mention the possibility of triglyceride increase. That likely will state that 1.9% of pts on olanzapine developed random triglyceride levels more than 2 but less than 3 times the fasting upper limit of normal. Note that the Seroquel label carries a precaution related to TG elevation. We've included TG only in recent trials, but these and outside trials are consistent in showing mean increase in random TG of roughly 30-70 mg/dl for olanzapine-treated pts. There can be significant artifact in non-fasting samples; the only presented work that to my knowledge claims to be fasting was Pfizer's head to head trial; there median increase after 6 weeks on OLZ was 28 mg/dl. Some of product team's ongoing work will illuminate triglyceride effects. So far it seems most likely to be tied to weight, and pts with clinically relevant change are most likely to be found among those with significant obesity. There is some sentiment and info among outside researchers (eg Dufrene at Brown) that TG increase on any psychotropic could contribute to beneficial effects due to TG role in brain.

Regarding cholesterol, most available data, including our own, suggest little impact of olanzapine on total cholesterol. There does tend to be some increase among those who gain the most, not

CONFIDENTIAL: Internal Lilly Use Only
Document Owner: Patrick Toalson
Last Modified: November 8, 2001

ZY 8608 1235
unique to OLZ. Your note suggests that Pfizer reps are emphasizing HDL decrease. Study 054 found significant decrease in Total Cholesterol to HDL ratio on ziprasidone (as well as haloperidol). Ratio worsened significantly on thioridazine and quetiapine. Numerical but non significant worsening was seen on olanzapine and even more on risperidone. In the head to head study, Pfizer reports "fasting HDL increased insignificantly in both olanzapine treated and ziprasidone treated patients, ziprasidone vs olanzapine NS".
## Index

<table>
<thead>
<tr>
<th>Name</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aladjem AD</td>
<td>8</td>
</tr>
<tr>
<td>Bari M</td>
<td>15</td>
</tr>
<tr>
<td>Boyd JA</td>
<td>13</td>
</tr>
<tr>
<td>Buckley PF</td>
<td>11</td>
</tr>
<tr>
<td>Cagliero E</td>
<td>7</td>
</tr>
<tr>
<td>Caro J</td>
<td>27</td>
</tr>
<tr>
<td>Casey DE</td>
<td>5, 28</td>
</tr>
<tr>
<td>Chong, YS</td>
<td>12</td>
</tr>
<tr>
<td>Cohn TA</td>
<td>20</td>
</tr>
<tr>
<td>Cooper BP</td>
<td>17</td>
</tr>
<tr>
<td>Danielson EM</td>
<td>28</td>
</tr>
<tr>
<td>DeSouza L</td>
<td>10</td>
</tr>
<tr>
<td>Fishman NB</td>
<td>28</td>
</tr>
<tr>
<td>Frank BL</td>
<td>12</td>
</tr>
<tr>
<td>Friedman L</td>
<td>11</td>
</tr>
<tr>
<td>Fucetola R</td>
<td>17</td>
</tr>
<tr>
<td>Gianfrancesco F</td>
<td>25</td>
</tr>
<tr>
<td>Glick ID</td>
<td>15</td>
</tr>
<tr>
<td>Goldman M</td>
<td>21</td>
</tr>
<tr>
<td>Grogg AL</td>
<td>25</td>
</tr>
<tr>
<td>Gupta S</td>
<td>12</td>
</tr>
<tr>
<td>Hammond C</td>
<td>10</td>
</tr>
<tr>
<td>Haupt DW</td>
<td>17</td>
</tr>
<tr>
<td>Henderson DC</td>
<td>7</td>
</tr>
<tr>
<td>Horne RL</td>
<td>15</td>
</tr>
<tr>
<td>Kameh H</td>
<td>20</td>
</tr>
<tr>
<td>Kemner J</td>
<td>30</td>
</tr>
<tr>
<td>Khandat A</td>
<td>6</td>
</tr>
<tr>
<td>Kopala L</td>
<td>27</td>
</tr>
<tr>
<td>Lage MJ</td>
<td>30</td>
</tr>
<tr>
<td>Leiter L</td>
<td>20</td>
</tr>
<tr>
<td>Levinton C</td>
<td>27</td>
</tr>
<tr>
<td>Lindenmayer JP</td>
<td>6</td>
</tr>
<tr>
<td>Lockwood C</td>
<td>12</td>
</tr>
<tr>
<td>Maguire GA</td>
<td>12</td>
</tr>
<tr>
<td>Mahmoud RA</td>
<td>25</td>
</tr>
<tr>
<td>Massanyi EZ</td>
<td>11</td>
</tr>
<tr>
<td>Melson AK</td>
<td>17</td>
</tr>
<tr>
<td>Meng LR</td>
<td>13</td>
</tr>
<tr>
<td>Meyer J</td>
<td>8</td>
</tr>
<tr>
<td>Milner KK</td>
<td>21</td>
</tr>
<tr>
<td>Nasrallah HA</td>
<td>25</td>
</tr>
<tr>
<td>Nathan DM</td>
<td>7</td>
</tr>
<tr>
<td>Newcomer JW</td>
<td>17</td>
</tr>
<tr>
<td>Newton MA</td>
<td>10</td>
</tr>
<tr>
<td>Pamies C</td>
<td>11</td>
</tr>
<tr>
<td>Parker B</td>
<td>6</td>
</tr>
<tr>
<td>Piggott T</td>
<td>15</td>
</tr>
<tr>
<td>Remington GA</td>
<td>20</td>
</tr>
<tr>
<td>Robinson K</td>
<td>27</td>
</tr>
<tr>
<td>Romano SJ</td>
<td>15</td>
</tr>
<tr>
<td>Sarkar W</td>
<td>10</td>
</tr>
<tr>
<td>Schwarz ME</td>
<td>8</td>
</tr>
<tr>
<td>Schweiger JA</td>
<td>17</td>
</tr>
<tr>
<td>Selke G</td>
<td>17</td>
</tr>
<tr>
<td>Shriberg RF</td>
<td>21</td>
</tr>
<tr>
<td>Simpson G</td>
<td>15</td>
</tr>
<tr>
<td>Singer B</td>
<td>11</td>
</tr>
<tr>
<td>Singh A</td>
<td>6</td>
</tr>
<tr>
<td>Smith RC</td>
<td>6</td>
</tr>
<tr>
<td>Steinmeyer C</td>
<td>12</td>
</tr>
<tr>
<td>Ward A</td>
<td>27</td>
</tr>
<tr>
<td>Weiden P</td>
<td>15</td>
</tr>
<tr>
<td>Wilson D</td>
<td>10</td>
</tr>
<tr>
<td>Wirshing D</td>
<td>13</td>
</tr>
<tr>
<td>Wirshing, WC</td>
<td>13</td>
</tr>
<tr>
<td>Yu BP</td>
<td>12</td>
</tr>
</tbody>
</table>

CONFIDENTIAL: Internal Lilly Use Only

Document Owner: Patrick Toalson
Last Modified: November 8, 2001