

ATYPICAL ANTIPSYCHOTICS ISSUES MANAGEMENT

HYPERGLYCEMIA / DIABETES CONCERNS

TRIGLYCERIDE ISSUES

COMPETITIVE LITERATURE / POSTERS REVIEW

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Internal Lilly Communications

Zyprexa Label Changes to the Japanese Label

Key Points About the Zyprexa Label Change in Japan

- The Japanese label change consists of the following:
 - a warning about patients experiencing marked increases in blood glucose
 - a recommendation that observations, such as measurement of blood glucose, may be indicated for patients with diabetes or with risk factors for diabetes
 - a contraindication for the use of ZYPREXA in patients with diabetes mellitus and those who have a history of diabetes
- We do not feel this rate of occurrence (9 cases in 137,000 exposures, $\leq 1\%$) justifies the action taken by the Ministry of Health, Labor and Welfare (MHLW)
- These changes were prompted by 9 severe case reports of hyperglycemia, including two deaths, in patients taking olanzapine.
 - Many of these patients had preexisting diabetes
 - All cases involved other risk factors for these diabetes-related events, such as personal and family history of diabetes, obesity, or confounding causes
 - The MHLW would not consider any data not obtained in Japan. Therefore, epidemiology studies, treatment emergent diabetes data from our clinical trials, and the hyperglycemic clamp data were not considered in the decision.
- Regarding the impact on the US and EU labels:
 - The European Union has one label for all countries. Any indication that the label will be changed in one country, i.e. the UK, is obviously false.
 - Personnel from Lilly have proactively informed the regulatory agencies the EU, Canada, US, and other countries of the MHLW decision. These agencies have informed us that they do not plan a similar action. If a label change is requested in the future, all available scientific data will be considered.
- ZYPREXA is the best medication for most patients suffering from schizophrenia or bipolar disorder. If there is an association between antipsychotics and diabetes, then it occurs at comparable rates among the atypical class of antipsychotics.

FAQs

Q: What additional information can you share about the two deaths?

A: Some of the details we do know are that one patient had preexisting diabetes, and the other had a severe preexisting medical condition. Both patients had exacerbation of diabetes during olanzapine treatment due to concomitant medications and co-morbid conditions (the patient with preexisting diabetes was also on risperidone and had a serious infection). The two deaths in Japan are indeed a tragedy. Unfortunately, it is likely that both of these patients could have survived if their medical treatment and follow-up had been appropriate. Lilly supports the ADA guidelines that for patients with diabetes, or significant risk factors, good clinical practice includes assessment and follow-up regardless of what agent a patient is receiving.

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Q: Are Japanese patients more likely to develop diabetes?

A: Asians in general and the Japanese in particular are thought to be one of the ethnic groups that are at elevated risk for diabetes. However, if you look at the case reports at hand, many of the patients had diabetes or co-morbid risk factors before taking ZYPREXA. We believe the real difference in Japan is with the regulatory environment. The Japanese regulatory body based their decision on looking at nine serious case reports. We disagree with this decision because we have examined evidence across 8 million ZYPREXA patients worldwide and have found no causal association or any difference in rates of diabetes with other drugs.

Q: What can you tell us about the labels for other antipsychotics in Japan? Is the Japanese regulatory body looking at any other products? How likely is it that this will become class labeling in Japan? Are there other cases of labels in Japan being considerably different than labels in other countries?

A: We, too, are curious about these topics and the ZYPREXA Product Team is currently compiling this information from our colleagues in the Japan affiliate. Understandably, the affiliate has been devoting its efforts to working with the Japanese regulatory body to communicate our scientific data so that they, too, can understand that there are comparable rates and that this labeling for ZYPREXA will do a great injustice to patients for whom ZYPREXA is truly the best choice based on its overall efficacy and safety profile. As such, we have not yet received answers to these questions. We will communicate with you as we learn more.

Q: What is the incidence of diabetes of patients on ZYPREXA vs. placebo?

A: This is difficult to study because ZYPREXA is indicated for schizophrenic and bipolar mania patients and those patients, due to the nature of their illness, may not be treated with placebo for extended periods of time. We do have limited data to suggest comparability between ZYPREXA patients and placebo patients. However, they tend to be short-term and small studies and in no way definitive. More reliable data supports the fact that ZYPREXA patients have comparable rates of diabetes compared with patients on other treatments.

Q: Is it advisable for physicians to prescribe ZYPREXA to patients who have pre-existing diabetes?

A: A decision to prescribe any product should be based on that product's overall efficacy and safety profile. Lilly supports the ADA guidelines that for patients with diabetes, or significant risk factors, good clinical practice includes assessment and follow-up regardless of what agent a patient is receiving.

Q: Are the label changes in Japan equal to a black box warning in the U.S.? What is a black box warning and what is a contraindication?

A: The label change in Japan is a "red box" warning. It is our understanding that this serves to heighten awareness of the issue, but does not carry with it the regulatory requirements of a "black box" as we know it in the U.S.

A "black box" in the U.S. requires that the information contained in the box be included in any and all promotional material and/or presentations. It is the highest level of warning available for U.S. labels.

A contraindication is a statement that an agent should not be used in a specific situation – they are rare and imply a need for additional monitoring. We are not aware of any products, including ZYPREXA, for which there is a contraindication in the U.S. label for use in patients with diabetes.

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British MCA Newsletter Review, May 3rd 2002

Early last week, the UK regulatory agency reported in its quarterly newsletter a language change with respect to appropriate clinical monitoring of patients with diabetes in the ZYPREXA European label which took place more than a year ago. Since December 2000, the European label has contained language consistent with the information contained in the US label.

On May 3, an article referencing the UK regulatory agency report appeared in Reuters News, inaccurately characterizing the language change in our European label as having taken place recently. The article appears to suggest causal relationship between Zyprexa and hyperglycemic events; this is not an accurate reflection of the European label or of current scientific understanding. In addition, the article does not provide critically important context, such as: 1) the very high prevalence of diabetes in severely mentally ill patients that has been identified for decades; 2) the reports of treatment-emergent diabetes during treatment with most current and past antipsychotic medications; 3) the evidence from multiple epidemiology studies that identified comparable rates of treatment-emergent diabetes across commonly prescribed antipsychotic agents, and; 4) that ZYPREXA has now been used in 8 million patients world wide, with a very favorable track record of safety and efficacy.

Subsequently to the publication of the Reuters article, Bloomberg (a financial news agency) also published an article referencing the UK regulatory agency's report. The article quotes an analyst at Deutsche Bank Securities Inc. as stating, "Other drug makers will be able to use this, and that's a challenge Lilly faces now." The analyst then states, "This is an issue that has been around for a while, and I think doctors know it's a risk, but that many feel it's the most effective drug."

Good clinical practice suggests that psychiatric patients should be evaluated for the development of diabetes, as should the general population, based on risk factors defined by the American Diabetes Association and World Health Organization. Given the vast evidence that the risk of diabetes is comparable across widely prescribed psychotropic agents, concerns regarding diabetes should not be a differentiating factor in treatment selection. The primary consideration for choosing a psychotropic agent continues to be its overall risk/benefit profile, i.e. its efficacy in treating the psychiatric illness at hand and its overall tolerability. It is our obligation to let our customers know not only that ZYPREXA is safe, but that to not prescribe based on a fear of diabetes would be to potentially deny patients the best available medication to move their lives forward.

Patients and health care providers must be careful in interpreting news reports like the one published by Reuters because taken out of context they could potentially endanger the health and safety of patients suffering from severe and persistent mental illness.

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Posters

Diabetes Prevalence in Schizophrenia

Prevalence and Correlates of Diabetes in National Schizophrenia Samples.
Schizophrenia Bulletin. 2000;26(4):903-912.

*Dixon L{ XE "Dixon L" }, Weiden P{ XE "Weiden P" }, Delahanty J{ XE "Delahanty J" },
 Goldberg R{ XE "Goldberg R" }, Postrado L, Lucksted A, Lehman A*

Introduction: People with schizophrenia may be at increased risk for Type II diabetes because of the side effects of antipsychotic medication, poorer overall physical health, less healthy lifestyles, and poorer health care.

Methods: The present study uses databases collected by the Schizophrenia Patient Outcomes Research Team (PORT) to assess the prevalence and demographic and clinical correlates of diabetes within large populations of persons receiving treatment for schizophrenia.

Results: In the Schizophrenia PORT, Medicaid and Medicare data from 1991 and more recent interview data were collected regarding the comorbidity of schizophrenia and diabetes: prevalence, quality of life, physical health, services utilization and costs. The study found that rates of diagnosed diabetes exceeded general population statistics well before the widespread use of the new antipsychotic drugs. Risk factors for diabetes were similar to those observed in the general population. The linkage of diabetes to poor physical health, medical morbidity, and increased utilization and cost requires attention.

Conclusions: This study of diabetes in the early 1990's suggests that even before the widespread use of the atypical antipsychotic drugs, diabetes was a major problem for persons with schizophrenia.

Review Comments:

- The PORT study was designed to examine patterns of treatment for persons with schizophrenia in usual care settings. Claims data from the national Medicare program, Medicaid in one state, and primary data collected from a field study of patient interviews in two states were used in the study.
- Prevalence rates of current treated diabetes varied from 9 to 14 percent, with a lifetime rate reported in the field surveys of 15%. The field study sample had a mean age of 43 years, these prevalence rates compare to a NHIS rate of 6.3% for persons aged 45-64 and 1.2% for ages 18-44. Therefore prevalence rates seen in this analysis are roughly 2-4 times higher than the general population figures.

Increased Cardiovascular Disease in Patients with Schizophrenia

Curkendall SM{ XE "Curkendall SM" }, Mo J, Jones JK, Glasser D

Objective: To determine whether patients with schizophrenia are at increased risk of cardiovascular morbidity and mortality compared with the general population.

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Methods: Medical claims and death records of 3,022 subjects with diagnostic evidence of schizophrenia between 1994 and 1995 were obtained from the Saskatchewan Health database. The prevalence and incidence of cardiovascular morbidity and mortality were compared with that in an age- and gender-matched population group (n=12,088), adjusting for risk factors such as hypertension, hyperlipidemia, and serious pulmonary disease.

Results: The prevalence of all cardiovascular comorbidities during 1994 and 1995 was higher in patients with schizophrenia than in controls. Significantly increased odds ratios were as follows: for arrhythmia, 1.5 (CI 1.2-1.8); syncope, 4.0 (CI 2.0-7.9); stroke 2.1 (CI 1.6-2.7); transient cerebral ischemia, 2.5 (CI 1.7-3.7); diabetes mellitus, 2.1 (CI 1.8-2.4); and heart failure, 1.7 (CI 1.4-2.2). The incidence of cardiovascular outcomes and mortality were computed during 39 months of follow up (from January 1996 through March 1999). The adjusted relative risk was significantly increased for stroke, 1.5 (CI 1.2-2.0); ventricular arrhythmia, 2.3 (CI 1.2-4.3); diabetes, 1.8 (CI 1.2-2.6); heart failure, 1.6 (CI 1.2-2.0); all-cause mortality, 2.8 (CI 2.3-3.4); nonsuicide mortality, 2.7 (CI 2.3-3.3); and cardiovascular mortality, 2.2 (CI 1.7-2.8).

Conclusions: Persons with schizophrenia appear to be at greater risk for cardiovascular morbidity and mortality than those in the general population.

Review Comments:

- This study looked at patients defined as diabetic based upon a diabetes diagnosis, or prescription for oral hypoglycemic medication or insulin.
- The Saskatchewan health database is recognized as a reliable record of schizophrenia diagnoses and overall contains the health records for approximately 1 million residents.
- For each person identified as schizophrenic during the 2 year study period (1994, 1995) four age and gender matched non-schizophrenic controls were selected randomly from the health database to serve as a comparison control group.
- Median age of both groups was 47 years old, a mid-range age for assessing type II diabetes prevalence. Both groups had 49.5 % men and equivalent rates of hyperlipidemias and hypertension.
- Across the board cardiovascular comorbidities were higher in the schizophrenic group than the control group.
- ☆ Of particular interest in this review, the rate of diabetes was approximately 2.5 times greater than the control group, which is in line with other prevalence assessments of the schizophrenic population.
- ☆ The time frame of this study was prior to the widespread introduction of atypical antipsychotic medications, thereby negating the likelihood of an atypical drug effect on the increased prevalence of diabetes.

Where Presented: APA Annual Meeting, May 2001, New Orleans LA.

Mortality and Cardiovascular Morbidity Among Patients with Schizophrenia

Enger C{XE "Enger C"}, Weatherby L, Reynolds R, Glaser D, Walker A

Objective: To estimate mortality, cardiovascular morbidity, and frequency of new-onset diabetes among patients with schizophrenia.

Methods: Study population included 1,920 patients in the UnitedHealthcare research database who received antipsychotic medication between 4/1/95 and 3/31/99, and physician services with

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an associated diagnosis of schizophrenia. Patients were matched by age, sex, and health plan to 9,600 persons randomly selected from the general membership of UnitedHealthcare. Mortality, cardiovascular morbidity and new-onset diabetes were determined using the National Death Index search and medical claims records.

Results: After adjustment for covariates, the risk of death was 4 times greater in the schizophrenia group than in the control group, regardless of whether patients were dispensed a typical or atypical antipsychotic. Schizophrenic patients taking typical antipsychotics had increased risk of myocardial infarction (MI) (RR=5.34; 95% CI 1.75-16.30) and arrhythmia (RR=2.38; 95% CI 0.54-10.55) compared with patients without schizophrenia. Schizophrenic patients regularly taking either typical or atypical antipsychotics had an increased risk of diabetes (RR=3.41; 95% CI 1.62-7.15).

Conclusions: Mortality and cardiovascular morbidity among patients with schizophrenia are significantly elevated compared with rates in matched controls. Users of typical and atypical antipsychotics do not differ in their overall mortality or risk of new-onset diabetes. Typical antipsychotics appear to be associated with a higher risk of MI and arrhythmia.

Review Comments:

- This study covers a longer time frame (4 years) as compared to the 2 year time frame in the previous Saskatchewan prevalence analysis.
- Patients were identified as being schizophrenic by having both a prescription for an antipsychotic and a physician claim associated with a diagnosis of schizophrenia. This eliminates confounding patient diagnostic groups that are included in other claims database studies (ie, PCS, Caro, Gianfrancesco)
- For each schizophrenic patient identified there were 5 controls matched for age, sex, and health plan type.
- Covariates in their analysis included history of diabetes (diagnosis or treatment), year in which the index antipsychotic was dispensed (to control for new atypical entries to the market), age and sex.
- ☆ They found that patients with schizophrenia were 2 times more likely to have a history of diabetes than controls based upon claims during the 90 day time period prior to the antipsychotic index date.
- ☆ The rate (per 100,000 person years) of new-onset diabetes was about 2.5 times greater in the schizophrenic group versus the control group.
- ☆ The new-onset diabetes adjusted rate ratios for typical antipsychotic use versus controls was 1.14 and the ratio for atypicals versus controls was 0.8. Neither was statistically significant. However, the risk of diabetes was significantly increased in patients who had the highest adherence to their medication.

Where Presented: APA Annual Meeting, may 2001, New Orleans LA.

Impaired Fasting Glucose in First Episode Schizophrenia

Thakore JH{ XE "Thakore JH" }, Ryan MCM{ XE "Ryan MCM" }

Introduction: Most of the literature indicating that schizophrenia and diabetes mellitus are associated has been confounded by the fact that all of the patients studied to date were on or had been exposed to a variety of different neuroleptics. The aim of this study was to determine the

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frequency of impaired fasting glucose (IFG) in patients with first-episode, drug naïve schizophrenia.

Methods: Twenty six subjects who fulfilled DSM IV criteria for schizophrenia and 26 age and sex matched normal volunteers had their fasting plasma glucose, insulin and cortisol plasma levels measured.

Results: The major findings of this study were that 15% of patients with schizophrenia had IFG as opposed to none of the control subjects ($\chi^2 = 4.33$, $p > 0.05$). Patients with schizophrenia in comparison to controls had higher fasting glucose levels (95.8 ± 16.9 vs. 88.2 ± 5.4 mg/dl; $p > 0.03$), higher fasting insulin levels (9.8 ± 3.9 vs. 7.7 ± 3.7 μ U/ml; $p > 0.05$), higher cortisol levels (499.0 ± 161.0 vs. 303.0 ± 110.0 nmol/l; $p > 0.005$) and greater insulin resistance (2.3 ± 1.0 vs. 1.7 ± 0.7 ; $p > 0.01$).

Conclusions: This study shows that first episode, drug naïve patients with schizophrenia have increased rates of IFG and insulin resistance and therefore, a greater propensity to developing type 2 diabetes mellitus.

Review Comments:

- Another example of the increased risk for developing diabetes in the schizophrenic population. This is however the first study to look at first episode patients.

Where Presented: Biennial Winter Workshop on Schizophrenia, February 2002, Davos Switzerland.

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Retrospective Database Analyses / Case Reports

Prevalence of Diabetes During Extended Clozapine and Olanzapine Treatment

Casey DE{ XE "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.

Review 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.

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The Effect of Typical and Atypical Antipsychotics on Diabetes Mellitus

Matchett JL{ XE "Matchett JL" }, Radmaker SB{ XE "Radmaker SB" }, Fishman NB, Casey DE{ XE "Casey DE" }

Introduction: An association between psychosis, typical antipsychotic drugs and diabetes mellitus (DM) has been postulated for several decades. However, recent observations more strongly suggest that there is an increased rate of DM with the atypical antipsychotic agents and patients with preexisting DM may have more difficulty managing DM during treatment with atypical antipsychotic drugs. The objectives of our investigation were to assess in patients with DM who were taking either typical or atypical antipsychotics the time to onset of 1) new cases of DM and 2) clinically relevant changes in weight and measures of glucose regulation.

Methods: Patients at the Portland VA Medical Center who were taking antipsychotics and had DM were identified. Patients who were taking a typical antipsychotic drug (haloperidol, perphenazine, fluphenazine, thiothixene) or an atypical antipsychotic (clozapine, olanzapine, risperidone, quetiapine) for 3 months or more had their medical records reviewed to identify those with a weight gain of 10 or more pounds, or clinically relevant increases in medicines to treat DM, or increases in glucose or hemoglobin A1c (HbA1c) levels.

Results: Results show that 4 developed DM during treatment with typical agents after an average of 19 years. However, 9 patients developed DM during treatment with atypical agents after an average of 1.2 years (3 on clozapine developed DM after an average of 1.2 years, 5 on olanzapine after 1.3 years, and 1 on risperidone after .9 years). Additionally, in those patients with preexisting DM, most showed an increase in one or more of the assessed clinically relevant factors. In the typical antipsychotic drug treatment group, 8 of 14 (57%) showed these effects at an average of 85 months. These changes occurred in 3 of 4 (75%) clozapine patients at an average of 13 months, in 37 of 44 (84%) olanzapine patients at an average of 10 months, and in 9 of 11 (82%) risperidone patients at an average of 12 months, and in 1 of 2 (50%) quetiapine patients at an average of 13 months.

Conclusions: Thus, DM appears to occur more quickly in patients taking atypical than typical antipsychotics. Additionally, in those patients with preexisting DM, clinically relevant increases in weight, DM medicines, glucose and HbA1c occur more often and sooner in patients taking atypical agents. Thus the atypical antipsychotics clozapine, olanzapine, risperidone and quetiapine are associated with greater clinical challenges in managing DM.

Review Comments:

- In discussion with Dan Casey the bottom line to his poster was that all of the atypicals agents examined have an equal propensity to be associated with new diabetes mellitus cases or worsening of pre-existing diabetes in schizophrenic patients. Therefore, prudent monitoring of blood glucose levels in these patients on a routine basis should become a part of their standard care.
- For this analysis, Casey defined signs of "worsening of diabetes control" as any new or existing diabetic patient exhibiting one or more of the following changes: > 7% increase in weight, > 7% increase in BMI, > 10% increase in HbA1C or >25% increase in DM meds. In his poster graphics and conclusions he associates the changes in these parameters as attributable to the particular typical or atypical antipsychotic agent they were taking. This in fact may or may not be the case or have relevance. A 10% increase in HbA1C may or may not be of clinical significance depending upon their starting point (ie, a patient at an HbA1c of 7% going to 7.7% versus a patient at 10% going to 11%). Also, patients DM meds may be

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increasing simply due to poor diabetes control without any influence from the antipsychotic medication. Perhaps a patient with pre-existing diabetes is in unstable psychosis control and is cognitively impaired with whatever antipsychotic med they are on. It is very plausible that they would then be unable or unwilling to employ good diabetes management and therefore are in poor diabetes control which could lead to their PCP clinician to increase or change their diabetes medication. This scenario may have nothing to do with their antipsychotic being directly causal in disrupting glucose levels as Casey is stating. I challenged him on this point and he agreed that it could be the case but was unwilling to concede that it was likely. In talking with Missy Sowell recently she said that even 80% of diabetics without schizophrenia would likely have a 25% increase in their diabetes meds in a years time.

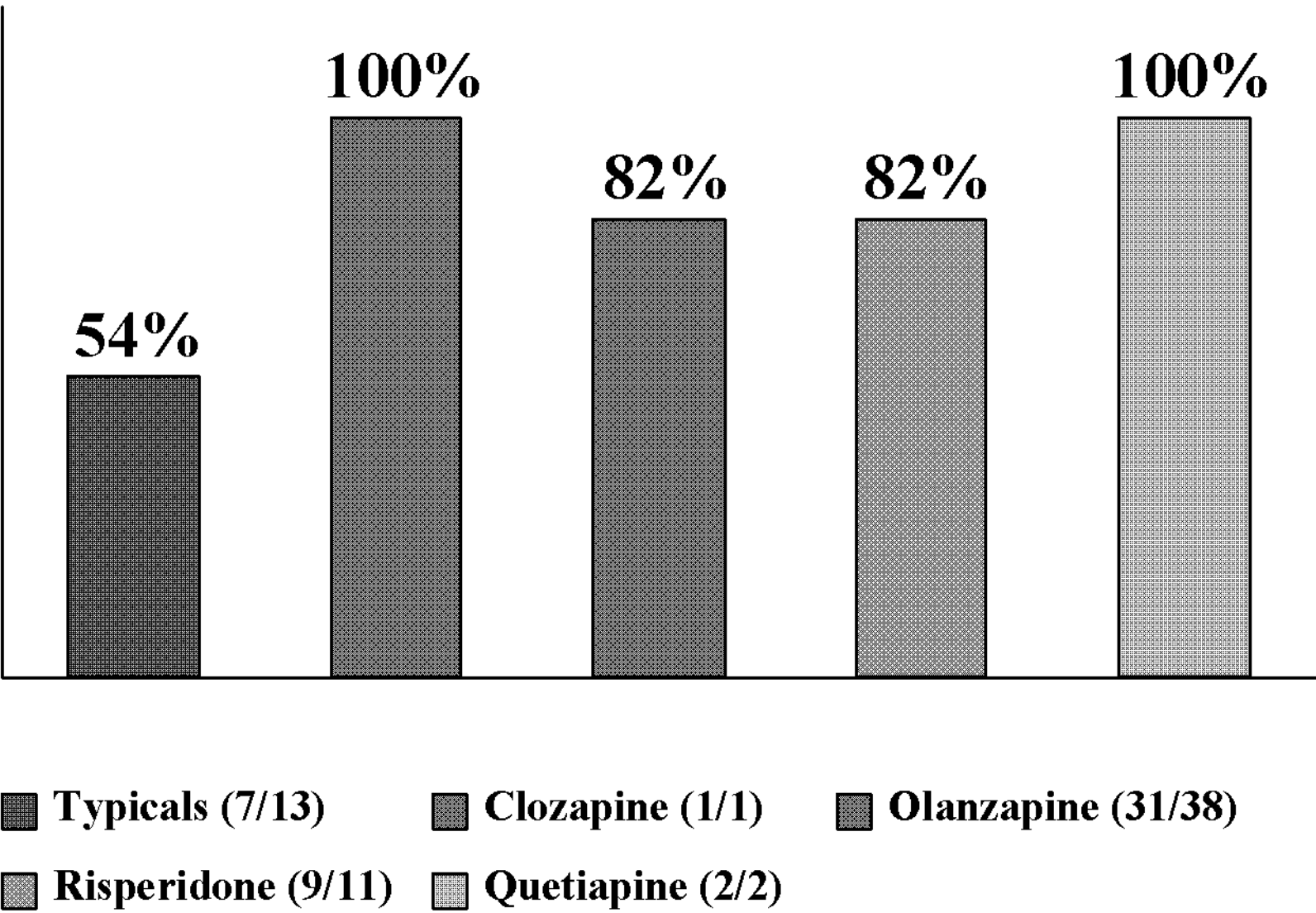
- The actual poster had a little bit of differing data than the above abstract from the abstract book. The total number of patients he examined in retrospective chart reviews was 80 split into 2 groups. They went back over the past 5 years and identified either patients with pre-existing diabetes who went onto an antipsychotic medication or those who developed new-onset diabetes while taking an antipsychotic medication for greater than 3 months time. They then broke these patients down into those taking typicals (n=17) or Clozapine (n=3), Olanzapine (n=45), Risperidone (n=13) or Quetiapine (n=2).
- The number of cases of new onset diabetes occurring after patients were already taking an antipsychotic were 16 total (Typicals - 5, Clozapine - 2, Olanzapine - 7 and Risperidone - 2). These numbers are different than those in the results section of the abstract based upon ongoing, revised analyses of the data.
- The percentage / number of patients who had a clinically relevant change in DM status (met any of his pre-defined 4 change parameters for worsening diabetes control as outlined in point #2 above) and the # of months on average until occurrence were as follows: Typicals 54% (7/13 patients, # of months until change exhibited = 53), Clozapine 100% (1/1 patient, # of months until change exhibited = 25), Olanzapine 82% (31/38 patients, # of months until change exhibited = 8), Risperidone 82% (9/11 patients, # of months until change exhibited = 8), and Quetiapine 100% (2/2 patients, # of months until change exhibited = 4).
- The percentage and number of patients who exhibited a greater than or equal to 25% increase in their diabetes meds were as follows: Typicals 31% (4/13 patients), Clozapine 100% (1/1 patient), Olanzapine 58% (22/38 patients), Risperidone 27% (3/11 patients), Quetiapine 0% (0/2 patients).
- Dan's final discussion points as identified on the poster: 1) New DM cases occur more quickly in atypical versus typical treated patients, 2) Early vigilance for new DM cases and increased monitoring is warranted in patients receiving atypical antipsychotics, 3) Increases in weight and BMI were not correlated with changes in DM status.

Where Presented: ACNP Annual Meeting, Dec 2001, Waikoloa, HI.

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% of Patients with Clinically Relevant Change in DM Status



Hyperglycemia in Schizophrenic Patients Treated with Olanzapine and Clozapine

Smith RC{ XE "Smith RC" }, Lindenmayer JP{ XE "Lindenmayer JP" }, Khandat A{ XE "Khandat A" } Parker B{ XE "Parker B" }, Singh A{ XE "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 \geq 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.

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Review 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 glucoses (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{ XE "Cagliero E" }, Henderson DC{ XE "Henderson DC" }, Nathan DM{ XE "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

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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 \pm SD), body mass index (BMI) was 30.2 ± 5.4 , four were males, four were Caucasian, one African American, and one 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 A1c (HbA1c) $12.25 \pm 1.29\%$. 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.

Where Presented: APA Annual Meeting, May 2001, New Orleans LA. Institute of Psychiatric Services Meeting, October 2001, Orlando FL.

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

Schwarz ME{ XE "Schwarz ME" }, Aladjem AD{ XE "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

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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.

Where Presented: APA Annual Meeting, May 2001, New Orleans LA.

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

Meyer JM{ XE "Meyer JM" }

NOTE – THIS STUDY IS NOW PUBLISHED AND A REVIEW CAN BE FOUND IN THE PUBLISHED MANUSCRIPTS SECTION OF THIS DOCUMENT

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 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.

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- 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.

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- 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.

Where Presented: ACNP Annual Meeting, Dec 2000, San Juan PR; International Congress on Schizophrenia Research, April 2001, Whistler British Columbia, Canada; APA Annual Meeting, May 2001, New Orleans LA; NCDEU 41st Annual Meeting, May 2001, Phoenix AZ;

Glucose Intolerance with Atypical Antipsychotics

Wilson D{ XE "Wilson D" }, DeSouza L{ XE "DeSouza L" }, Sarkar W{ XE "Sarkar W" }, Newton MA{ XE "Newton MA" }, Hammond C{ XE "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 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.

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Where Presented: Biological Psychiatry, May 2000, Chicago IL; Institute of Psychiatric Services, Oct 2000, Philadelphia PA.; ACNP Annual Meeting, Dec 2000, San Juan PR; International Congress on Schizophrenia Research, April 2001, Whistler British Columbia, Canada.; APA Annual Meeting, May 2001, New Orleans LA.

Atypical Antipsychotics & Hyperglycemia: An Analysis Of 11,994 Persons Treated In Ohio DMH Hospitals, 1994-2001

Wilson D, { XE "Wilson D" } Hammond CC{ XE "Hammond CC" }, Buckley PF{ XE "Buckley PF" }, Petty F{ XE "Petty F" }

Introduction: Clinical reports associate atypical antipsychotic (AAP) treatment with a syndrome of hyperglycemia, new-onset diabetes mellitus and diabetic ketoacidosis (DKA). However, systematic analyses of large-scale data-bases are as yet too few and insufficient to reliably and validly define clinical risks, optimal monitoring or best practices. Moreover, inferences derived from naturalistic settings and/or free of perceived corporate considerations are even less common. Hence, this naturalistic study -- in a 'benchmark' public mental health system and independent of commercial support -- was undertaken to better define syndromes of AAP-associated hyperglycemia.

Methods: Computer archive records of all patients in ODMH facilities from 1.1.1994 - 7.31.2001 were reviewed on a 'rolling incidence' basis. Registers of patients treated with any AAP or hypoglycemic agent were collated from pharmacy orders and then cross-tabulated with lists of patients documented, via clinical laboratory assay, as diabetic. A 2% subsample of clinical charts was hand-reviewed to further validate research methods and findings.

Results: Analysis of this sample is on-going toward the further elucidation of other associated findings including, (1) features of hyperglycemia and diabetes associated with AAP treatment, (2) relative risk *vis a vis* specific compounds and a variety of demographic descriptors, (3) possible insights into etiopathogenesis including differential risks for DKA or Type I vs Type II new-onset diabetes, and (4) evolving patterns of AAP prescriptions. In the period under study, 11,994 unique patients were identified as having been treated with an atypical antipsychotic. Of these, 861 (7.2%) were also treated with hypoglycemic agents. Diagnosis and treatment of diabetes followed prescription of an AAP in 719 (6.0%) persons, as documented by abnormal fasting glucose levels or treatment with hypoglycemic medication after treatment with AAPs. 'Critically High' findings (FBS > 300 with risk of DKA) were recorded in 91 (0.77%) persons.

Conclusion: Clozapine, olanzapine, quetiapine, risperidone and ziprasidone all appeared to induce hyperglycemia. Hand-validation of records was robust with no false positives. Pandemic hyperglycemia and new-onset diabetes mellitus were associated with atypical antipsychotic treatment in this sample.

Review Comments:

- This is a continuation of a previous study which has been presented at prior ACNP meetings. However, this is the first time the poster has been presented independently without support from Janssen.
- In contrast to prior versions of this poster, for the first time here the authors report that all of the atypical antipsychotics appear to be associated with a rate of hyperglycemia at similar levels (about 6%), including Ziprasidone.

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- The one additional bit of information on the poster which was not included in the abstract above was a statement that preliminary relative risk calculations for confirmed cases of diabetes in the dataset were as follows: Clozapine (9.8%), Olanzapine (9.4%), Risperidone (5.8%), Quetiapine (6.4%), and Ziprasidone had insufficient power to calculate a specific figure. No mention to raw number of cases seen in the dataset was provided.

Where Presented: ACNP Annual Meeting December 2001, Waikoloa, HI.

Weight Gain, Diabetes Mellitus and the Pharmacology of Schizophrenia

Singer B{ XE "Singer B" }, Buckley PF{ XE "Buckley PF" }, Friedman L{ XE "Friedman L" }, Massanyi EZ{ XE "Massanyi EZ" }, Pamies C{ XE "Pamies C" }

Review Comments:

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 Antipsychotic Medications in Diabetes: A Retrospective Review

Yu BP{ XE "Yu BP" }, Maguire GA{ XE "Maguire GA" }, Chong, YS{ XE "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-two subjects (aged 23 to 86, 14 female, 8 male) with diabetes mellitus and

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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: Eleven subjects received olanzapine (doses from 2.5mg to 30mg), nine subjects received risperidone (doses from .25mg to 8mg), and two subjects received quetiapine (doses from 25mg to 800mg) with a mean duration of therapy of 36.6 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 11 cases analyzed.

Review Comments:

- This study was looking at the critical question of does prescription of an atypical antipsychotic worsen diabetic control in pre-existing diabetes patients.
- Analysis revealed no worsening of fasting blood glucose associated with any of the novel antipsychotic medications studied ($p < 0.05$), and no one medication showed a statistical worsening of diabetes over any other ($p < 0.05$).

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

Novel Antipsychotics: Hyperglycemia, Hyperlipidemia, and EKG Changes in the “Real World”

Gupta S{ XE "Gupta S" }, Frank BL{ XE "Frank BL" }, Steinmeyer C{ XE "Steinmeyer C" }, Lockwood C{ XE "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.

Review Comments:

- Retrospective chart review looking at “fasting” lab value comparison across various antipsychotics. The N is larger than many reviews, however because the patient charts are

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from a variety of setting it is questionable if truly fasting measures are depicted versus a mix of fasting and random measurements.

- Bottom line showed no difference in glucose or lipid values between conventionals, olanzapine, risperidone and quetiapine.

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

Antipsychotic Medication: Impact on Coronary Artery Disease Risk Factors

Wirshing D{ XE "Wirshing D" }, Wirshing, WC{ XE "Wirshing, WC" }, Boyd JA{ XE "Boyd JA" }, Meng LR{ XE "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.

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- 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).

Where Presented: Institute of Psychiatric Services Meeting, October 2000, Philadelphia PA; International Congress on Schizophrenia Research, April 2001, Whistler British Columbia, Canada.

Schizophrenia and Syndrome X: A Correlative Study

Khan M{ XE "Khan M" }, Smith RC{ XE "Smith RC" }

Introduction: Diabetes mellitus comprises a heterogeneous group of diseases. The recently described syndrome X has been shown to possess a constellation of factors including truncal obesity, hyperinsulinemia, hyperglycemia, hypertension, hyperuricemia, and dyslipidemia. There are no reports in the literature on the existence of this syndrome in schizophrenic patients.

Methods: Here we document syndrome X, for the first time, in an obese 46 year old African-American woman with a confirmed diagnosis of schizophrenia.

Results: Her mean values of glucose and, lipids and related chemical indices were as follows: insulin 90 (ref. 6-27 uIU/ml); c-peptide 10 (0.9-4.0 ng/ml), blood glucose 138 (70-105), cholesterol 240 (149-199 mg/dl); HDL 37 (high risk <35); cholesterol/HDL ratio 6 (ref. 4.44); prolactin 120 (2.2-19.2 ng/ml); blood pressure 200/99 (controlled with antihypertensives); uric acid level 9 (2.1-7.2); and BUN 21 (6-19 mg/dl). Thus this patient has met all known criteria of syndrome X. This patient has a higher level of c-peptide; this has been previously correlated with obesity, hypertension and high BMI. Our patient's BMI is 39. The epidemiological observations of the last decade have elucidated that insulin resistance and hence compensatory hyperinsulinemia exist not only in type 2 diabetes, but in other conditions such as ischemic vascular disease, hypertension, coagulation disturbances, obesity, and indeed in syndrome X. The prevalence of hyperinsulinemia and insulin resistance has been correlated with increased muscle triglyceride in both human syndrome X, and the animal model of syndrome X. Conceivably, this muscle accumulation derives from ongoing sequestration of circulating FFA, and reduced muscle fatty acid oxidation. There is of course a known correlation between accumulation of muscle lipid, abdominal obesity and the whole body insulin resistance. Although Cushing's syndrome shares features with both syndrome X and NIDDM, there is a relative insulinopenia in Cushing's syndrome. Despite a number of studies dealing with syndrome X, its genetic basis remains poorly understood. The Trp64Arg allele of beta 3 receptor is more frequent in the syndrome X patients; however, homozygotes, but not heterozygotes for this allele, exhibited lower triglyceride levels. Our patient consistently showed a lower triglyceride level also. It has been suggested that those with this mutation belong to a subset of patients characterized by decreased lipolysis in their visceral adipose tissue.

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Conclusions: Syndrome X patients accumulate atherogenic and cardiac risk factors; they should be closely monitored and given special attention in terms of their cardiovascular health.

Review Comments:

- No poster mini was provided so comments are based strictly upon the abstract.
- Case report describing a schizophrenic patient with all of the symptomatology of the metabolic syndrome, which has been infrequently documented in the literature. There is an upcoming poster from another investigator which has been submitted to the 2002 APA meeting which indicates that 56% of the schizophrenic patients studied in a 32 patient cross sectional study exhibited the characteristics of Syndrome X.

Where Presented: ACNP Annual Meeting December 2001, Waikoloa, HI.

Literature Review of Case Reports of Comorbid Diabetes and DKA Associated with Atypical Neuroleptics

Schwartz M{ XE "Schwartz M" }, Aladjem A{ XE "Aladjem A" }

Introduction: There has been little research published on the association of atypical neuroleptics with diabetes and diabetic ketoacidosis (DKA). Diabetes is a serious and chronic medical condition with serious morbidity and mortality that often is not considered when starting medications. Consultation psychiatrists are often the physicians who treat these patients when medical complications occur. They are in the unique position to help educate other psychiatrists and primary care physicians on the risks of abnormal blood glucose and the necessity to closely monitor these patients.

Methods: This abstract reviews 26 published case reports of new onset diabetes after antipsychotic treatment initiation. Although the number of case reports is few, these reports are worrisome, as 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 of diabetic blood glucose control after initiation of olanzapine. Five (33%) 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 hypoglycemic treatment. There also have been twelve case reports of diabetes, DKA, or worsening glucose control after the initiation of clozapine. Six (55%) 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 increase in blood glucose with thioridazine, loxapine, and quetiapine. In each case, blood glucose levels normalized after medication discontinuation. No published case reports of diabetes associated with risperidone and ziprasidone were found.

Conclusions: The total number of case reports is very small compared to the thousands to millions of patients that have been treated with the medications. However, these few case reports are significant enough to stimulate further research into an association of secondary diabetes and DKA with all atypical neuroleptics. Clinicians should keep this in mind when starting these neuroleptics since diabetes and DKA can have serious morbidity and mortality.

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- This is a very basic and poorly done poster. In talking with the authors at the APM meeting they claimed that their literature search was current through October 2001. However I pointed out to them numerous case reports on all agents which they had failed to include.
- Results bring nothing new to light not already known and presented previously.

Where Presented: Academy of Psychosomatic Medicine Annual Meeting, November 2001, San Antonio, Texas.

Olanzapine Induced Hyperglycemia: A Comparison of Caucasians and African Americans

Nasrallah HA{ XE "Nasrallah HA" }, Love E, Perry CL, Nasrallah AT

Introduction: Of all the first line atypical antipsychotics, olanzapine has been associated with the highest frequency of developing hyperglycemia and diabetes. There are, however, no published studies of ethnic differences in olanzapine-induced hyperglycemia. We report here a comparison of hyperglycemia in Caucasians versus African-Americans receiving olanzapine. We hypothesized that hyperglycemia induced by olanzapine is likely to be higher in African-Americans because they have a higher baseline prevalence of diabetes than Caucasians.

Methods: Patients receiving olanzapine in our follow up clinic were retrospectively studied for fasting blood sugar (FBS) levels before and after several months of receiving olanzapine. Ninety-five percent of the sample were males. The Caucasian ($N = 94$) and African-American ($N = 130$) subgroups were compared for the development of significant hyperglycemia, which was defined as an increase of 20mg/dl or greater in FBS above the pre-olanzapine baseline value.

Results: The mean FBS for Caucasians after olanzapine treatment was 111.47 mg/dl, up from 94.99 mg/dl, and the mean FBS for African-Americans was 113.19 mg/dl, up from 93.13 mg/dl. FBS increase of ≥ 20 mg/dl was observed in 22/94 Caucasians and in 38/130 African-Americans. The difference approached but did not reach significance ($p = 0.08$).

Discussion: The strong trend of African-Americans to develop serious hyperglycemia with olanzapine suggests that ethnicity may play a role in the susceptibility to the diabetogenic effects of olanzapine. Further studies with larger samples, as well as in female subjects, are needed to further clarify the role of ethnicity in this serious iatrogenic complication.

Review Comments:

- This study looks at an important issue of risk differentials in high risk populations. Bottom line finding in this rather sizeable sample is no difference in the rate of hyperglycemia between the two groups.
- As a retrospective study, the potential for bias exists when looking at fasting blood sugars. Are they “fasting” or “random” measurements?
- The author’s bias is apparent in this attempt to hunt out differences in order to place blame on olanzapine as a culprit in causing diabetes. This is evidenced by the final statement of the abstract calling the development of hyperglycemia a “*serious iatrogenic complication*”. Iatrogenic means that it is “*physician caused*”, implying that physicians prescribing olanzapine are in conflict with their hippocratic oath to “do no harm” when they intentionally choose to prescribe olanzapine to a patient.

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Where Presented: Biennial Winter Workshop on Schizophrenia, February 2002, Davos Switzerland.

Hyperglycemia and Dyslipidemia with Atypical Antipsychotics in Geriatric Patients

Nasrallah HA{ XE "Nasrallah HA" }, Herndon NC, Love E, Perry CL, Nasrallah AT

Introduction: Atypical antipsychotics (AP) have been reported to produce metabolic adverse effects such as hyperglycemia and dyslipidemia. However, there have been no studies as to whether geriatric patients of different ethnicity (African-Americans or Caucasians) are differentially affected.

Methods: We retrospectively examined the records of patients receiving the atypical antipsychotics risperidone and olanzapine. Comparisons were made between geriatric (> 65 years) patients who are African-American or Caucasians with regards to mean fasting blood sugar (FBS), cholesterol, and triglyceride levels. The data were analyzed using ANOVA.

Results: Geriatric Caucasian patients (N=5) had significantly higher ($p=.034$) triglyceride level (121.40 ± 18.28 ug/dl) compared to geriatric African American patients (N=12) (74.50 ± 42.56 ug/dl). All other comparisons were not statistically different.

Discussion: These preliminary data indicate that there are few differences in metabolic side effects of atypical antipsychotics between geriatric patient groups of different ethnicity. However, prospective studies with larger samples are necessary to provide more definitive data as to whether ethnicity may increase or decrease the risks of metabolic side effects of atypical antipsychotics in geriatric populations.

Review Comments:

- This is one of the first papers to look at effects in the geriatric population. It is interesting that no data is presented concerning the actual mean FBS levels for the 2 groups. One might assume that the levels are representative of a normal geriatric population.
- The only data of significance they found was a difference in triglyceride levels. However, the levels were higher in the Caucasian group. Based upon known risk factors of African Americans being at higher risk for diabetes and dyslipidemia, this finding is the opposite of what might be expected. Is this due to the data set, small patient numbers or something else?

Where Presented: International College of Geriatric Psychoneuropharmacology, 1st Annual Meeting, December 2001, Waikoloa HI

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Randomized Controlled Studies

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

Glick ID{ XE "Glick ID" }, Romano SJ{ XE "Romano SJ" }, Simpson G{ XE "Simpson G" }, Horne RL{ XE "Horne RL" }, Weiden P{ XE "Weiden P" }, Piggott T{ XE "Piggott T" }, Bari M{ XE "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 ($\text{HOMA IR} = [\text{Ins} \times \text{Glu}] / 22.5$) 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.

Review 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 $\text{Fasting Insulin} \times \text{Fasting Glucose} / 22.5$. 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

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- 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 HGAJ 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.

Normalization of Olanzapine-Associated Abnormalities of Insulin Resistance and Insulin Release After Switch to Risperidone

Berry SA{ XE "Berry SA" }, Lange DS{ XE "Lange DS" }, Mahmoud RA{ XE "Mahmoud RA" }

Introduction: Abnormalities of glucose metabolism, including increased incidence of hyperglycemia and diabetes, have been associated with at least two atypical antipsychotics: olanzapine and clozapine. It has not been determined if glucose metabolism abnormalities induced by such medications are reversible. Herein we report on the Risperidone Rescue Study, a multicenter, randomized clinical trial that assesses changes in diabetes-related laboratory values in schizophrenic patients who had been treated with olanzapine for at least 30 days and then were switched to risperidone. We hypothesize that glucoregulatory abnormalities associated with olanzapine may improve when therapy is changed to risperidone.

Methods: This is an interim analysis of an on-going clinical trial in which 120 patients with schizophrenia or schizoaffective disorder will be enrolled. All subjects had previously received

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olanzapine treatment at a stable dosage for a minimum of 30 days. Entry criteria included a total PANSS score of greater than 60 or glucose tolerance test results indicating increased risk for serious adverse cardiovascular events such as myocardial infarction or stroke. Subjects were randomized to one of three strategies for transitioning from the prior olanzapine treatment onto risperidone. Patients were assessed weekly with standard psychiatric rating scales. Vital signs including anthropometric measures and laboratory tests including a modified oral glucose tolerance test were repeated at six weeks or endpoint. Insulin resistance and beta cell function were evaluated by Homeostasis Model Assessments (HOMA IR and HOMA Beta Cell, respectively). HOMA IR (insulin resistance index) is a measure of the resistance of peripheral tissues to insulin (e.g., higher levels of insulin are required to induce the same uptake of glucose from serum by muscle), classically impaired in type 2 diabetes. HOMA Beta Cell (insulin release index) is a measure of beta cell capacity to release insulin in response to stimulus (e.g., high serum glucose levels), classically impaired in type 1 diabetes.

Results: We report on 48 subjects who have completed this phase of the study. The mean insulin resistance index improved substantially, from 8.91 at baseline (after at least 30 days of olanzapine treatment) to 5.08 at endpoint (post 6 weeks of risperidone treatment.) The mean insulin release index also improved substantially after the switch to risperidone, from 299 at baseline to 221 at endpoint.

Conclusion: It is surprising to note large improvements in both insulin release and insulin resistance, particularly when abnormalities of release are not typically a feature of the weight-related abnormalities which might be expected with olanzapine. Data for the full cohort of patients will be presented and discussed in the context of confounding variables such as age, ethnicity and adiposity, and implications for clinical treatment decisions will be discussed.

Review Comments:

- The original abstract in the ACNP abstract book reported on 40 patients vs 48 on the actual poster. Interestingly, the addition of 8 more patients reduced the magnitude of changes seen in HOMA IR and HOMA beta cell function substantially.
- This study 's results are based upon taking patients stabilized on Olanzapine for greater than 30 days (no mention of mean Olz dose prior to switch), doing a baseline OGTT, switching the patients to Risperidone (titrated up to 4mg/day over one week then dose adjusted as needed for symptoms, no mention of mean dose given), then after 6 weeks of Risperidone they undergo a second OGTT assessment.
- They use the results of these two OGTTs to calculate HOMA IR and HOMA beta cell function statistics at baseline and endpoint. The appropriate caveat needs to be stated that HOMA calculations are very sensitive to having true fasting values for the calculations, otherwise they can be biased by a non-fasting value.
- These patients are all outpatients, no control was taken for insuring fasting status done prior to OGTTs. Patients were verbally instructed to come to the test in a fasting state. Also no control taken for exercise or exertion level just prior to the OGTT being conducted which can have a significant impact on OGTT results.
- They report on mean fasting plasma glucose and fasting insulin values. Are these fasting levels taken just prior to the OGTT? Or are they using values at the end of the 2 hour OGTT? It is unclear which they are using, if they are fasting values used just prior to the OGTT, then what results did the OGTT show since they don't report any information on them as such?
- The poster has a graphic representation (line graph of each patient's baseline and endpoint fasting plasma glucose level based on OGTT result) which indicates that of the 48 patients, approximately 7 patients had large changes (4 patients had large decreases baseline to endpoint, 3 had large increases) which may have had a significant impact on the mean levels

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reported. Median values may be a more valid determination based upon these outliers. If they are removed from the analysis it is doubtful that a significant change would be observed.

- Patients with known diabetes were not excluded from the study. There is no mention as to how many patients with pre-existing diabetes are included nor how they were being managed for diabetes treatment. The graph shows 3 patients whose baseline OGTT results were diagnostic for diabetes and each of these patients had significant drops in their fasting plasma glucose at study endpoint. Are these drops due to a switch to Risperidone or did the patients begin diabetes treatment? No mention is made as to whether these patients could be treated for diabetes if they were new diagnoses or were they pre-existing diabetics whose control improved due to changes in diabetes treatment or improvement in psychosis? The magnitude of their changes baseline to endpoint definitely has a very significant impact on the HOMA IR and HOMA beta cell values.
- Because this study is an open label switch, selection bias becomes a concern. As one can already see from the inclusion of 8 patients more than the original abstract, as the N rises the 2 groups begin to move closer in their values and selection bias will become a smaller factor. When the full 120 patients are included the results could be quite different than what is reported here.
- Investigators (Janssen) conclusions are that 6 weeks of Risperidone therapy (after a switch from Olanzapine) was associated with a large reduction in insulin resistance and improvement in beta cell function that was not related to any weight reductions which may have occurred.

Where Presented: ACNP Annual Meeting December 2001, Waikoloa, HI.

2-Hr Post-Prandial Glucose, Lipid, and Body Mass Indices in Olanzapine-Treated Schizophrenia Patients Before and After Switching to Risperidone: A Prospective Trial

Litman R{ XE "Litman R" }, Peterson SW{ XE "Peterson SW" }, Singh I{ XE "Singh I" }, Robbins DC{ XE "Robbins DC" }, Berry SA{ XE "Berry SA" }

Objective: To determine the effect of switching from chronic olanzapine therapy to risperidone therapy on glucose metabolism, lipids, and body mass in schizophrenia patients.

Methods: Fasting blood glucose, insulin, total cholesterol and triglycerides, hip/waist girth and body mass index (BMI) were measured in 7 physically healthy patients (4M, 41.4±10.4 years old) with schizophrenia or schizoaffective disorder (12.7±7.1 years ill) on chronic (69.7±82.5 weeks) on olanzapine therapy (22.9±5.7 mg/D). Patients then underwent oral glucose challenge with 75 g dextrose solution and 2-hr post-prandial glucose levels were measured. Olanzapine therapy was tapered and risperidone therapy was titrated over a week and maintained at stable doses (5.8±1.4 mg/D). Fasting blood glucose, lipid levels, body mass indices, and oral glucose challenge were repeated after patients were on stable doses of risperidone for ≥6 weeks. Measures (mean(SD)) on olanzapine therapy were compared with measures on risperidone therapy utilizing a paired t-test.

Results: Decreases were found after switching to risperidone therapy in fasting blood glucose (fasting glucose on olanzapine: 87.7 (8.5) mg/dl; on risperidone 82.3 (6.8) mg/dl), in 2-hr post-prandial glucose (2-hr glucose on olanzapine: 105.5 (37.8) mg/dL; on risperidone: 80.0 (19.1) mg/dL) and in waist circumference (waist circumference on olanzapine: 104.7 (23.6) cm; on risperidone 101.1 (21.5) cm). Decreases were significant or were approaching statistical significance (p<0.04, 0.09, and 0.07 respectively). Decreases after switch to risperidone were

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also observed for total cholesterol (olanzapine: 227.5 (54.1) mg/dL; risperidone: 200.8 (21.9) mg/dL), and triglycerides (olanzapine: 169.3 (145.6) mg/dL; risperidone: 102.0(60.4) mg/dL); although these differences were not statistically significant, they were substantial and clinically significant for individual patients. Other measures, including fasting blood sugar, insulin levels, measures of insulin resistance, and other body mass indices, were essentially unchanged.

Conclusions: These preliminary data suggest the possibility that a switch to risperidone therapy may improve glucoregulatory function in olanzapine-treated patients. Decreases in waist circumference suggest the possibility that the improvement may be related to re-distribution of intra-abdominal adipose tissue, although other possible mechanism cannot be ruled out. Due to the exploratory nature of the design and the small sample size, definite conclusions cannot be drawn at this time. Further studies, utilizing crossover design and repeated measures in larger numbers of patients are warranted.

Review Comments:

- This study is somewhat similar to the previous one done by Janssen in their Risperidone Rescue Study. This study is also an open label switch from chronic (>6 weeks) olanzapine treatment to risperidone therapy for 7 weeks (1 week of overlapping titration and 6 weeks of Ris). They conducted a baseline and endpoint (after 6 weeks of Ris monotherapy) glucoregulatory function assessment using the OGTT.
- The study has a very small sample size (n=7), all outpatients. The abstract in the ACNP book lists data for 5 patients but the poster is based upon 7 patients. Once again the numbers change substantially based upon the additional 2 patients. This is indicative of the wide fluctuations seen from one patient to another on these metabolic parameters (likely disease state influenced).
- They describe the atypical treatment as monotherapy but did allow the patients to be on concomitant mood stabilizers or antidepressants at stable doses, which confounds the results reported.
- Only 3 out of 7 patients completed a full six weeks on Risperidone after the switch. Four patients discontinued Risperidone due to worsening of psychosis (3) or adverse events (1). One patient required psychiatric hospitalization due to worsening of psychotic symptoms, one required hospitalization for persistent hypotension.
- Three of the patients required Cogentin augmentation for EPS after the switch to Risperidone.
- Only 6 of 7 patients are included in the glucoregulatory assessments (the patient with persistent hypotension is excluded due to no follow up OGTT). They report that fasting glucose had a statistically significant decrease after the switch. Interestingly fasting insulin and HOMA IR both increased after the switch but they report it as non-significant (no P value provided to gauge if they were approaching significance).
- No significant changes were seen in triglycerides, HDL, LDL cholesterol after the switch.
- BMI actually increased after the switch to Risperidone, weight decreased by 1 pound, waist circumference decreased after the switch to a level approaching significance and they attribute this to a redistribution of body adipose stores.

Where Presented: ACNP Annual Meeting December 2001, Waikoloa, HI.

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A Prospective Study of Glucose and Lipid Metabolism in Patients Treated with Atypical and Conventional Antipsychotics

Smith RC{ XE "Smith RC" }, Lindenmayer JP{ XE "Lindenmayer JP" }, Khandat A, Wahab M, Bodala P, Rosenberger J

Introduction: There have been contradictory reports of the relative potency of atypical antipsychotic medications to induce type 2 diabetes and related glucose and lipid abnormalities in psychiatric patients.

Methods: We report preliminary results of a prospective study of fasting measures of glucose and lipid metabolism in schizophrenic patients on conventional antipsychotics (TYP), olanzapine (OL), risperidone (RS), and clozapine (CL), with additional glucose-tolerance tests (GTT) in patients showing borderline fasting glucose abnormalities (≥ 110 mg/dl).

Results: The results of our preliminary analyses of variance of the first 84 patients, indicated that there were no significant differences ($P < .05$) in mean fasting chemical values, between the four drug groups, on the following variables = glucose, glycohemoglobin, insulin, c-peptide, fructosamine, cholesterol, triglycerides, HDL, LDL, chol/HDL ratio. Only three patients had fasting glucose levels > 126 mg/dl. Leptin values are being currently analyzed. There were trends ($P < .10$) for differences between some of the four drug groups in the mean values of the following variables: glycohemoglobin, c-peptide, fructosamine in the overall ANOV. Post-ANOV multiple comparison between drug groups showed the following trends ($P < .10$ or $P < .05$):

Glycohemoglobin - OL < RS; C-Peptide - OL < RS, CL < RS Fructosamine - OL < RS, OL < CL. GTT performed on 4 patients treated with risperidone all showed markedly elevated glucose and insulin levels. One GTT performed on a patient receiving clozapine also showed markedly elevated glucose and insulin values. Higher tardive dyskinesia scores on two measures (AIMS and Smith-TRIMS TD scales) were not related to higher values on glucose or lipid measures. In fact (except for fructosamine) patients characterized as having no or minimal TD scores had slightly higher mean values on these chemical indices than patients with somewhat higher scores or definite TD. For glycohemoglobin, c-peptide, and insulin, the cross tabulation of categorized TD vs. categorized chemical values was statistically significant or showed strong trend (c², maximum likelihood, or fishers exact test P 's = .039-.098).

Conclusions: Our results indicate that there are no marked differences in tendency to produce hyperglycemia or triglyceridemia among hospitalized chronic schizophrenic patients treated with three different atypical antipsychotics; in our sample there was a tendency for a slightly greater degree of abnormalities on some chemical indices in risperidone treated patients.

Review Comments:

- No poster mini was provided so comments are based strictly upon the abstract.
- This is a cross sectional analysis versus a baseline/endpoint assessment as seen in the Berry Poster on switching from Olz to Ris. All patients were hospitalized chronic schizophrenics so fasting measures are likely better controlled to insure fasting status.
- The results here indicate no difference between olanzapine, risperidone or clozapine although trends indicated higher frequency of abnormal values of glycohemoglobin in risperidone patients.
- Four risperidone patients versus 1 olanzapine patient had abnormal glucose and insulin values based upon an OGTT.

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Does Clozapine Treatment Cause Diabetes Mellitus? A Prospective Longitudinal Study

Howes OD{ XE "Howes OD" }, Pilowsky L{ XE "Pilowsky L" }

Introduction: The primary aim is to test the hypothesis that there is a significant increase in glucose intolerance in patients following treatment with clozapine.

Methods: Adult patients receiving antipsychotic treatment from the South London and Maudsley NHS Trust were recruited for the study. They received a baseline assessment before starting clozapine treatment. This consisted of blood tests and assessment for risk factors for diabetes. An oral glucose tolerance test (OGTT) was performed according to WHO 2000 criteria. Blood was also taken for glucose HbA1C, insulin and insulin like growth hormone measurement. Body mass index, ethnicity, family and personal history of endocrine disorders were recorded. The blood tests and body mass index measurements were repeated after 8 weeks treatment with clozapine. Clozapine blood levels were also measured at this time.

Results: Twenty-three subjects, 33% female, with a mean age of 32.1 years and a mean BMI of 29.1 participated. Following clozapine treatment there is a statistically significant increase in fasting and final OGTT glucose levels ($p < 0.01$). 45% of subjects developed impaired glucose tolerance or diabetes mellitus after commencing clozapine. There was no significant increase in body mass index during the study period ($p = 0.89$).

Conclusions: The results suggest that clozapine alters glucose metabolism leading to glucose intolerance. This effect seems to be independent of changes in body mass index.

Review Comments:

- Significant rate of patients developing IGT or diabetes (45%) correlates with some of the reports by David Henderson we've seen. No data on how many had actual diabetes diagnosis versus IGT.
- Surprising extent of effect after only 8 weeks of clozapine therapy. No comment on whether or not the clozapine was monotherapy or what concomitant meds they may have been taking that could also increase the rate of IGT.

Where Presented: Biennial Winter Workshop on Schizophrenia, February 2002, Davos Switzerland.

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Cross Sectional Studies Examining Insulin Sensitivity, Disease Risk Factors

Glucose Metabolism During Antipsychotic Treatment in Schizophrenia

Newcomer JW{ XE "Newcomer JW" }, Fucetola R{ XE "Fucetola R" }, Haupt DW{ XE "Haupt DW" }, Melson AK{ XE "Melson AK" }, Schweiger JA{ XE "Schweiger JA" }, Cooper BP{ XE "Cooper BP" }, Selke G{ XE "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.

Review 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 effect 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 ($20 \times \text{Fasting Ins} / \text{Fasting glucose} - 3.5$). 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.

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- 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.

**THIS STUDY IS NOW PUBLISHED IN ARCH GEN PSYCHIATRY
2002;59:337-345. SEE FULL REVIEW IN THIS DOCUMENT**

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“Schizophrenia-Related Abnormalities in Glucose Regulation”

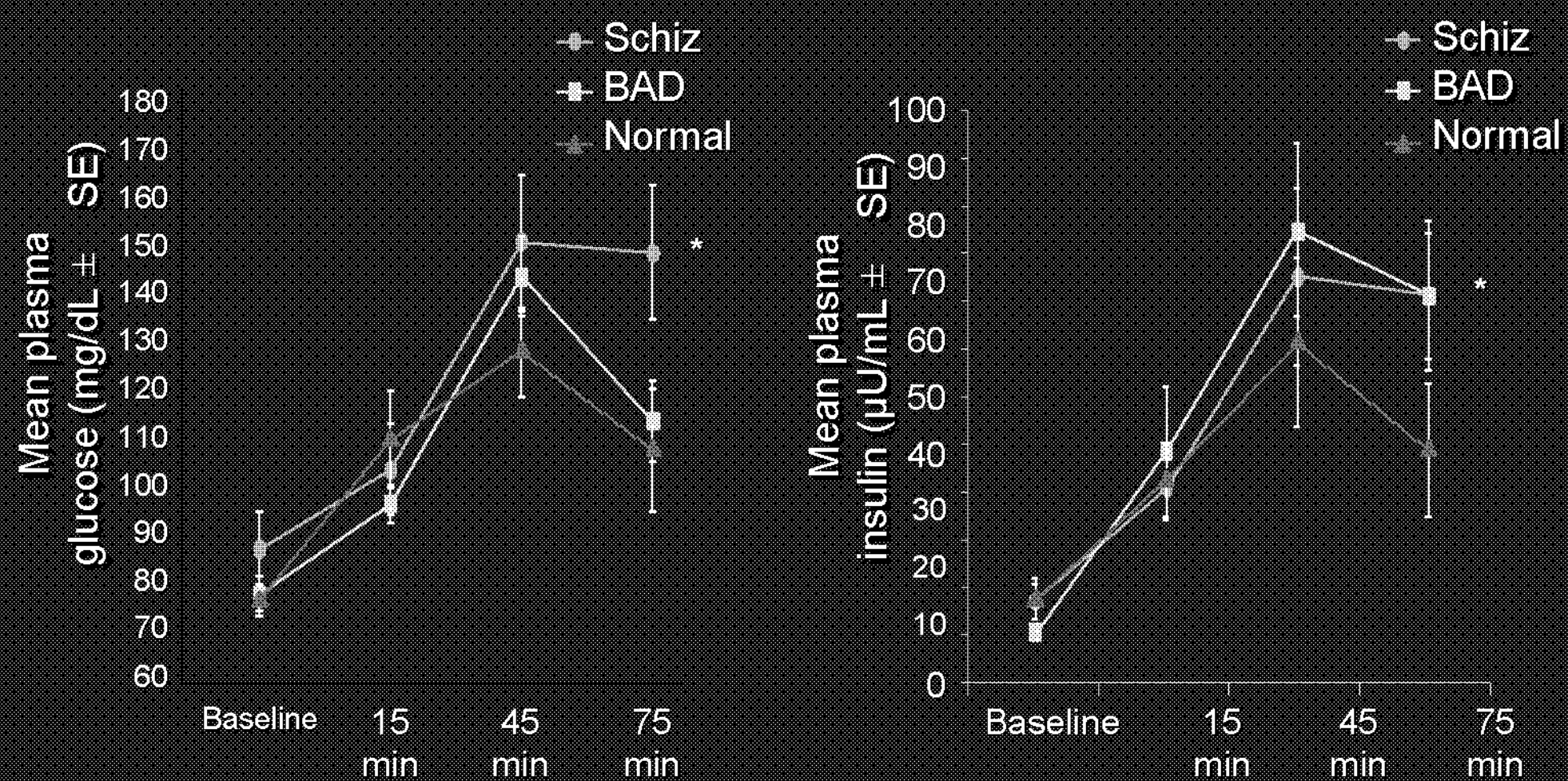
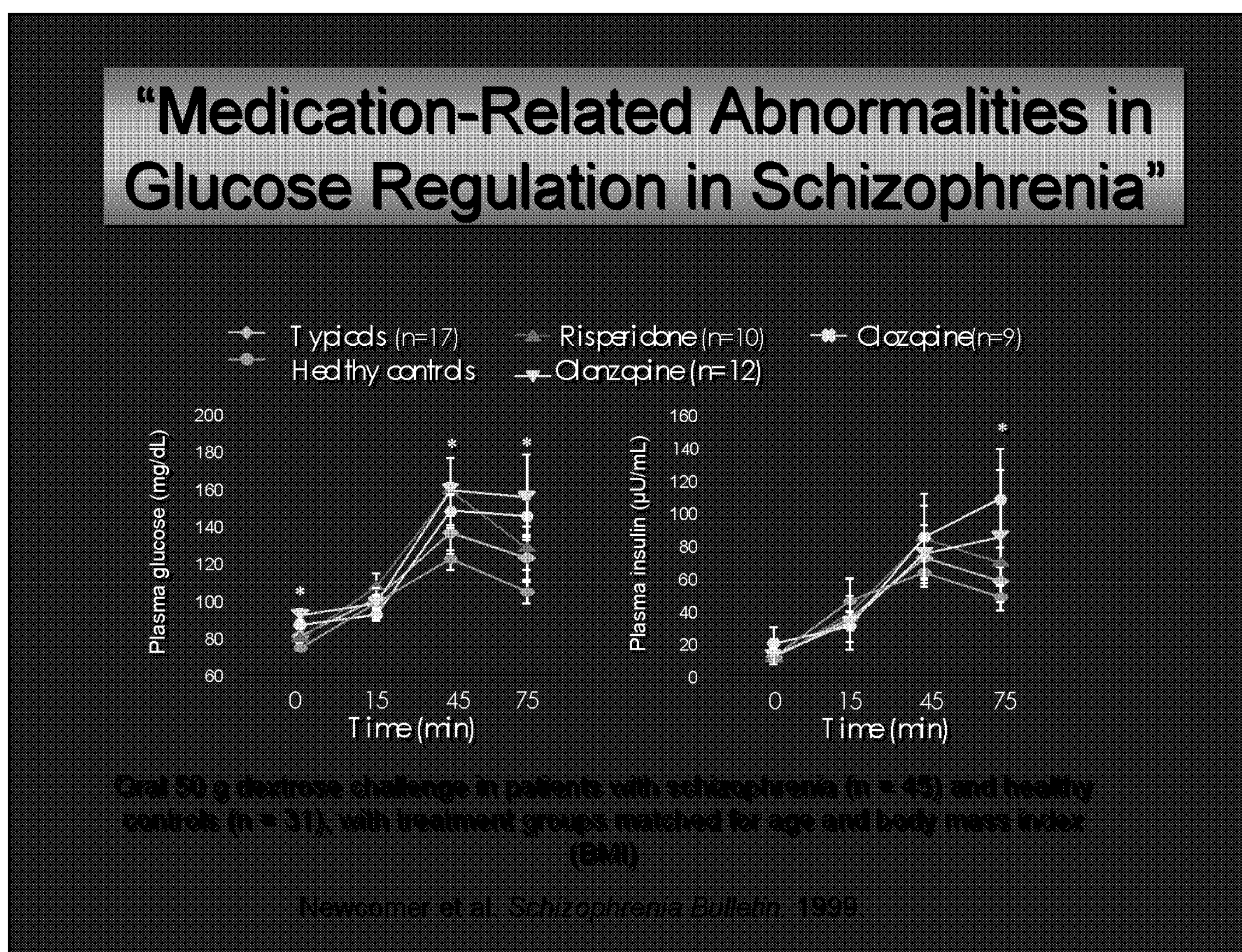


Figure 1a & 1b: Mean plasma glucose (mg/dL ± SE) and insulin (μU/mL ± SE) before and after 50g oral dextrose in patients with schizophrenia (n = 10) and bipolar affective disorder (BAD, n = 10), and normal healthy controls (n = 10)

Source: Newcomer et al. *Schizophrenia Bulletin*. 1999.

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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 $2.44 \pm 2.25 \times 10^{-4} \text{ min}^{-1} \text{ ml}^{-1}$) to risperidone (mean $10.45 \pm 7.00 \times 10^{-4} \text{ min}^{-1} \text{ ml}^{-1}$) ($p = 0.0007$) and olanzapine (mean $4.257 \pm 2.48 \times 10^{-4} \text{ min}^{-1} \text{ ml}^{-1}$) to risperidone ($p = .0051$). Controlling for gender, differences between the

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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.

Review 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.

Where Presented: NCDEU, May 2000, Boca Raton FL; Institute of Psychiatric Services Meeting, Oct 2000, Philadelphia PA.

Measuring Glucose Metabolism During Antipsychotic Treatment in Schizophrenia Using the Insulin Modified Intravenous Glucose Tolerance Test

Haupt DW{ XE "Haupt DW" }, Schweiger JA{ XE "Schweiger JA" }, Melson AK{ XE "Melson AK" }, Cooper BP{ XE "Cooper BP" }, Newcomer JW{ XE "Newcomer JW" }

Introduction: Type 2 diabetes mellitus may be more common in schizophrenia patients than in the general population. Type 2 diabetes mellitus is characterized by disturbances in insulin action on skeletal muscle, liver and adipose tissue. Diabetes can cause increased morbidity and mortality due to acute (e.g., diabetic ketoacidosis) and long-term (e.g., cardiovascular disease) complications. A progressive relationship between plasma glucose levels and cardiovascular risk (e.g., myocardial infarction, stroke) begins at glucose levels that are well below diabetic or "impaired" thresholds. Recent evidence indicates an association between antipsychotic

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medications and disturbances in glucose metabolism, with some early evidence suggesting a possible association between schizophrenia itself and diabetes. Treatment with antipsychotic medication, particularly with certain atypical antipsychotics, has been associated with impaired glucose metabolism, exacerbation of existing type 1 and 2 diabetes, new onset type 2 diabetes mellitus, and diabetic ketoacidosis.

Methods: Controlled studies indicate medication-related disturbances in insulin action, although changes in insulin secretion have not been ruled out (Newcomer et al., in press). Frequently sampled insulin-modified intravenous glucose tolerance tests (FSIVGTT) and analyses that include Bergman's Minimal Model can be used to assess insulin action and beta cell function in humans. In this ongoing study, nondiabetic schizophrenia patients and healthy controls receive insulin-modified FSIVGTTs along with measures of adiposity and clinical status.

Results: Preliminary results indicate that treated schizophrenia patients demonstrate decreased insulin sensitivity. In general, there appear to be differences between treated patients and healthy controls in rates of glucose disposal following exogenous insulin challenge, even after controlling for body mass index ($F[5,180]=3.316$, $p=0.0069$, G-G $p=0.0328$). This technique can be used to test additional hypotheses in this area.

Conclusions: The current results support concerns about the effects of weight gain and antipsychotic medication effects on glucose metabolism in patients with schizophrenia.

Review Comments:

- This study is a cross sectional analysis looking at one FSIVGTT test per individual included in the study. This approach provides a limited and potentially biased conclusion since this is a single snap shot in time without analysis for intraindividual variation.
- Total N for the study was 48 comparing 36 non-diabetic, schizophrenic patients with Olanzapine (12 patients, 9M/3F), Risperidone (12 patients, 9 M/3F), Haloperidol (12 patients, 6M/6F) versus Healthy Controls (12 patients, 6M/6F).
- According to the poster the patients were on a controlled diet for the 3 days prior to the FSIVGTT and then told to be fasting on the morning of the test. We are all aware of the limitations of simply asking schizophrenic patients to present in a fasting state with no control for this occurring. Controlling the diet consisted of having each patient come to the clinic for breakfast each morning for the 3 days prior and then providing them with a small cooler containing their meals for the day and instructions to eat only what was within the cooler. The following day the coolers were returned at breakfast and food consumed recorded. This has many limitations since no controls other than verbal instructions were in place to impact food consumption, although the most important parameter is being in a true fasting state on the morning of the FSIVGTT versus the 3 days prior.
- The FSIVGTT was conducted over a 2 hour period following a 75gm glucose load. Data was used to calculate an insulin sensitivity index using the MinMod methodology to determine "insulin resistance" caused by the antipsychotic administered.
- There was a numerical trend towards a greater decrease in insulin sensitivity with Olanzapine versus Risperidone and Haloperidol, however no representation of statistical significance was provided. One therefore assumes that the differences are not significant.
- They controlled for differences in BMI between the groups, however no control for differences in sex or age were noted.

Where Presented: ACNP Annual Meeting December 2001, Waikoloa, HI.

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Assessment of Insulin Secretory Responses Using the Hyperglycemic Clamp in Normal Subjects Treated With Olanzapine, Risperidone, or Placebo

Beasley CM{ XE "Beasley CM" }, Sowell MO{ XE "Sowell MO" }, Cavazzoni P{ XE "Cavazzoni P" }, Breier A{ XE "Breier A" }, Steinberg HO{ XE "Steinberg HO" }, Dananberg J{ XE "Dananberg J" }

Introduction: Patients with acute onset hyperglycemia with ketoacidosis or hyperosmolar state during treatment with atypical antipsychotic drugs have been reported. Insulin resistance alone is generally not sufficient to produce such severe metabolic decompensation and some degree of impaired insulin secretion is thought to be required. The goal of this study was to determine if atypical antipsychotics have an intrinsic effect on pancreatic beta cell function that causes decreased insulin secretion.

Methods: Healthy volunteers were randomly assigned to single-blind therapy with olanzapine 10 mg/day (N=17), risperidone 4 mg/day (N=13), or placebo (N=18) for approximately 2 weeks. At baseline and endpoint, insulin secretion was quantitatively assessed using the hyperglycemic clamp. Briefly, blood glucose levels were clamped at 200 mg/dl for 4 hours and insulin and C peptide levels measured at regular intervals. Total insulin and C peptide responses were calculated as the area under the curve after subtracting pre-clamp levels. Insulin sensitivity index (ISI) was calculated as the ratio of mean glucose infusion rate/mean insulin during the final hour of the clamp.

Results: There were no significant differences between the placebo and olanzapine groups in baseline characteristics of age, gender, ethnicity and body mass index. The risperidone group contained 30% fewer subjects and no females and due to study discontinuations with blinded replacement of these subjects. Weight increased during treatment with olanzapine (2.8 ± 1.7 kg, $p < 0.001$ within group) and risperidone (3.1 ± 2.1 , $p < 0.001$ within group) but not during placebo treatment. Fasting glucose did not change within any group ($p > 0.05$). Fasting insulin and C peptide decreased slightly with placebo. Comparable increases in fasting insulin (olanzapine, $p = 0.011$ vs. placebo, risperidone, $p = 0.041$ vs. placebo) and C peptide levels (olanzapine, $p < 0.001$ vs. placebo, risperidone, $p = 0.020$ vs. placebo) were seen during active therapy. Using the hyperglycemic clamp, the total C peptide response was unchanged in all groups. Within the placebo group, total insulin response and ISI were also unchanged. The total insulin response was increased in both the olanzapine ($p = 0.002$ within) and risperidone ($p = 0.054$ within) groups. A small decrease in ISI was seen during treatment with both olanzapine ($p = 0.038$ within) and risperidone ($p = 0.157$ within). Regression analysis to account for the impact of weight gain did not demonstrate significant changes in insulin or C peptide levels (fasting or clamp) during active therapy.

Conclusion: We found no evidence in this study that olanzapine or risperidone treatment was associated with a decrease in fasting insulin or in insulin secretion in response to a prolonged hyperglycemic challenge. Weight-related increases in insulin levels were observed in subjects during active therapy.

Review Comments:

- One needs to understand that the purpose of this study was to determine the effects of Olanzapine and Risperidone on *insulin release*, and is the gold standard study for this purpose. This study was not designed to measure insulin sensitivity directly, a euglycemic clamp is the gold standard for that determination. The reason for doing a study that examines effects on *insulin release* is to determine if the drugs have a direct inhibitory action on insulin

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production in the body which could be directly linked to the development of diabetic ketoacidosis (DKA).

- One criticism of the study is that it was done in normal patients instead of schizophrenics, however we know the potential difficulties in doing a study of this nature in mentally ill patients. A cross sectional look may be possible in schizophrenics, but doing a repeat clamp would have a high drop out rate as was seen even in this study of normals.
- The strengths of the study are that it compares and endpoint evaluation versus a baseline study with each person serving as their own control. Patients were randomized to treatment and blinded to the investigator, and a placebo arm was included. Doses were standard and should have exhibited an effect if one was present.
- Limitations of the study beyond using normals include, patients were outpatient status so although an isocaloric diet was recommended to patients their dietary intake was not controlled and substantial weight gain was seen overall, however there was no difference between treatment arms. The study also had a smaller Risperidone group with no female participants in this group. The study does not provide a direct measure of insulin sensitivity but rather a calculated figure is obtained.
- The study demonstrated that both drugs in fact did not decrease insulin release (a positive finding based upon the objective of the study). Both drugs actually increased insulin levels at the endpoint clamp as compared to baseline and these increases appear to be a result of increased weight.

Where Presented: ACNP Annual Meeting December 2001, Waikoloa, HI.

Antipsychotic Medication and Insulin Resistance

Cohn TA{ XE "Cohn TA" }, Remington GA{ XE "Remington GA" }, Leiter L{ XE "Leiter L" }, Kameh H{ XE "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

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- 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.

Where Presented: International Congress on Schizophrenia Research, April 2001, Whistler British Columbia, Canada.; APA Annuals Meeting, May 2001, New Orleans LA.

Glucose Metabolism and the Treatment of Schizophrenia: A Complex Relationship

Goldman M{ XE "Goldman M" }, Milner KK{ XE "Milner KK" }, Shriberg RF{ XE "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.

Review Comments:

- This poster is a point prevalence examination of Diabetes Mellitus in schizophrenic patients that identified a rate of about 18% or a little over twice the rate of the general population, which are in line with other published prevalence assessments in schizophrenics.
- The authors found no difference in DM rates among atypical or typical agents.

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

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Coronary Heart Disease Risk Factor Profile of Risperidone versus Olanzapine Treated Patients: A Cross Sectional Comparison

Bouchard RH{ XE "Bouchard RH" }, Demers MF{ XE "Demers MF" }, Villeneuve J, Cadrin C, Mottard JP, Despres JP

Introduction: We conducted a cross sectional , multi-center study to compare morphological indices of obesity, adipose tissue distribution and a full fasting metabolic risk profile in patients receiving either risperidone or olanzapine.

Methods: Inclusion criteria included treatment for at least 6 months with risperidone or olanzapine. Exclusion criteria were previous exposure to atypicals, recent smoking cessation, endocrine disease, drugs altering blood pressure, plasma lipids, insulin and body weight. Anthropometric measurements, laboratory assessments and psychiatric assessments were completed. Preliminary results on 63/90 patients were analyzed.

Results: The mean duration of treatment was 17.3 ± 9.9 months for risperidone and 18.4 ± 8.5 months for olanzapine ($p=ns$). Olanzapine treated subjects had significantly higher plasma triglyceride levels (195 ± 115 for OLZ versus 135 ± 74 for RIS, $p<0.01$) and a higher cholesterol/HDL-cholesterol ratio (5.40 ± 1.77 for OLZ versus 4.49 ± 1.16 for RIS, $p < 0.04$). Finally, 31% of olanzapine treated patients were characterized by the atherogenic metabolic triad (hyperinsulinemia, elevated apo-B and small dense LDL) as opposed to 13% in the risperidone group.

Conclusions: These preliminary results suggest that olanzapine patients are characterized by an altered metabolic risk profile compared to risperidone patients and raise concerns that require further investigation.

Review Comments:

- The authors reference a 1998 JAMA article by Lamarche which states that a cluster of metabolic abnormalities known as the atherogenic metabolic triad (elevated levels of insulin, apolipoprotein B and small dense LDL particles) has been shown to increase coronary heart disease (CHD) risk 20 fold in middle aged men.
- The authors suggest that BMI is not a sufficient assessment for CV risk, but rather measurements of waist circumference which is an estimation of visceral adiposity is a better predictor of risk for diabetes and CHD.
- The authors claim the results suggest an increased risk for diabetes and CHD with Olanzapine based upon 31% of the patients exhibiting the atherogenic metabolic triad. This compares to 13% of Risperidone patients and 20% of their control population from the Quebec Health Survey. Because this is a cross sectional examination however, there is no control for selection bias therefore the results may simply be a factor of who gets selected for what drug versus a true drug effect.
- When looking at all of the individual parameters measured in the study, there is no significant difference between OLZ and RIS in fasting glucose, fasting insulin, fasting leptin, total cholesterol, LDL cholesterol, HDL cholesterol, apolipoprotein B, blood pressure or heart rate. Nor is there a difference in waist circumference or BMI.

Where Presented: International Congress on Schizophrenia Research (ICSR) Meeting, April 2001, Whistler British Columbia, Canada.

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Increased Intra-abdominal Fat Distribution in Schizophrenia

Thakore JH{ XE "Thakore JH" }, Mann JN, Vlahos I, Reznick MR

Introduction: Schizophrenia is associated with the development of various physical disorders, some of which collectively form the metabolic syndrome whose principal somatic manifestation is increased intra-abdominal fat (IAF). The aim of this study was to determine abdominal fat distribution in patients with schizophrenia and controls.

Methods: Fifteen subjects (7 drug free and 8 drug-naïve) who fulfilled DSM IV criteria for schizophrenia and 15 age and sex-matched normal volunteers had their baseline plasma cortisol measured and a CT scan was performed at the level of the pedicles of their 4th lumbar vertebra.

Results: The major findings of this study were that patients with schizophrenia had over 3.4 times as much IAF ($13,232 \pm 2666.5$ vs. 3897.9 ± 571.9 mm², respectively; $p < 0.005$) and higher plasma cortisol (1600 h) as did controls (253.9 ± 40.5 vs. 134.3 ± 12.8 nmol/l, respectively; $p < 0.008$). In addition there were no differences in terms of IAF stores between those patients who were drug-naïve and those who were drug free ($12,442.4 \pm 9762.6$ vs. $14133.9 \pm 11,656.8$ mm², respectively; $p < 0.76$).

Conclusions: This study shows that drug-naïve patients with schizophrenia have increased IAF which in turn may lead to the development of the metabolic syndrome leading to premature mortality from “natural” causes.

Review Comments:

- Interesting findings that suggest schizophrenics are predisposed to obesity with visceral adiposity as a predominant factor. Increased waist circumference may be a valuable predictor of future complications including hyperglycemia, diabetes and cardiovascular disease.

Where Presented: Biennial Winter Workshop on Schizophrenia, February 2002, Davos Switzerland.

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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

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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.

(Statistical Issues in Drug Development by Stephen Senn, 1997, John Wiley and Sons Ltd., West Sussex, England, pp 337-338)

Association of Diabetes Mellitus with Atypical Neuroleptics

Sernyak MJ{ XE "Sernyak MJ" }

NOTE – THIS STUDY IS NOW PUBLISHED AND A REVIEW CAN BE FOUND IN THE PUBLISHED MANUSCRIPTS SECTION OF THIS DOCUMENT

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).

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

Review Comments:

- 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.

Where Presented: APA Annual Meeting, May 2001, New Orleans LA.

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

Gianfrancesco F{ XE "Gianfrancesco F" }, Grogg AL{ XE "Grogg AL" }, Mahmoud RA{ XE "Mahmoud RA" }, Nasrallah HA{ XE "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 conventionals 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 conventionals (OR = 2.13, 1.10-4.13); and low-potency conventionals (OR = 3.46, 1.52-7.79). The odds of developing diabetes with olanzapine, clozapine, and high-potency conventionals 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.

Review 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?

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- 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.
- 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.

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- 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.

Where presented: ACNP Annual Meeting, Dec 2000, San Juan PR; APA Annual Meeting, May 2001, New Orleans LA; NCDEU 41st Annual Meeting, May 2001, Phoenix AZ; ECNP Annual Meeting, Oct 2001, Istanbul Turkey.

Antipsychotic-Induced Type 2 Diabetes: Evidence from a Large Health Plan Database

Gianfrancesco F{ XE "Gianfrancesco F" }, White RE{ XE "White RE" }, Yu E{ XE "Yu E" }

Objective: The objective of this study was to evaluate the association of antipsychotic treatment with type 2 diabetes in a large health plan database.

Methods: Claims data for patients with psychosis within a health plan of nearly 2 million patients were analyzed using statistical models. Frequencies of newly treated type 2 diabetes in patients untreated with antipsychotics and among patients treated with risperidone, olanzapine, quetiapine, and conventional antipsychotics were compared.

Results: Based on exposure measured in months of antipsychotic treatment, risperidone and quetiapine patients had estimated odds of receiving treatment for type 2 diabetes that were lower than those patients untreated with antipsychotics (not statistically significant); patients treated with conventional antipsychotics had estimated odds that were virtually equivalent to those of patients untreated with antipsychotics; olanzapine alone had odds that were significantly greater than those of patients untreated with antipsychotics ($p < 0.05$). Odds ratios based on 8 months of prescreening for pre-existing type 2 diabetes and assuming 12 months of antipsychotic treatment were: risperidone = 0.652 (95% CI, 0.306 – 1.393); olanzapine = 1.426 (95% CI, 1.049 – 1.945); quetiapine = 0.953 (95% CI, 0.408 – 2.227); and conventional antipsychotics = 1.024 (95% CI, 0.669 – 1.564).

Conclusions: Case reports have increasingly implicated olanzapine as causing or exacerbating type 2 diabetes, while few have implicated quetiapine and risperidone. This study supports these findings. Additional studies are needed to evaluate the association of antipsychotic treatment with type 2 diabetes.

Review Comments:

- This is another pharmacoepidemiology study done by Gianfrancesco, this time supported by Astra Zeneca. This study contains the same basic methodology flaws of the previous Janssen

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sponsored study. As in the previous study, if you look at the unmanipulated odds ratios you once again see very comparable rates across the various drugs studied.

- This study has a larger sample size than the Janssen study done by Gianfrancesco. This study examined data in 16,878 “psychotic” patients (n = 6,582 who were taking antipsychotic therapy for 60 contiguous days, n = 10,296 psychosis patients who were “untreated”). The authors describe the patients as having psychosis, however they include 2 figures identifying the patient diagnoses for the treated and untreated groups. These figures indicate that the “untreated” group is primarily patients with Major Depressive Disorder (76%), Bipolar patients (16%) and other psychoses. The treated group is primarily MDD (38%), Bipolar (35%), with the remainder being schizophrenia (14%) and other psychoses (13%). Clearly the two groups are not comparable and significant differences may exist within the “treated” group concerning diagnosis and severity of illness across the various drugs being studied.
- The authors once again use “treatment episodes” which means that some individual patients are being counted multiple times, e.g., if they came on and off drugs. This is evident in the poster as they cite 2860 treatment episodes for Risperidone, 2703 treatment episodes for olanzapine, 922 treatment episodes for quetiapine and 2756 for conventionals. This amounts to 9,241 treatment episodes in 6,582 patients. 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 and quetiapine’s numbers. Dr. Gianfrancesco verbally reported that such patients were predominately in the risperidone group in the previous Janssen study.
- In the earlier Janssen study done by Gianfrancesco, diabetes was identified via ICD-9 criteria or current antidiabetic medication usage. In this study they chose to identify patients with diabetes based solely on the patient receiving treatment with insulin or oral antidiabetic agents.
- The patients in this study are not on monotherapy as in the PCS study.
- Of the 16,878 patients identified during the study period, 1,964 were excluded because they had medical claims for diabetes but no prescription for insulin or diabetes medication. This left 14,914 total patient observations used in the logistic regression analyses. Of this group there were 117 patients treated for diabetes (< 1%). The authors don’t report the actual number treated for diabetes within each antipsychotic treatment group. They state only that among the four antipsychotic categories, quetiapine and risperidone had the lowest percentages of patients treated for type 2 diabetes, while olanzapine and conventional antipsychotics had the highest.
- Once again as in the earlier Janssen study done by Gianfrancesco, they report the calculated odds ratio based upon a one month treatment period calculated by dividing the incidence for each drug by the mean time of exposure, which assumes linear exposure over time. Once again, mean exposure was slightly longer on risperidone and conventionals, and could account for some small numerical risk advantages. For their overall analysis, no statistical test is reported for olanzapine vs risperidone or quetiapine, but the difference is very likely not significant.
- As in the previous Gianfrancesco study, they use the one month odds ratio value to then calculate a “12 month odds ratio” **by raising monthly risk to the power of 12**. This exponential maneuver amplifies a small olanzapine difference in risk. This is the finding which Astra Zeneca and Janssen will most likely emphasize, claiming a substantial increase in risk for olanzapine patients. However, one should not that in the abstract as well as the graphic in the poster the 95% Confidence Intervals for each group are overlapping meaning one cannot claim any significant difference between groups. This approach to modeling of risk is inappropriate, given that this was a longitudinal study and the authors could have used

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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.

Where presented: CPNP Annual Meeting, April 2002, Seattle WA.

The Risk of Developing Diabetes in Users of Atypical Antipsychotics

Caro J{ XE "Caro J" }, Ward A{ XE "Ward A" }, Levinton C{ XE "Levinton C" }, Robinson K{ XE "Robinson K" }, Kopala L{ XE "Kopala L" }, Caro Research

Objective: To Assess the risk of diabetes among patients undergoing treatment with risperidone versus olanzapine. A series of case reports had previously associated olanzapine or clozapine treatment with the development of hyperglycemia, diabetes, and diabetic ketoacidosis.

Methods: Two cohorts totaling 33,945 patients were identified from the Quebec Medicare database between January 1997 and 31st of December 1999. One cohort consisted of patients who had at least one prescription for olanzapine but not clozapine during that period (n=19,153) and the other of patients receiving risperidone but not olanzapine or clozapine (n=14,792). In either case, patients with a diagnosis of diabetes (defined as either a recorded ICD9 250.0 to 250.93 or a prescription for insulin or an oral hypoglycemic agent) before beginning antipsychotic therapy were excluded. New diabetes diagnoses after the first antipsychotic prescription were tabulated until the 31st of December 1999; censoring occurred at this date or at the last service date if there was no record of using any services during the last six months of follow up. Crude hazard ratios and proportional hazards analyses were carried out.

Results: 319 patients developed diabetes after being prescribed olanzapine, and 217 after risperidone, a crude hazard ratio of 1.08 (95% CI, 0.89 to 1.31). When correcting for severe imbalances in age and gender using proportional hazards analysis, the hazard ratio increased to 1.20 (95% CI, 1.00 to 1.43). In addition, women had a 68% (95% CI, 32 to 169%) higher risk than men for developing diabetes on olanzapine treatment, after adjusting for age. There was a 31% (95% CI, 5 to 65%) higher risk for women prescribed olanzapine compared to risperidone after adjusting for age.

Conclusions: Olanzapine was associated with an increased risk of developing diabetes compared to risperidone, especially amongst women. More studies are required to confirm the association of olanzapine with hyperglycemia and also to investigate the biological basis for this association.

Review 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.
- Based upon the inclusion criteria described, 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 patients on Olanzapine plus Risperidone compared to those on either alone.

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- Exclusion criteria were any patient having an ICD-9 for diabetes (250.0 to 250.93) or a 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 reassurance, 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

A Retrospective Cohort Study of Diabetes Mellitus and Antipsychotic Treatment in The United Kingdom

Breier A{ XE "Breier A" }, Kwong K{ XE "Kwong K" }, Hornbuckle K{ XE "Hornbuckle K" }, Cavazzoni P{ XE "Cavazzoni P" }, Carlson C{ XE "Carlson C" }, Wu J, Kotsanos J{ XE "Kotsanos J" }, Holman R

Introduction: Treatment-emergent diabetes mellitus has been reported in the literature for both conventional and atypical antipsychotics. However, no large-scale epidemiological studies have

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been carried out that systematically assessed the risk of developing diabetes for patients taking these agents. In this retrospective cohort study, we explored the UK General Practice Research database (GPRD) to determine the hazard ratio of diabetes for patients prescribed antipsychotics compared with the general adult population in the UK.

Methods: An antipsychotic cohort comprised of patients exposed to both conventional antipsychotics (N= 43,561), and atypical antipsychotics (N=2,550), individual antipsychotic cohorts comprised of patients exposed to a single antipsychotic during the study period and a general patient population cohort (N=266,272) derived from the GPRD database were studied. The Cox proportional hazard regression model was used to determine the hazard ratio (HR) of diabetes development between these cohorts. The covariates included in the model were age, gender, and the presence or absence of obesity.

Results: Compared to the general population cohort in the UK, patients exposed to antipsychotics had a higher risk of developing diabetes [HR=1.5 (CI 1.1-1.9)]. The most commonly prescribed agents were thioridazine (44%) and fluopenthixol (22%) among conventional antipsychotics, and risperidone (71%) and olanzapine (21%) among atypical antipsychotics. The risk of developing diabetes during exposure to thioridazine and risperidone was significantly higher than that of the general patient population. Assessment of other antipsychotics was limited by the sample size of the cohorts.

Review Comments:

- Definition of a patient with diabetes was any patient with a computer recorded diagnosis of type 1 or 2 diabetes or was prescribed any hypoglycemic agent indicated for treating diabetes.
- All patients were limited to monotherapy during the study period. For the individual atypical cohorts patients were included even if they had prior therapy with conventional antipsychotics.
- Limitations of the study were that the atypical cohort is relatively small in comparison to the conventional group. In addition, most of the atypical group was on Risperidone (71%). There was also a lack of consistent information on the family history of diabetes and ethnic origins.
- This study is consistent with previous observations of elevated risk of diabetes in patients treated with antipsychotics. In this study only Thioridazine in the conventional group had a risk ratio (1.5) versus the general population which was significant.. Risperidone's risk ratio of 3.2 was also significant versus the general population group. Olanzapine had a hazard ratio of 2.0 but did not reach significance, likely due to the small number of patients on Olanzapine (n=528).

Where Presented: ACNP Annual Meeting, December 2001, Waikoloa HI; Biennial Winter Workshop on Schizophrenia, February 2002, Davos Switzerland, CPNP Annual Meeting, April 2002, Seattle WA.

Assessment of the Independent Effect of Olanzapine and Risperidone on the Risk of Diabetes in Patients with Schizophrenia

Buchanan R{ XE "Buchanan R" }, Koro CE, Weiss S, Magder L, L'Italien GJ, Fedder DO

Introduction: The newer class of antipsychotic agents exhibits a superior safety profile compared to conventionals. However, case studies suggest an association between the use of

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these agents and diabetes. We sought to quantify this association using a large health care database.

Methods: The study was derived from the UK-based General Practice Research database (GPRD), followed between 1987 and 2000. A total of 19,637 patients with a diagnosis of schizophrenia were identified. We used a 6:1 matched nested case-control design. Conditional Logistic Regression was used to derive adjusted odds ratios controlling for gender, age, and co-mediations. Exposure to antipsychotic was defined as at least one prescription for antipsychotic medication within 2 months prior to the date of diagnosis.

Results: There were 451 incident cases of diabetes in the cohort, matched to 2,696 controls. Use of olanzapine was associated with a significantly increased odds for developing diabetes (OR = 5.2, 95% CI 1.8 – 14.6, p=0.002) compared with nonuse of antipsychotics or conventionals (OR = 3.8, 95% CI 1.3 – 10.6, p=0.001). Risperidone showed a lesser increased odds of diabetes (OR = 2.1, 95% CI 0.88 – 5.00, p=0.095) compared to nonuse and conventionals (OR = 1.5, 95% CI 0.64 – 3.63, p=0.34).

Conclusions: Our study demonstrates a strong association between the use of olanzapine and the development of diabetes in schizophrenic patients. A lesser association was seen with risperidone. The metabolic consequences of atypical therapy should be given serious consideration by treating physicians.

Review Comments:

- This is an interesting analysis using the same GPRD database as the previous Lilly Poster. The 2 studies differ in that this one is looking only at schizophrenic patients whereas the Lilly study looked at any patient who received a single antipsychotic drug irrespective of indication. The Lilly study used a control population 100 times the size of this study's control group. The Lilly study identified 170 cases of new onset diabetes whereas this study identified 451 cases of diabetes (their diabetes definition is not given in the abstract).
- It is difficult to compare the differences in odd ratios between the 2 studies since the study populations are quite different. They show no comparison of the odds ratio for olanzapine compared to risperidone. Is this due to no significant difference?
- In the Lilly study there was a very small *N* for both Risperidone and Olanzapine which precluded doing many analyses. In this poster there is no mention of the sample size for each drug group. Therefore the odds ratios cited are of suspect credibility if the sample sizes were also small.

Where Presented: Biennial Winter Workshop on Schizophrenia, February 2002, Davos Switzerland.

Prevalence of Diabetes in Schizophrenia Patients Treated with Antipsychotics

Casey DE{ XE "Casey DE" }, Danielson EM{ XE "Danielson EM" }, Fishman NB{ XE "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.

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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.

Review 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.

Where Presented: APA Annual Meeting, May 2001, New Orleans LA

Atypical Antipsychotics and Concomitant Antidiabetic Use

Saklad SR

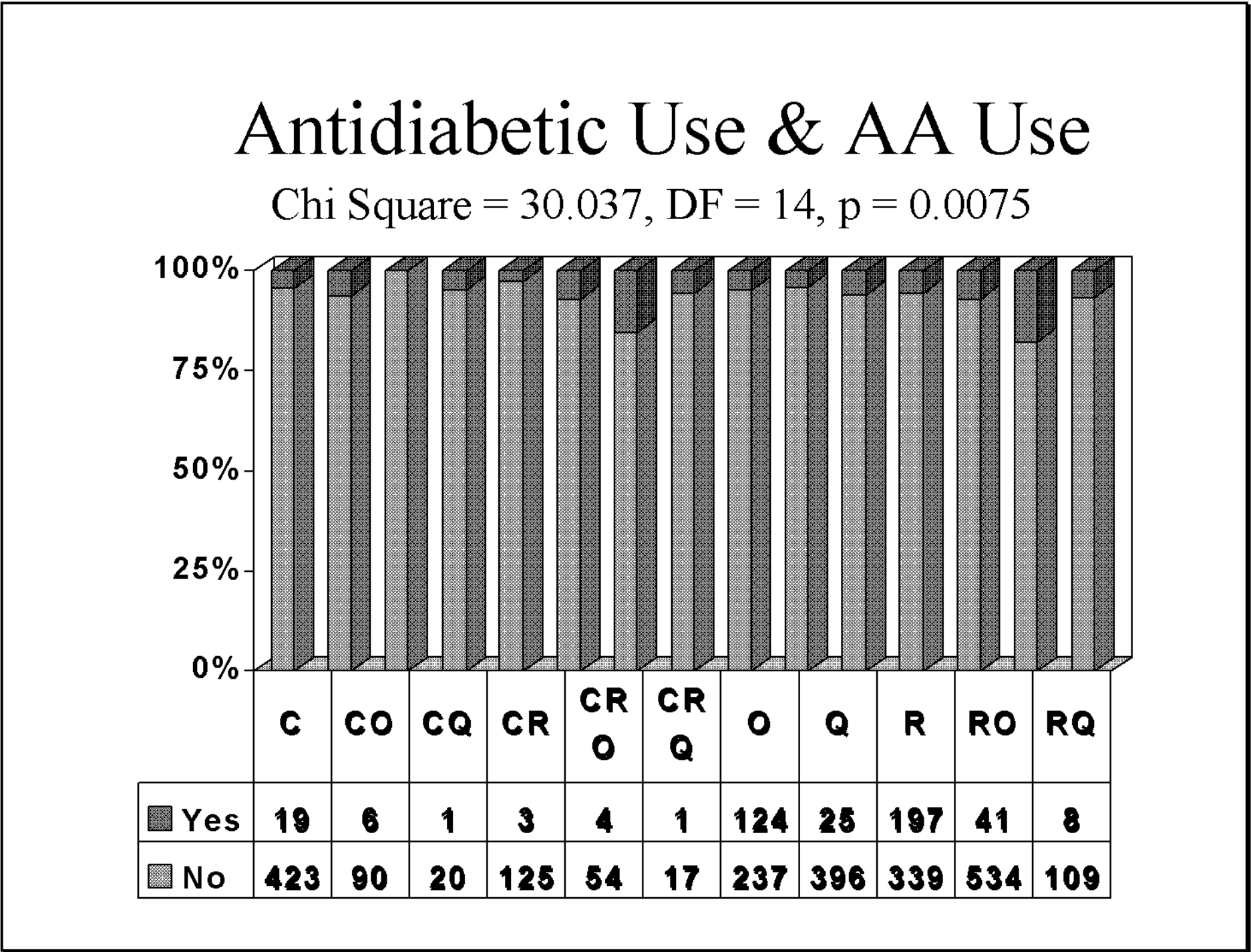
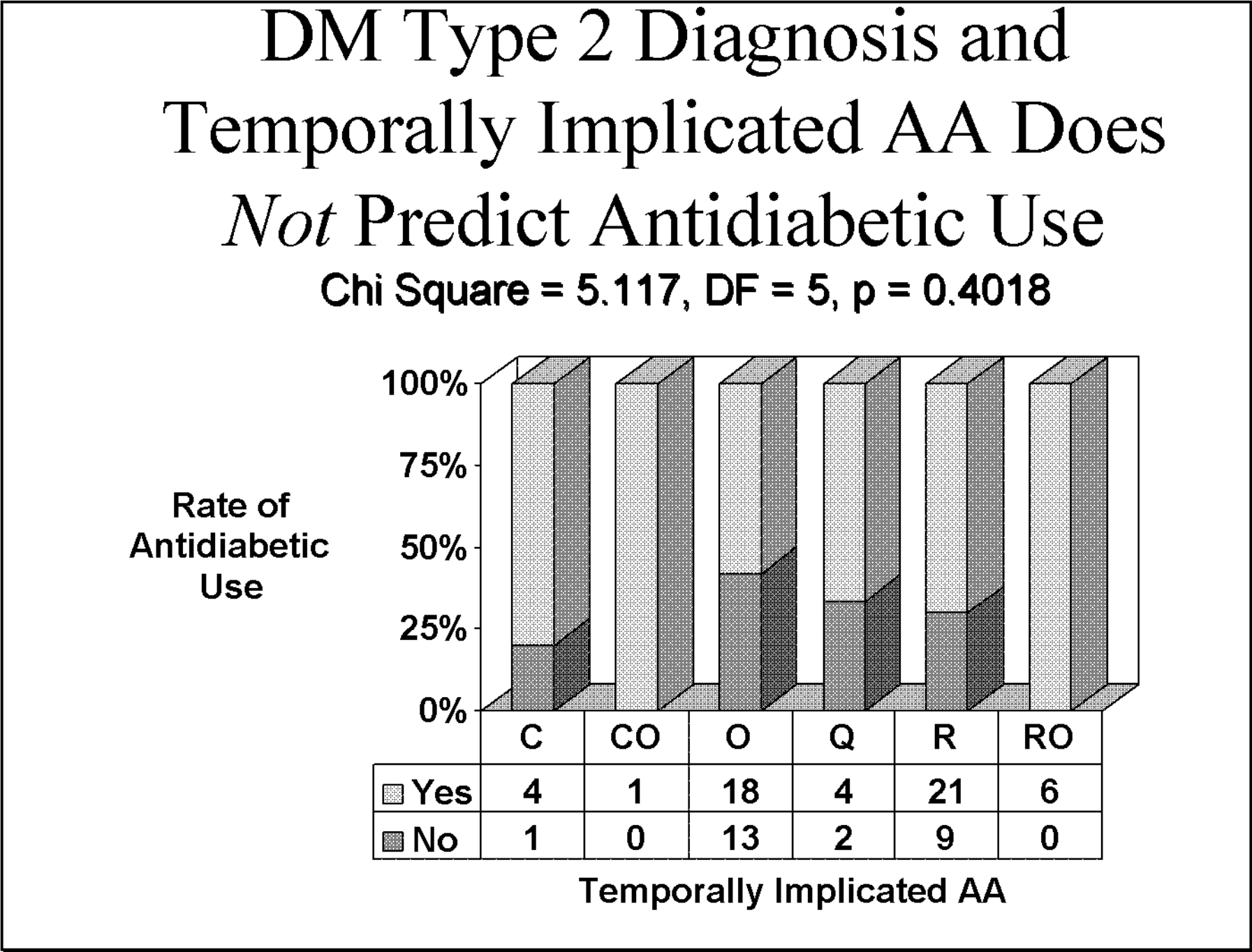
Introduction: The Atypical Antipsychotics (AA) have been implicated in causing decreased glucose tolerance. Routine monitoring of inpatients at a large state hospital and subsequent diagnosis and treatment of Type II Diabetes Mellitus (DM) with oral antidiabetic agents may differ depending upon which 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:

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Where Presented: College of Psychiatric and Neurologic Pharmacists (CPNP) Annual Meeting, March 2001, San Antonio TX; NCDEU 41st Annual Meeting, May 2001, Phoenix AZ.

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Use of Atypical Antipsychotics and the Incidence of Diabetes

Lage MJ{ XE "Lage MJ" }, Kemner J{ XE "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.

Review Comments:

- This analysis is consistent with other analyses of large prescription claims databases that found no statistically significant differences in the risk of developing diabetes in patients treated with atypical antipsychotics versus typical antipsychotics or in patients treated with OLZ versus RIS
- One strength of the study is that they looked at antipsychotic monotherapy to rule out confounding variables.

Where Presented: Institute of Psychiatric Services Meeting, October 2001, Orlando FL; Biennial Winter Workshop on Schizophrenia, February 2002, Davos Switzerland.

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Manuscripts

Case Reports / Case Series

New Onset Diabetes and Atypical Antipsychotics. European Neuropsychopharmacology. 2001;11:25-32.

Liebzeit KA{ XE "Liebzeit KA" }, Markowitz JS{ XE "Markowitz JS" }, Caley CF{ XE "Caley CF" }

Abstract: As a class, the atypical antipsychotics are the first line treatment choice for the psychopharmacologic management of psychotic disorders. Emerging evidence currently suggests that at least two of the atypical antipsychotics, clozapine and olanzapine, and possibly quetiapine may be associated with the risk of new onset diabetes or serum glucose dyscontrol. Computerized Medline and Current Contents searches from years 1966 through June 2000 were undertaken to retrieve all pertinent studies and case reports of typical and atypical antipsychotics and glucose-insulin problems. Historically, both schizophrenia and the older antipsychotics medications have been reported to be associated with a similar risk for causing disruptions in serum glucose control. Additionally, diabetes has well recognized associations with a number of medical disorders such as cardiovascular disease; it is therefore worthy of attention. Hypothesized mechanisms for antipsychotic induced diabetes ranges from the antagonism of several neurotransmitter receptors to insulin resistance. A total of thirty-five cases of induced or exacerbated diabetes are presently available in the published literature; the vast majority of cases implicate clozapine ($n=20$) and olanzapine ($n=15$). In multiple cases, diabetic ketoacidosis has been the presenting symptom; daily atypical antipsychotic doses have been within acceptable ranges and were not considered to be excessive.

Review Comments:

- This manuscript was simply a literature review of diabetes case reports associated with atypical usage (as reported through June 2000) and compiling them into one manuscript. It is already becoming dated quickly as newer reports continue to surface on not only clozapine and olanzapine, but also risperidone and quetiapine.
- The manuscript contains a pretty good review of possible mechanisms by which hyperglycemia may be occurring with atypicals, however many of these hypotheses are starting to be disproved. They suggest that risperidone may not share some of these mechanisms which are common to clozapine and olanzapine thereby supporting no risperidone case reports at the time this was written. However, today we know that risperidone does have cases of diabetes reported.

Atypical Antipsychotics and Hyperglycemia. International Clinical Psychopharmacology. 2001;16:63-74.

Mir S{ XE "Mir S" }, Taylor D{ XE "Taylor D" }

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Abstract: Hyperglycemia is known occasionally to occur with conventional neuroleptics, but has more recently been associated with atypical antipsychotics especially clozapine and olanzapine. This article examines more closely this association. A review of relevant published literature from 1970 to date was undertaken following Medline and Embase searches in June 2000. Hyperglycemia with clozapine was widely reported: spontaneous reports of either hyperglycemia or ketoacidosis were described in a total of 17 people. In a five year naturalistic study, 30.5% of patients taking clozapine were eventually diagnosed with Type 2 diabetes. With olanzapine, a total of 10 cases of hyperglycemia and 5 cases of ketoacidosis have been published. Reports of hyperglycemia with other atypicals are relatively scarce. The association of hyperglycemia or ketoacidosis with clozapine and olanzapine appears to be a true drug-induced effect. Risk factors may include male gender, age of around 40 years and being non-Caucasian. The management of hyperglycemia depends on the causative agent. With clozapine, treatment with oral hypoglycemics has been successful. With olanzapine, other atypical antipsychotics may be considered. Blood glucose monitoring is essential for all patients starting clozapine or olanzapine.

Review Comments:

- Another manuscript that was simply a literature review of diabetes case reports associated with atypical usage (as reported through June 2000) and compiling them into one manuscript. It is already becoming dated quickly as newer reports continue to surface on not only clozapine and olanzapine, but also risperidone and quetiapine.
- The authors go into an extensive analysis of why these drugs are likely causative for this adverse event situation. They include a comment that DKA is unknown in type 2 diabetes therefore these drugs are causing harmful damage. We know this is not the case from clamp study data and the diabetes literature documenting an increasing occurrence of DKA in type 2 patients.
- This manuscript is more direct than the previous one in suggesting that the appropriate action to take whenever a case of hyperglycemia is noted is a switching of the antipsychotic involved. The place very strong reliability of the case reports as being definitive for causality.

Diabetes Mellitus Associated with Atypical Antipsychotic Medications: New case Report and Review of the Literature. *Journal American Board of Family Practice*. 2001;14:278-282.

Muench J{ XE "Muench J" }, Carey M{ XE "Carey M" }

Background: Since the introduction of atypical antipsychotic medications, beginning with clozapine in 1990, several case reports in the psychiatric literature have suggested that they might be associated with new onset of diabetes mellitus as well as with diabetic ketoacidosis.

Methods: We report the case of a 38 year old patient with schizophrenia who suddenly developed diabetes mellitus and ketoacidosis 12 months after starting olanzapine. Similar cases in the literature were found through a Medline assisted search using the keywords "schizophrenia," "diabetes mellitus," "ketoacidosis," and "adverse drug reaction."

Results: Including this case, 30 patients have been reported in the literature to have developed diabetes or have lost diabetic control after starting clozapine, olanzapine, or quetiapine. Twelve of these 30 developed diabetic ketoacidosis. Two limited quantitative studies have added evidence toward this association.

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Conclusion: Although a causal relationship has not been definitively proved, the number of cases reported in the literature suggests there might be an association between atypical antipsychotic medications and diabetes mellitus. Primary care physicians who care for patients with schizophrenia should be aware of this possible association.

Review Comments:

- Another basic review paper, no mention is given for the date sequence for their Medline search but it must have been no more recent than July 2000 based upon the number of cases they identified. The literature review section of this paper provides no new learning to the field.
- The case report on the 38 year old is very interesting to examine. The patient had been treated with a variety of antipsychotics, antidepressants, and mood stabilizers over several years including risperidone for at least two years prior to switching to olanzapine. He had substantial weight gain over the years and at the time of diabetes diagnosis was considerably overweight with a BMI in excess of 31. He had a history of drug abuse, smoking and potentially a family history of diabetes. Three years prior to his diabetes and DKA episode the report says he was seen in the PCP office for "leg pain, tensions headaches and onychomycosis. Could the leg pain been an early sign of diabetic neuropathy (which usually begins many years prior to most diabetes diagnoses)? This report indicates that the patient had infrequent check ups but just months prior to his switch to olanzapine he had a random glucose value of 170 mg/dl. He was referred for a fasting glucose measurement following the random with two separate fasting glucose measurements of 73 and 97 mg/dl obtained. In April 1999 he was switched to olanzapine from risperidone during a psych hospitalization. He gained another 30 pounds over the next year and in April 2000 complained of polyuria and polydipsia. At the time he was taking olanzapine, valproic acid, venlafaxine, atorvastatin and propranolol. (based upon this combo of meds one can assume he had high cholesterol and hypertension, in addition to being obese and now hyperglycemic, all the signs of the metabolic syndrome). He was put on metformin as an outpatient and five days later was hospitalized for DKA with a blood glucose of 765 mg/dl. He had a HbA1C of 13.4% (this would indicate to me that he had undetected hyperglycemia for many months). He was placed on insulin and two months later his insulin dose was cut in half. This patient was kept on olanzapine after the diagnosis of diabetes because it was effective in controlling his psychosis.
- The last page of the manuscript has an interesting discussion of the prevalence of DKA in type 2 diabetes patients.

Risperidone-Associated New Onset Diabetes. *Biological Psychiatry*. 2001;50:148-149.

Wirshing DA{ XE "Wirshing DA" }, Pierre JM, Eyeler J, Weinbach J, Wirshing WC{ XE "Wirshing WC" }

Background: Weight gain, and its associated complications such as the development of diabetes, is becoming increasingly recognized as an important potential side effect of the novel antipsychotic drugs.

Methods: Two retrospective cases are described in which patients with schizophrenia developed diabetes while taking the antipsychotic medication risperidone.

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Results: Both patients had preexisting risk factors for diabetes and developed insulin resistance in the context of weight gain. Both cases necessitated medical intervention and one patient requires ongoing treatment with insulin.

Conclusions: Although the exact mechanism of antipsychotic induced diabetes remains obscure, weight gain appears to be a significant risk factor. Careful monitoring of weight and fasting glucose is recommended for any patient taking novel antipsychotic medications.

Review Comments:

- Two cases reports on Risperidone which debunk the belief that Risperidone is not associated with hyperglycemia or diabetes. One case, although not identified as DKA was admitted to the hospital and had a small amount of ketosis present.
- Authors conclude that “our cases suggest that risperidone, along with other NAPDs, carries a liability for the development of diabetes in some patients.”
- This case report is consistently “overlooked” by Janssen speakers when discussing the “lack of cases with Risperidone” (ie, Newcomer).

Diabetic Ketoacidosis associated with Olanzapine in an Adolescent Patient. *Journal of Pediatrics*. 2001;138:936-938.

Selva KA{ XE "Selva KA" }, Scott SM{ XE "Scott SM" }

Abstract: Olanzapine (Zyprexa) is an atypical neuroleptic used in adult and pediatric patients for the management of schizophrenia. Common side effects include increased appetite and weight gain. An uncommon but severe adverse effect is the development of diabetic ketoacidosis, reported until now only in adults. We report a case of acute onset diabetic ketoacidosis presenting in a 16-year-old girl during olanzapine therapy.

Review Comments:

- This case report is in a 16 year old Hispanic girl with visual hallucinations and major depressive disorder. Upon the presentation of DKA she had been taking Olanzapine continuously for 6 months, but she was also taking Risperidone and Venlafaxine. In the hospital her Olanzapine was discontinued by her psych, however she remained on RIS and Venlafaxine. Her admission HbA1C was 17.7% indicating that she had been hyperglycemic for quite some time. She was discharged from the hospital on insulin and remained on Risperidone and Venlafaxine, but 17 days later her insulin therapy was discontinued. She was never put back on Olanzapine. Six months later her blood sugars again began to increase and repeat HbA1C was 10.5% and she was judged to have diabetes. The patient had a strong maternal and paternal history of diabetes.
- This patient sounds like a classic case of juvenile type 2 diabetes occurring in a patient with a strong family history and other risk factors. Yet it is identified as an “olanzapine-associated” case, even though risperidone was being taken by this patient through out her course of therapy.

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Olanzapine-Induced Diabetes Mellitus. *Annals of Pharmacotherapy*. 2001;35:563-565.

Bonanno D{ XE "Bonanno D" }G, Davydov L, Botts SR{ XE "Botts SR" }

Objective: To report two cases of new-onset diabetes mellitus resulting after the initiation of olanzapine treatment.

Case Summary: A 31 year old African American man and a 44 year old white man, both with schizoaffective disorder, developed diabetes mellitus within weeks or months of olanzapine initiation.

Discussion: Our reports of new-onset diabetes due to olanzapine are consistent with those in the literature. Although the mechanism is not yet known, it has been hypothesized that perhaps damage to the pancreatic islet cells, weight gain, dysregulation of the sympathetic system, and insulin resistance are contributing factors.

Conclusions: Diabetes mellitus secondary to olanzapine use seems to be a rare occurrence. However, certain risk factors such as obesity, family history, and concomitant medications may predispose an individual to development of diabetes mellitus while taking olanzapine. An increased awareness of this reaction is essential in the treatment of patients at risk. Periodic serum glucose monitoring in these individuals may be warranted.

Review Comments:

- Patient #1 had several risk factors for the development of diabetes: he was African American, overweight and with a family history of diabetes. At the time of diabetes diagnosis he was taking 1500 mg/d of divalproex, mirtazapine 30mg/d olanzapine 10mg/d, temazepam 15mg/d and benztropine 4mg/d. He presented with polyuria, polydipsia and blurred vision six weeks after starting olanzapine and had a random glucose of 509 mg/dl and an HbA1C of 10.7%. The patient was stabilized on insulin and switched from olanzapine to perphenazine. Seven months later he was readmitted in crisis, he had stopped all his medications 3 months prior to hospitalization. His random BG was 468 mg/dl and he was restarted on olanzapine and insulin. Blood glucose was stabilized but still somewhat elevated. The patient was lost to follow up after hospital discharge.
- Patient #2 had a 20 year history of schizoaffective disorder and was hospitalized after a random glucose of 936 mg/dl was noted. This patient was overweight and had a family history of diabetes. On admission he was being treated with Divalproex, Olanzapine, Sertraline and Propranolol. The patient was said to have had a fasting BG of 82 mg/dl one month prior to starting olanzapine. The patient was treated with an oral hypoglycemic agent and kept on olanzapine at a slightly reduced dosage. Within 2 days his blood glucose stabilized and the patient remains on olanzapine and a low dose oral hypoglycemic.
- Both of these cases demonstrate a rather typical type 2 diabetes presentation and there is no strong data that would indicate causality due to olanzapine therapy.

Hyperglycemia and Hypertriglyceridemia Secondary to Olanzapine. *Journal of Child and Adolescent Psychopharmacology*. 2001;11(3):285-288.

Domon SC{ XE "Domon SC" }, Webber J{ XE "Webber J" }C

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Abstract: Olanzapine is an atypical antipsychotic that is becoming more widely used in children and adolescents. There have been reports of olanzapine-induced hyperglycemia and hypertriglyceridemia in adults. This case report describes the development of both hyperglycemia and hypertriglyceridemia in an male adolescent that resolved with discontinuation of olanzapine and without dietary changes or the use of insulin or oral hypoglycemics.

Review Comments:

- This is one of the few case reports of hyperglycemia occurring in an adolescent or child (patient was 15 years old). It has become well established in the endocrinology community that diabetes and hyperglycemia are rising rampantly in the general adolescent patient population with many papers being published on this issue in recent years.
- This patient has several diabetes risk factors present: African American descent, very strong maternal history of diabetes, overweight (prior to antipsychotic therapy), rapid weight gain (BMI increased 19%, 5.4 kg/m² in 6 months).
- This patient looks like a “classic” juvenile type 2 diabetes presentation with the development of polyuria, polydipsia and significant weight loss (19kg) just prior to presenting with a fasting BG of 368 mg/dL.
- The patient had been taking valproic acid for 21 months, olanzapine for 12 months and buspirone for 5 months prior to presenting with symptoms of diabetes. His olanzapine was discontinued although he remained on the concomitant valproic acid and buspirone. Over the next 8 weeks the patient's blood glucose level dropped steadily each week to a normal level and remained at this level for the next 12 weeks.
- Was olanzapine causing a slight increase in insulin resistance that bumped this high risk patient over the edge? Is this patient a juvenile type 2 diabetic experiencing a “honeymoon” period in symptomatology and diabetes is highly likely to return regardless of medication regimens?

Olanzapine-related Hyperglycemia in a Non-diabetic Woman. *Canadian Journal of Psychiatry*. 2001;46(5):457.

Kropp S{ XE "Kropp S" }, Emrich HM{ XE "Emrich HM" }, Bleich S{ XE "Bleich S" }, Degner D{ XE "Degner D" }

Letter to the Editor: Olanzapine is an atypical antipsychotic agent similar in chemical structure and in mechanism of action to clozapine. Compared with typical neuroleptics, olanzapine has a reduced incidence of extrapyramidal reactions. Antagonism at muscarinic receptors, H₁ receptors and alpha₁ receptors may explain some side effects of olanzapine, including anticholinergic actions, somnolence, and orthostatic hypotension, respectively. The mechanism of action concerning glycemic control is yet not fully understood. Meanwhile, several reports of olanzapine-related hyperglycemia are available. Most of the cases were either African American patients, patients with diabetes, or patients on more than 10mg daily of olanzapine. To our knowledge, there is no report of hyperglycemia in a white patient on only 2.5mg olanzapine daily.

Case Report: We report the case of a 79-year old, white woman, with a height of 152cm and weight of 48.1kg. She revealed being weary of life, and a marked delusion of poverty was prominent. She admitted to continual suicidal thoughts, and her Hamilton Depression Rating Scale (HDRS) score was 41 points on admission. A major depressive disorder (MDD) according to DSM-IV criteria, with psychotic symptoms, was diagnosed. Her medical history included

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chronic obstructive lung disease (treated with cloprednole 5mg daily), stable hyperthyroidism, subcortical arteriosclerotic encephalopathy, and osteoporosis. Blood glucose on admission (189mg/dL) indicated no prior history of diabetes mellitus, but slight glucose intolerance. Initial treatment was started with 30mg mirtazapine and 2mg risperidone daily, but parkinsonism necessitated a change to olanzapine 2.5mg daily. After 6 weeks of olanzapine treatment, the patient became distraught, withdrew into herself, and lost orientation as to time, place, and person. Because it was unclear why she had worsened, blood examinations were done. These revealed a blood glucose level of 496 mg/dL, and a sliding insulin regime was established. Even then, blood glucose levels remained up to 320 mg/dL, and olanzapine was therefore discontinued. After 2 days, blood glucose levels returned to normal, with a maximum of 111 mg/dL. This case was estimated to be a severe drug-related adverse effect: it required insulin therapy, and the condition of the patient clinically worsened but improved significantly after discontinuation of olanzapine. It seems possible that the systemic glucocorticoid might have played a dispositional role in this case of hyperglycemia, but under continuation of cloprednole, this did not happen again. We conclude that patients on olanzapine therapy – even those without risk factors for diabetes – might need regular control of their blood glucose levels.

Review Comments:

- As with many case reports, it is difficult to tease out a causal relationship based upon the limited amount of data presented. Although this patient had fewer risk factors than many case report patients she was not without risk for diabetes. The patient was elderly although not overweight. She was taking steroid medications which are known to increase insulin resistance and hyperglycemia development risk.
- This patient presented on admission with a random glucose of 189 mg/dL the first time before any antipsychotic was ever begun, signifying that she had glucose intolerance and some degree of either insulin resistance or beta cell exhaustion. Unfortunately, no blood glucose value is reported at the time she was switched from Risperidone to Olanzapine. She may have had a significantly high BG at that time with no additional change in blood glucose being caused by Olanzapine. However she was on Olanzapine at the time the next reported blood glucose was taken, therefore Olanzapine is the culprit.
- The case would lead you to believe that once Olanzapine was discontinued, her diabetes spontaneously resolved. However they don't mention if she was still on insulin therapy, which I suspect is the case, or what alterations to insulin dose was made during this time period.

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Published Studies

Abnormalities in Glucose Regulation During Antipsychotic Treatment of Schizophrenia. *Archives General Psychiatry*, 2002;59:337-345

Newcomer JW{ XE "Newcomer JW" }, Haupt DW{ XE "Haupt DW" }, Fucetola R{ XE "Fucetola R" }, Melson AK, Schweiger JA, Cooper BP, Selke G

Background: Hyperglycemia and type 2 diabetes mellitus are more common in schizophrenia than in the general population. Glucoregulatory abnormalities have also been associated with the use of antipsychotic medications themselves. While antipsychotics may increase adiposity, which can decrease insulin sensitivity, disease- and medication-related differences in glucose regulation might also occur independent of differences in adiposity.

Methods: Modified oral glucose tolerance tests were performed in schizophrenic patients (n=48) receiving clozapine, olanzapine, risperidone, or typical antipsychotics, and untreated healthy control subjects (n=31), excluding subjects with diabetes and matching groups for adiposity and age. Plasma was sampled at 0 (fasting), 15, 45, and 75 minutes after glucose load.

Results: Significant time X treatment group interactions were detected for plasma glucose ($F_{12,222} = 4.89$, $P < .001$) and insulin ($F_{12,171} = 2.10$, $P = .02$) levels, with significant effects of treatment group on plasma glucose level at all time points. Olanzapine-treated patients had significant (1.0-1.5 SDs) glucose elevations at all time points, in comparison with patients receiving typical antipsychotics as well as untreated healthy control subjects. Clozapine-treated patients had significant (1.0-1.5 SDs) glucose elevations at fasting and 75 minutes after load, again in comparison with patients receiving typical antipsychotics and untreated control subjects. Risperidone-treated patients had elevations in fasting and postload glucose levels, but only in comparison with untreated healthy control subjects. No differences in mean plasma glucose level were detected when comparing risperidone-treated vs typical antipsychotic-treated patients and when comparing typical antipsychotic-treated patients vs untreated control subjects.

Conclusion: Antipsychotic treatment of nondiabetic patients with schizophrenia can be associated with adverse effects on glucose regulation, which can vary in severity independent of adiposity and potentially increase long-term cardiovascular risk.

Review Comments:

- This study was stimulated by work done by Dr. Newcomer looking at glucose and insulin effects on cognitive function. It is cross-sectional in design providing a snap shot picture of what may be occurring. Because of this design a cause-effect relationship can't be determined.
- Dr. Newcomer uses a challenge procedure similar to an oral glucose tolerance test, yet with several non-standard features that limit interpretability and comparison to defined standards. Patients underwent a 9 hour overnight fast prior to the baseline fasting plasma glucose test (standard fasting tests are done after a 12 hour fast). Patients in the study then underwent a "modified" glucose tolerance test consisting of a 50 gm glucose challenge followed by glucose measurements at 15, 45 and 75 minutes. In a standard oral glucose tolerance test (OGTT) patients are given a 75 gm glucose challenge and then plasma glucose is measured at the end of a 120 minute waiting period. Interpreting a 75 minute test result and then correlating this to a relative risk for glucose intolerance, hyperglycemia or diabetes is unconventional as no standard of comparison exists. The differential between patients regarding peristaltic action in the gut, and the impact of medications on variations in gastric emptying/glucose absorption can dramatically alter subsequent glucose and insulin curves.

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Endocrinologists will tell you the due to these potential differing effects among patients, any measurement before 90 minutes post challenge is uninterpretable and therefore the standard is a 120 minute assessment of glucose levels. Dr Newcomer answers this criticism in his paper by stating that his purpose was not one of diabetes diagnosis, which is the basis for the OGTT, but rather to characterize glucose regulation during administration of a cognitive battery of similar 75 minute length. However, conclusions are being made in the paper concerning diabetes risk which are not supportable with a 75min test procedure.

- This study examines glucose levels in 79 subjects using this modified OGTT method. Of these 79 subjects, there are $N=31$ who are healthy untreated controls, and an $N=48$ chronically ill schizophrenics (Clozapine $N=9$, Olanzapine $N=12$, Risperidone $N=10$, Typicals $N=17$). These patients were recruited within both an outpatient and inpatient setting. Possible confounders to the results are that there is a significant length of treatment difference between these groups. The outpatient subjects had to be on stable antipsychotic dosing for > 3 months to be included. However, the inpatient group ranged between 3-6 weeks on therapy. No mention is provided as to any between treatment group assessments for time on drug prior to the glucose testing procedures.
- There is a skewed distribution of patient ethnicity in this study with the Olanzapine group being primarily African American, a higher risk group for diabetes and glucose intolerance, which may be leading to the higher glucose curves.
- The patients in this study were not on antipsychotic monotherapy. The typical antipsychotic group is mostly Haloperidol patients, which has demonstrated a lower effect on glucose versus other typicals. The only patients taking concomitant mood stabilizers (depakote or lithium, $N=4$) were in the Olanzapine group. The authors state that when patients receiving concomitant mood stabilizers and/or antidepressants were removed from the analysis, there was still a significant time x treatment group interaction. They do acknowledge as a limitation that 3 patients in the Olanzapine group were on adjunctive valproic acid which can cause hyperglycemia itself.
- They state that they explored the relationship of symptom severity (using BPRS total scores) to glucose and insulin. These patients were all chronically ill schizophrenics. Were the Olanzapine patients more severe based upon concomitant mood stabilizers and high dosage levels, although their BPRS was lower (better response to therapy)?
- The Clozapine and Olanzapine groups had the highest fasting baseline glucose values, this may be an indication of more severely ill patients, which is consistent with other treatment resistant patient studies.
- This study only reports mean glucose values. It would be interesting to know what the median glucose values at the various time points was also. Are there one or two significant outliers that are causing a substantial shift in the mean away from the median? In a study where wide patient variation is possible this is a critical missing piece of information for study interpretation.
- In conducting the modified OGTT test the authors simply state that patients arrived for the testing between 8 and 9 AM in a fasting state for the baseline evaluation. Was there consistency between patients in the amount of time between arrival and the start of blood sampling and oral glucose challenge? Recent exercise such as walking a considerable distance from a parking area to the lab can dramatically alter results of an OGTT. If in some patients their metabolism had not adjusted prior to the start of testing then a bias has been introduced to the results.
- The procedures section of the study indicates that plasma glucose levels were acutely monitored during the OGTT using a blood glucose meter which is reading capillary glucose levels and then also with a glucose analyzer in the lab. Which measurements are used in the reporting of data at various time points? Are they comparable ways to measure? How often

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did they calibrate the Lifescan meter and did they use multiple meters? All of these can introduce sampling bias.

- Were the HOMA IR calculations made using the baseline fasting blood glucose values or glucose values from other time points, paper doesn't state which was used? According to the HOMA IR formula, fasting glucose and insulin levels are required
- Olanzapine had significantly higher fasting blood glucoses as well as glucose levels at 15, 45, and 75 minute time points in comparison to untreated healthy controls and the typical antipsychotic treated group ($p < 0.005$). Clozapine had significantly higher fasting and 75 minute levels in comparison to untreated healthy controls and the typical antipsychotic treated groups ($p < 0.005$). Risperidone also had a significant increase in fasting blood glucose and glucose levels at 45 and 75 minute time points versus healthy untreated control group only ($p < 0.005$).
- The authors acknowledge that any conclusion regarding relative differences in glucoregulatory effects between specific antipsychotic treatments is limited by the sample size of the study and a type II error cannot be excluded (however, a type I error can not be excluded either). Nonrandom sampling bias may also be present.
- No standardization of carbohydrate intake was done prior to the study, which may bias the results.
- Patients were matched for BMI rather than abdominal adiposity which has a stronger correlation with insulin resistance and glucose intolerance.

Study review/critique prepared by Patrick Toalson R.Ph., Neuroscience Medical Liaison on 4/18/02

Association of Diabetes Mellitus With Use of Atypical Neuroleptics in the Treatment of Schizophrenia. *American Journal of Psychiatry*, 2002;159:561-566

Sernyak MJ { XE "Sernyak MJ" }, *Leslie DL* { XE "Leslie DL" }, *Alarcon RD*, *Losonczy MF*, *Rosenheck R* { XE "Rosenheck R" }

Objective: The development of both type I and type II diabetes after initiation of some atypical neuroleptics has been reported, primarily in studies involving small series of patients. This study used administrative data from a large national sample of patients with a diagnosis of schizophrenia to compare the prevalence of diabetes mellitus in patients receiving prescriptions for atypical and typical neuroleptics.

Method: All outpatients with schizophrenia treated with typical and atypical neuroleptics over 4 months in 1999 in the Veterans Health Administration of the Department of Veterans Affairs (VA) were included in this study. Patients treated with atypical neuroleptics were those who received prescriptions for clozapine, olanzapine, risperidone, or quetiapine. Patients with a diagnosis of diabetes were also identified by using ICD-9 codes in VA administrative databases. The prevalence of diabetes mellitus across age groups and among patients receiving prescriptions for different atypical neuroleptics was examined with multiple logistic regression.

Results: A total of 38,632 patients were included in the study: 15,984 (41.4%) received typical neuroleptics and 22,648 (58.6%) received any atypical neuroleptic (1,207 [5.3%] received clozapine; 10,970 [48.4%], olanzapine; 955 [4.2%], quetiapine; and 9,903 [43.7%], risperidone; 387 patients received prescriptions for more than one atypical neuroleptic). When the effects of age were controlled, patients who received atypical neuroleptics were 9% more likely to have diabetes than those who received typical neuroleptics, and the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine, but not

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risperidone. However, for patients less than 40 years old, all of the atypical neuroleptics were associated with a significantly increased prevalence of diabetes.

Conclusions: In this large group of patients with schizophrenia, receipt of a prescription for atypical neuroleptics was significantly associated with diabetes mellitus.

Review Comments:

- **Authors' Conclusions:** Schizophrenia patients who received atypicals were more likely to have diabetes than those who received typicals, and the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine, but not risperidone. The authors also state that the results are strongly suggestive of a causal relationship.
- **Brief Overview of the Method:** VA administrative claims database identified 38,632 outpatients with schizophrenia who were treated with antipsychotics over a 4-month period in 1999. The proportion of patients diagnosed with diabetes mellitus (DM) was compared between patients who received typicals and those who received atypicals, and again between patients who received typicals versus those who received a specific atypical antipsychotic (clozapine, olanzapine, quetiapine, and risperidone), adjusted and unadjusted for age (5 age groups).
- **Major Shortcomings:**
 1. **No cause-effect relationship.** Although the authors claim that the results strongly suggest a causal relationship, the findings merely point to a correlational association between the prescription of atypical antipsychotics and the diagnosis of DM. It does not demonstrate that atypical antipsychotics **cause** an increase in the odds of being diagnosed with DM. It is highly likely that schizophrenia patients who are treated with atypical antipsychotics are different from those who are treated with typical antipsychotics on a host of characteristics, including risk factors for DM, such as family history of DM, ethnic background, weight, physical activity, hypertension, low HDL/high TG, and a history of impaired glucose intolerance. None of these risk factors was addressed in this study.
 2. **Olanzapine vs. risperidone.** The study findings need to be interpreted in their correct context, which is that compared with typical antipsychotics, risperidone prescriptions were significantly associated with increased odds for DM on 2 of 5 age groups, while olanzapine prescriptions were significantly associated with increased odds for DM on 3 of 5 age groups. There is a difference on only **1 of 5** age groups (on the age group 40-49). Furthermore, the odds of having a diagnosis of DM when prescribed olanzapine or risperidone in the 40-49 age group were extremely similar (1.19 vs. 1.04, respectively), with overlapping confidence intervals (1.06-1.34; 0.92-1.17, respectively) which indicate that the 2 values are **not** different reliably from each other (please see figure below).
 3. **Prior diagnosis of diabetes mellitus.** Patients may have been diagnosed with DM **prior** to receiving the antipsychotic drug. The study's cross-sectional design does not allow one to address this crucial detail, thus providing no way to preclude this directional possibility.
 4. **Duration on the antipsychotic drug.** The study did not take into account the duration that the patients were prescribed antipsychotic drugs. This is another crucial variable, as some patients might have recently switched from another antipsychotic, while others might have used the same antipsychotic for a long time.
 5. **Pre-existing medical conditions.** The study did not take into account patient's pre-existing medical conditions, including those that are clearly associated with DM (e.g., hypertension). If medically sicker patients were more likely to be treated with atypicals than typicals, then one would expect to see an increased prevalence of DM among those treated with atypicals, as a mere artifact.
 6. **Risperidone-treated patients might be less severely ill.** In a previous publication¹ the authors used the same VA schizophrenia sample to report that one of the strongest predictors of severity of illness and polypharmacy with antipsychotics is having been hospitalized for 19 or more days in the previous year for a psychiatric disorder. They also reported¹ (Table 2, pp. 381) that among patients receiving atypical antipsychotics, risperidone-treated patients were significantly **less** likely to have had such psychiatric hospitalizations. This suggests that risperidone-treated patients were

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less severely ill than olanzapine-treated patients and less prone to polypharmacy. Severity of illness and/or polypharmacy may constitute risk factors for DM and may explain some of the differences in the prevalence of DM.

7. **Exclusion of patients on depot medication.** The authors did not mention one important detail about the current study that they did report in two previous articles^{1,2} in which they used the same sample: that the schizophrenia sample excluded all patients on depot medications (in 1999, all were typical antipsychotics). At the VA, the nurses dispense depot medications on site in their clinics without specific prescriptions, thus the VA database lacks patient-level information for depot drugs. This indicates an incomplete and possibly skewed assessment of DM in patients treated with typical antipsychotics.
8. **Monotherapy.** The study compared patients who were treated with typicals versus atypicals as if they were mutually exclusive (monotherapy). This was not the case, as the study included patients who received both typicals and atypicals concurrently (9%), as well as patients who were co-prescribed 2 atypicals (1%). The failure to exclude patients on multiple antipsychotics and confine the analysis to patients on antipsychotic monotherapy may have introduced additional error variance that may jeopardize the validity of the authors' conclusions.
9. **Perplexing discrepancies.** The authors used in the present study the same VA database as in their prior two publications^{1,2}. Although the prior publications defined the schizophrenia patient population in exactly the same manner, studied the use of antipsychotics in the same 4 months in 1999, and defined diagnosis and antipsychotics in the same way, the resulting sample size in this paper is different. Surprisingly, the authors got this time a much larger sample size (+3,707 patients). Compared with the previous sample, the current sample has more patients on atypical antipsychotics (+2,156 patients) but fewer patients on typicals (-275 patients). The authors do not address the reasons for these discrepancies.
10. **Possible underestimation of DM.** The authors identified DM by the presence of DM diagnosis in patient's medical record. Reliance on the diagnosis of DM rather than the inclusion of patients with DM diagnosis *and* patients who lack this diagnosis but are prescribed diabetic medication, may have led to underestimation of the true prevalence of DM in the studied population.

In summary: Due to the cross-sectional design of this study and a number of shortcomings, the findings do not permit one to conclude that schizophrenia patients who are treated with atypical antipsychotics are at an increased risk for DM than those prescribed typical antipsychotics. Nor do the findings warrant the authors' conclusion that the findings strongly suggest a causal relationship.

This study not only failed to demonstrate cause-effect relationship, but it also failed to address the high likelihood that the patient groups differed on a host of relevant characteristics, including risk factors for DM. Furthermore, the odds of having a diagnosis of DM was significantly higher for patients prescribed risperidone than patients prescribed typical antipsychotics on 2 of the 5 age groups, while this was found for patients prescribed olanzapine on 3 of the 5 age groups. These findings point to potential differences between olanzapine and risperidone on only 1 of 5 age groups. However, examination of the odds ratios for the olanzapine and risperidone patients on that one specific age group (age 40-49) reveals that the odds ratios are **not** different reliably from each other. This indicates that the olanzapine and risperidone groups have not been demonstrated to reliably differ from each other on the odds for being diagnosed with DM.

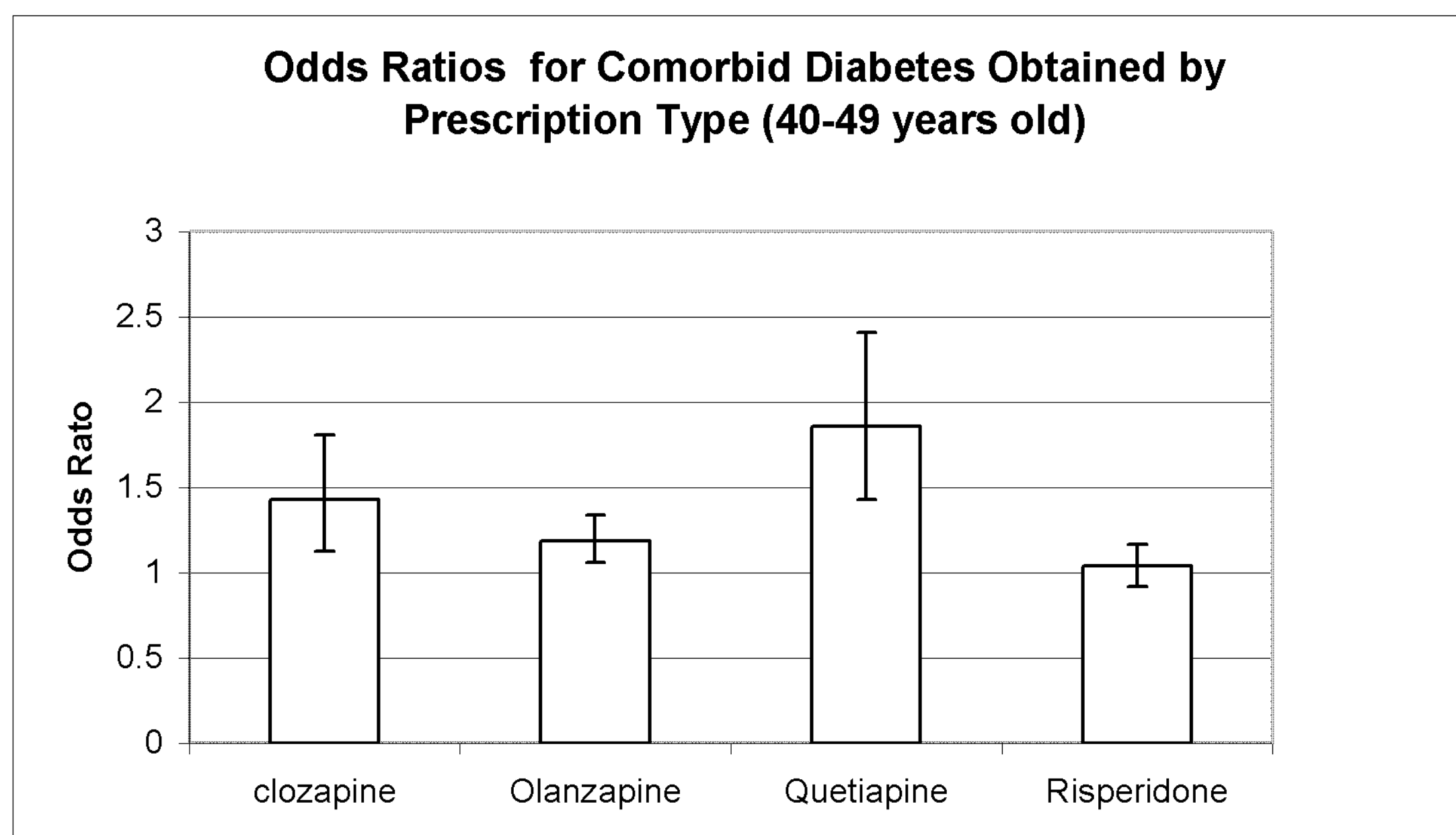
¹ Leslie DL, Rosenheck R. The effect of institutional fiscal stress on the use of atypical antipsychotic medications in the treatment of schizophrenia. *The J of Nervous and Mental Disease* 2001;189:377-383.

² Leslie DL, Rosenheck RA. Use of pharmacy data to assess quality of pharmacotherapy for schizophrenia in the national health care system. *Med Care* 2001;39:923-933.

Prepared by Haya Ascher-Svanum, US Outcomes Research 4/3/02

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A Retrospective Comparison of Weight, Lipid, and Glucose Changes Between Risperidone and Olanzapine Treated Inpatients: Metabolic Outcomes After 1 Year.
Journal Clinical Psychiatry, 2002;63:425-433

Meyer JM{ XE "Meyer JM" }

Background: Metabolic side effects have been increasingly noted during therapy with novel antipsychotics, but there is a dearth of comprehensive comparative data in this area. The goal of this retrospective study was to examine the changes in weight parameters, fasting glucose, and fasting lipids in long-term inpatients treated with either risperidone or olanzapine.

Method: A retrospective study was performed by reviewing charts of patients at Oregon State Hospital, Salem, who were treated during July and August 1999, comparing metabolic outcomes during the first year of therapy with either risperidone or olanzapine. Data were analyzed also by age, sex, and concurrent use of lithium or valproate. Included for analysis were patients at least 18 years old with baseline weights obtained within 3 weeks of drug initiation, and baseline fasting triglycerides, cholesterol, and glucose obtained within 3 months prior to drug initiation and at 1 year of treatment (± 4 weeks). The patients meeting these criteria in each drug cohort (risperidone, N = 47; olanzapine, N = 47) included 1 patient with diagnosed diabetes mellitus prior to onset of treatment.

Results: Among those patients under 60 years old, olanzapine patients (N = 37) experienced significantly greater increases at 1 year in all metabolic parameters than the risperidone group (N = 39), except for weight variables: triglycerides +104.8 mg/dL (olanzapine) versus +31.7 mg/dL (risperidone) (p=.037); cholesterol +30.7 mg/dL (olanzapine) versus +7.2 mg/dL (risperidone) (p=.004); glucose +10.8 mg/dL (olanzapine) versus +0.74 (risperidone) (p=.030). Patients under 60 years of age with concurrent use of lithium or valproate were associated with greater weight gain in both drug groups, but this difference was statistically significant only for the olanzapine cohort. Neither weight change nor use of lithium or valproate was associated with increases in glucose or lipids among those under 60 years of age for either drug.

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Conclusion: Olanzapine therapy is associated with significantly greater increases in fasting glucose and lipid levels for nongeriatric adult patients than risperidone, and the increases are not correlated with changes in weight parameters. Appropriate monitoring of fasting glucose and serum lipid levels should be considered during extended treatment with atypical antipsychotics.

Review Comments:

- This was a Janssen sponsored IIT 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. **Fifteen risperidone and 20 olanzapine patients received concurrent lithium or valproate. This factor is the main driver of statistical significance, refer to table 3, page 428. In patients without concomitant Li or Valproate use, olanzapine had no effect on glucose levels.**
- 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. The authors note that one patient on Olanzapine developed new onset diabetes during the 1 year review period, however no additional information is provided on this patient's risk factors prior to the study..
- 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 has acknowledged in past conversations that many tests likely are non-fasting. 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.
 - ▶ 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

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- ▶ No adequate justification of focus on one subgroup (age <60), presumably post-hoc. Again refer to Table 3 and note the effect of the 10 Olanzapine patients over 60 on blood glucose, cholesterol and TGs. Factoring out these patients has a substantial effect on the stats of the study.
- ▶ Patients on olanzapine are relatively more likely to receive concomitant lithium or divalproex. This had a major impact on statistical significance of the data.
- 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.

The Apparent Effects of Ziprasidone on Plasma Lipids and Glucose. *Journal Clinical Psychiatry*. 2001;62(5):347-349.

Kingsbury SJ { XE "Kingsbury SJ" }, *Fayek M, Trufasiu D, Zada J, Simpson GM* { XE "Simpson GM" }

Background: We examined the effects of ziprasidone on body mass index (BMI) and serum levels of glucose, cholesterol, and triglycerides.

Method: As part of a multi-center study examining different strategies for switching to ziprasidone done from other antipsychotics, we evaluated weight and serum glucose, cholesterol, and triglyceride measurements at baseline and following 6 weeks on ziprasidone treatment in 37 patients at our site.

Results: Short term treatment with ziprasidone appeared to lead to significant reduction in serum cholesterol ($p < .001$) and triglyceride levels ($p = .018$) independent of changes in BMI.

Ziprasidone treatment appeared to have no significant effect on BMI or glucose level, perhaps due to the small number of subjects.

Conclusion: Ziprasidone appears to independently lead to a lowering of serum lipid levels.

Review Comments:

- 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.
- 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,

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small sample size and short trial duration as possible design flaws which interfere with drawing inferences from secondary lab data such as this.

- 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.

Euglycemic Clamp Study in Clozapine-Induced Diabetic Ketoacidosis. *Annals of Pharmacotherapy*. 2001;35:1381-1387.

Avram AM{ XE "Avram AM" }, Patel V{ XE "Patel V" }, Taylor HC, Kirwan JP, KalhanS

Objective: To describe the fifth case of clozapine-induced diabetic ketoacidosis (DKA) with complete resolution of abnormal glucose metabolism after discontinuation of clozapine as assessed by oral glucose tolerance testing (OGTT) and the first to be serially studied with markers of pancreatic autoimmunity; to demonstrate insulin resistance using the euglycemic clamp study and reduced pancreatic insulin reserve using intravenous glucose tolerance testing (IVGTT) in clozapine-induced diabetes mellitus and DKA, when the OGTT was normal; and to systematically review the previously described cases of clozapine-induced diabetes mellitus and DKA.

Case Summary: A 33-year-old white man without past or family history of diabetes mellitus presented with DKA after eight months of clozapine therapy (50 mg twice daily). After treatment of DKA and discontinuation of clozapine, glucose tolerance and concurrent serum insulin concentrations reverted to normal as measured by two OGTT performed 60 and 320 days after resolution of DKA.

Discussion: Anti-islet-cell antibodies, antiglutamic acid decarboxylase antibodies, and human insulin antibody were negative on two separate occasions. Euglycemic clamp study demonstrated insulin resistance manifested by a glucose disposal rate of approximately 55% of mean normal values. IVGTT demonstrated a low rate of glucose disappearance ($KG = 0.95$) and diminished first-phase insulin response when OGTT was normal, indicating impairment in insulin sensitivity and reduction in β cell function 323 days after discontinuance of clozapine. This adverse reaction is considered probable according to the Naranjo probability scale.

Conclusions: The occurrence of cases of DKA and new or worsening diabetes mellitus in patients using clozapine suggests a causal relationship. We hypothesize that the mechanism by which clozapine may produce glucose intolerance may require a preexisting latent defect in insulin secretion and insulin action. With the administration of clozapine, some of these patients may develop worsening insulin resistance and may fail to mount an appropriate compensatory β cell insulin secretion for the degree of insulin resistance. As a consequence, hyperglycemia develops and its persistence results in glucose toxicity, further suppressing β cell insulin secretion. Such combined defects in insulin secretion and sensitivity are known to be synergistic, leading to the development of abnormal glucose tolerance, which can be clinically manifested as a spectrum ranging from impaired glucose tolerance through severe hyperglycemia to DKA. Patients being started on clozapine should be carefully followed for the development or worsening of diabetes mellitus, regardless of the dose of the drug.

Review Comments:

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Clozapine-Associated Diabetes. *American Journal of Medicine.* 2001;111:716-723.

Koller E, Schneider B, Bennett K, Dubitsky G

Purpose Clozapine is a potent antipsychotic agent that has been marketed since 1990. Several published reports of diabetes mellitus occurring with clozapine therapy have appeared during the past 5 years. Because the risk and characteristics of clozapine-associated diabetes mellitus remain unclear, we conducted a descriptive epidemiologic study of spontaneous adverse event reports of hyperglycemia occurring in clozapine-treated patients.

Methods: The Food and Drug Administration MedWatch surveillance program was queried (January 1990 through February 2001), and the results were pooled with published cases. Parameters assessed included documentation of diabetes, clinical severity, new-onset diabetes versus exacerbation of preexisting disease, demographic characteristics of patients, time to onset of hyperglycemia, and effect of drug discontinuation and re-challenge.

Results: We identified 384 reports. Of these, new-onset diabetes was diagnosed definitively in 242 patients, and 54 patients had exacerbation of preexisting disease. The mean (\pm SD) age was 40 ± 12 years (range, 13 to 77). The male:female ratio was 2:0. Most cases appeared within 6 months of initiating clozapine therapy. One patient developed diabetes following a single 500-mg dose. There were 80 cases of metabolic acidosis or ketosis. Twenty-five patients died during hyperglycemic episodes. Forty-six patients had improved glycemic control after discontinuation or dose reduction of the drug.

Conclusions: A causal relationship between clozapine and diabetes is suggested by the number of reports, the temporal relation to clozapine initiation, the relatively young age of the affected patients, and the prompt reversibility on withdrawal of the drug in some patients. The severity of reported cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma.

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Journal Supplements

Journal of Clinical Psychiatry. Volume 62, Supplement 27, 2001

Diagnosis, Classification, and Pathogenesis of Diabetes Mellitus

Lebovitz HE{ XE "Lebovitz HE" }

Diabetes mellitus is a metabolic disorder that is characterized by inappropriate hyperglycemia and is associated with both acute and chronic complications. Currently, diabetes mellitus is diagnosed by blood or plasma glucose levels. A random plasma glucose level ≥ 200 mg/dL in an individual with classic symptoms is sufficient to make the diagnosis. Otherwise, a fasting plasma glucose level ≥ 126 mg/dL or a 2-hour plasma glucose level ≥ 200 mg/dL after an oral glucose challenge of 75 g on 2 occasions is sufficient evidence upon which to diagnose diabetes mellitus. The major types of diabetes mellitus are type 1 diabetes (insulin deficient) and type 2 diabetes (combination of insulin resistance and insulin deficiency). In both types, there is a genetic predisposition as well as environmental factors that contribute to the expression of the genetic predisposition. In type 1 diabetes, the primary abnormality is extensive deficiency of beta cell function. In type 2 diabetes, insulin resistance occurs, and the marked compensatory increases in insulin secretion necessary to maintain normal glucose tolerance cannot be achieved or maintained. As beta cell function continues to decrease, the individual progresses from normal glucose tolerance to impaired glucose tolerance to diabetes with primarily postprandial hyperglycemia to diabetes with fasting hyperglycemia. Drugs can cause diabetes by interfering with beta cell insulin secretion, by increasing insulin resistance, or by a combination of both. Atypical antipsychotic drugs have been reported to cause diabetic ketoacidosis, obesity and insulin resistance, type 2 diabetes, and hypertriglyceridemia. A monitoring system should be in place in patients started on treatment with these agents to detect metabolic abnormalities as they are evolving so that adequate and timely treatment can be initiated.

Review Comments:

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Clinical Experience with Insulin Resistance, Diabetic Ketoacidosis, and Type 2 Diabetes Mellitus in Patients Treated with Atypical Antipsychotics

Henderson DC{ XE "Henderson DC" }

Numerous reports have associated atypical antipsychotic agents with hyperglycemia, diabetes mellitus, and diabetic ketoacidosis. Although the mechanisms are poorly understood, clinical experience suggests that these adverse effects are major areas of concern and require attention by the psychiatric team and primary care clinicians. This article discusses my clinical experience with glucose metabolism impairment related to treatment with antipsychotic medications.

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Hyperglycemia and Antipsychotic Medications

Haupt DW{ XE "Haupt DW" }, Newcomer JW{ XE "Newcomer JW" }

Type 2 diabetes mellitus and impaired glucose tolerance are associated with antipsychotic treatment. Risk factors for type 2 diabetes and impaired glucose tolerance include abdominal adiposity, age, ethnic status, and certain neuropsychiatric conditions. While impaired glucose metabolism was first described in psychotic patients prior to the introduction of antipsychotic medications, treatment with antipsychotic medications is associated with impaired glucose metabolism, exacerbation of existing type 1 and 2 diabetes, new-onset type 2 diabetes mellitus, and diabetic ketoacidosis, a severe and potentially fatal metabolic complication. The strength of the association between antipsychotics and diabetes varies across individual medications, with the largest number of reports for chlorpromazine, clozapine, and olanzapine. Recent controlled studies suggest that antipsychotics can impair glucose regulation by decreasing insulin action, although effects on insulin secretion are not ruled out. Antipsychotic medications induce weight gain, and the potential for weight gain varies across individual agents with larger effects observed again for agents like chlorpromazine, clozapine, and olanzapine. Increased abdominal adiposity may explain some treatment-related changes in glucose metabolism. However, case reports and recent controlled studies suggest that clozapine and olanzapine treatment may also be associated with adverse effects on glucose metabolism independent of adiposity. Dyslipidemia is a feature of type 2 diabetes, and antipsychotics such as clozapine and olanzapine have also been associated with hypertriglyceridemia, with agents such as haloperidol, risperidone, and ziprasidone associated with reductions in plasma triglycerides. Diabetes mellitus is associated with increased morbidity and mortality due to both acute (e.g., diabetic ketoacidosis) and long-term (e.g., cardiovascular disease) complications. A progressive relationship between plasma glucose levels and cardiovascular risk (e.g., myocardial infarction, stroke) begins at glucose levels that are well below diabetic or 'impaired' thresholds. Increased adiposity and dyslipidemia are additional, independent risk factors for cardiovascular morbidity and mortality. Patients with schizophrenia suffer increased mortality due to cardiovascular disease, with presumed contributions from a number of modifiable risk factors (e.g., smoking, sedentary lifestyle, poor diet, obesity, hyperglycemia, and dyslipidemia). Patients taking antipsychotic medications should undergo regular monitoring of weight and plasma glucose and lipid levels, so that clinicians can individualize treatment decisions and reduce iatrogenic contributions to morbidity and mortality.

Review Comments:

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Putting Metabolic Side Effects into Perspective: Risks versus Benefits of Atypical Antipsychotics

Meltzer HY{ XE "Meltzer HY" }

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The lengthy list of the side effects and morbidity associated with the atypical antipsychotics might make a patient with psychosis and his or her caregivers so concerned about the use of any of these medications, particularly those associated with a higher risk of diabetes, weight gain, or increased lipid levels, that they would prefer to avoid all of them. However, schizophrenia is associated with a relatively high risk for several diseases, including diabetes, that is independent of the risks that are linked to atypical antipsychotic use. Therefore, the clinician who might think, 'Why use atypicals if using the typical drugs will escape the problems of monitoring and all the associated effects of diabetes and hyperglycemia?' needs to know that these problems cannot be avoided simply by choosing typical antipsychotics. Clinicians, patients, and concerned family members must balance the significant benefits of atypical antipsychotic treatment - improved cognition, reduced suicidality, and less depression - against the risks of metabolic disturbances and select a course of treatment that includes a realistic monitoring program.

Review Comments:

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Triglyceride / Cholesterol Issues

Introduction (Written by Robert Baker MD, Vicki Poole-Hoffmann PharmD)

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.

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

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 patients 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 patients. 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 patients 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 Dufresne 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 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".

Plasma Triglyceride Levels in Schizophrenia Patients Treated with Antipsychotic Medications

Newcomer JW{ XE "Newcomer JW" }, Haupt DW{ XE "Haupt DW" }, Melson AK{ XE "Melson AK" }, Schweiger JA{ XE "Schweiger JA" }, Cooper BP{ XE "Cooper BP" }

Introduction: Insulin can regulate whole-body glucose and lipid metabolism. Increases in plasma glucose and type 2 diabetes mellitus can occur in schizophrenia patients treated with antipsychotic medications. Controlled studies in which subjects are matched for adiposity indicate relatively large differences between patients treated with certain medications and healthy controls (e.g., 1 S.D. effect size), and suggest medication- and perhaps patient-related decreases in insulin action (insulin resistance). In clinical settings, decreases in insulin action are predicted to occur primarily as a consequence of treatment-induced increases in whole-body adiposity. Increases in plasma triglycerides have been reported in schizophrenia patients treated with certain

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antipsychotic medications, including some cases of marked hypertriglyceridemia, but most of this has been limited to case reports and case series, without controls.

Methods: For this report we examined plasma triglyceride levels in non-diabetic schizophrenia patients (n=63) treated with a variety of antipsychotic medications (typicals, risperidone, olanzapine, clozapine) as well as in healthy controls (n=20), with all treatment groups matched for age and adiposity (body mass index, BMI, kg/m²). Using ANOVA and treating plasma triglyceride as a continuous variable, no statistically significant effect of treatment group was observed on plasma triglycerides. However, plasma triglyceride is not treated as a continuous variable in clinical practice. In this sample, healthy controls had relatively low mean plasma triglyceride levels with limited variance (mean + S.D. = 87.7 + 49.9 mg/dl). In contrast, some treatment groups had elevated mean plasma triglyceride values, classified as "borderline high" (150-199 mg/dl; National Cholesterol Education Program; NIH) (clozapine: 177 + 152.6 mg/dl; olanzapine 175.5 + 250 mg/dl), with higher variance in these groups due to increased numbers of subjects with clinically elevated values.

Results: Olanzapine-treated subjects were more likely to have "borderline high" or greater plasma triglyceride values (Chi-square=3.73, p=0.054; G-squared=4.10, p=0.043), compared to adiposity- and age-matched healthy controls. In contrast to more consistent treatment-related effects on plasma glucose in non-diabetic, adiposity-matched subjects (Newcomer et al. in press), non-diabetic, adiposity-matched schizophrenia subjects treated with antipsychotic medications may have more sporadic increases in plasma triglycerides as compared to healthy controls, with greater inter-subject variance. Several issues may be important to interpreting these results. While defects in insulin action can disturb glucose and lipid metabolism, more severe defects in insulin action (i.e., diabetes mellitus) may be required to alter plasma triglyceride versus plasma glucose. Individual patient factors and vulnerabilities may dictate which individuals experience treatment-related increases in plasma triglyceride at any given level of insulin resistance or deficiency.

Conclusion: Further studies using more sensitive measures of glucose and lipid metabolism will be necessary to explore these hypotheses and better understand medication-related effects. The results are relevant to the increased risk of diabetes mellitus and cardiovascular mortality in treated patients with schizophrenia.

Review Comments:

- No poster mini was provided so comments are based strictly upon the abstract.
- An examination of plasma triglyceride levels in age and adiposity matched schizophrenic patients treated with various typical and atypical agents, results revealed no statistically significant effects between treatment groups including healthy controls.
- Conclusions attempt to pin a significant difference (where one does not exist) on Olanzapine based upon more subjects being designated as "borderline" high triglyceride.
-

Where Presented: ACNP Annual Meeting December 2001, Waikoloa, HI.

Are There Ethnic Differences in Hypertriglyceridemia Secondary to Olanzapine Treatment?

Nasrallah HA{ XE "Nasrallah HA" }, Perry CL{ XE "Perry CL" }, Love E, Nasrallah AT{ XE "Nasrallah AT" }

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Introduction: Dyslipidemias have been observed in patients treated with atypical antipsychotics, especially those associated with excessive weight gain such as olanzapine. However, there are no studies of ethnic differences in antipsychotic-induced hyperlipidemia. We report here a study comparing triglyceride blood levels in Caucasian and African-American patients before and after receiving olanzapine.

Methods: A retrospective review was conducted of all patients in our outpatient clinic who had triglyceride levels documented before and after receiving olanzapine (N=103). In addition to comparing the mean values for Caucasians and African-Americans before and after treatment, we also calculated the proportion of patients in each ethnic group who experienced a large triglyceride increase of ≥ 100 mg/dl.

Results: The mean triglyceride levels for Caucasians before and after olanzapine treatments were 112.62 mg/dl and 203.08 mg/dl, respectively. The difference was not statistically significant, with both groups experiencing a substantial increase in triglyceride levels of 81% in Caucasians and 65% in African-Americans. There were no differences between the two ethnic groups in the proportion of patients gaining ≥ 100 mg/dl with olanzapine treatment (33% of Caucasians and 35% of African-Americans).

Conclusion: The data indicate that both ethnic groups in this study experienced a substantial increase in triglyceride blood levels, with no differences between them in the mean increase or proportion of patients gaining ≥ 100 mg/dl. This metabolic disturbance induced by olanzapine treatment should be monitored and addressed in all patients receiving olanzapine regardless of ethnicity.

Review Comments:

- This is a simple retrospective chart analysis looking only at olanzapine treated patients.
- Although it appears that the authors were on a witch hunt, they found a numerical increase in triglyceride levels with both ethnic groups examined but it was not a statistically significant increase.
- Although the increases in triglyceride levels appear substantial one must remember that these are random lipid levels pulled from charts. Triglyceride levels are dramatically effected by being in a fed versus fasting state, so few if any true conclusions can be drawn from the data set. One wonders what the same analysis would look like for other atypicals.
- Investigator bias is evident in the conclusion that triglycerides should be monitored and addressed in all patients taking olanzapine even though the results of the analysis would not support that conclusion.

Where Presented: ACNP Annual Meeting December 2001, Waikoloa, HI.

Effects of Oral Ziprasidone on Weight and Serum Lipids in Patients with Schizophrenia

Halmi KA{ XE "Halmi KA" }, Cutler N{ XE "Cutler N" }, Weiden P{ XE "Weiden P" }, Simpson GM{ XE "Simpson GM" }, Romano SJ{ XE "Romano SJ" }

Background: Atypical antipsychotics have been associated with varying degrees of weight gain, and deleterious changes in lipid profile (increases in triglycerides or cholesterol) have been observed with some agents. Excess body weight is an independent risk factor for cardiovascular disease and diabetes mellitus, and elevated cholesterol and triglyceride levels are risk factors for

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cardiovascular disease. The clinical development program for ziprasidone has included monitoring for changes in weight and lipid profile.

Methods: Weight and serum lipid levels were assessed at baseline and endpoint in five short-term clinical studies of patients with schizophrenia or schizoaffective disorder. Study 0548, a double-blind, randomized, multicenter trial, comprised 269 inpatients who received 6 weeks' treatment with ziprasidone (40 to 80 mg BID) or olanzapine (5 to 15 mg QD). Study 054, an open-label, parallel-group trial, assessed 164 patients administered ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, or haloperidol for mean duration of 14 to 24 days. Three 6-week, open-label, parallel-group switch studies evaluated stable outpatients switched to ziprasidone (40 to 160 mg/day) from olanzapine (n=104), risperidone (n=58), or conventional agents (n=108).

Results: Effect on weight: Study 0548: From week 2 through endpoint, the olanzapine group showed significantly greater increases in mean body weight than the ziprasidone group (3.57 kg vs 0.93 kg; $p<0.0001$ at endpoint). Study 054: The prevalence of substantial weight gain ($>7\%$ of baseline) was 23% with olanzapine (3.1 kg), 19% with risperidone (2.6 kg), 10% with quetiapine (1.8 kg), 10% with thioridazine (1.8 kg), 6% with ziprasidone (0.7 kg), and 3% with haloperidol (-0.2 kg). Switch studies: Significant mean weight loss was noted 6 weeks after the switch to ziprasidone from olanzapine (-1.8 kg, $p<0.001$) and risperidone (-0.8 kg, $p=0.05$). Patients switched from conventional antipsychotics gained 0.17 kg (NS).

Effect on lipids: Study 0548: Olanzapine, but not ziprasidone, was associated with a significant increase from baseline in fasting total cholesterol ($p<0.0001$), triglycerides ($p<0.001$), and LDL-C ($p<0.0001$). Between-group comparisons were significant for each parameter, as well ($p<0.01$). Study 054: Ziprasidone improved all fasting lipid measures compared with baseline. Median decreases were -14.5 mg/dL for total cholesterol ($p<0.001$), -37.0 mg/dL for triglycerides ($p<0.001$), and -11 mg/dL for LDL-C. The total cholesterol/HDL-C ratio also improved significantly ($p<0.01$). Changes with haloperidol were similar to those with ziprasidone, except for a -3 mg/dL decrease in HDL-C level ($p<0.01$). Triglyceride levels rose significantly in the olanzapine and quetiapine groups (25.0 and 43.0 mg/dL, respectively; both $p<0.001$). Switch studies: Significant reductions from baseline in median total cholesterol and triglycerides were observed in patients switched to ziprasidone from olanzapine ($p<0.001$ for both) and risperidone ($p<0.005$ and $p<0.01$, respectively).

Conclusions: In these studies, ziprasidone exhibited a weight-neutral profile and improved serum lipid levels. These findings suggest that ziprasidone does not worsen cardiovascular risk in patients with schizophrenia and may, indeed, reduce it. The effects of ziprasidone on weight and lipid profile carry important implications for patients' overall health status.

Review Comments:

- Compilation of several Pfizer clinical studies which measured weight and lipid changes.
- Presented as a body of evidence suggesting that Ziprasidone has a weight neutral profile and a positive effect of lowering lipid levels, thereby reducing cardiovascular risk.

Where Presented: ACNP Annual Meeting December 2001, Waikoloa, HI; Biennial Winter Workshop on Schizophrenia, February 2002, Davos Switzerland.

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Effects of Atypical Antipsychotics on Weight and Serum Lipid Levels. *Journal Clinical Psychiatry.* 2001;62(supp 27):27-34.

Meyer JM{ XE "Meyer JM" }

Psychiatrists have become particularly concerned about health issues in patients with schizophrenia because of emerging data that link some of the newer atypical antipsychotics with both significant weight gain and increases in serum triglyceride levels. Excessive weight gain during antipsychotic therapy has an adverse effect on health and medication compliance, while hyperlipidemia presents an additional cardiovascular risk factor in patients with schizophrenia who typically smoke, are inactive, and possess poor dietary habits. An understanding of appropriate monitoring for metabolic adverse effects is important for those who prescribe atypical antipsychotics, as is a working knowledge of behavioral and pharmacologic treatments for weight gain and hyperlipidemia.

Review Comments:

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Date: 10/02/2002 10:54:39 AM

From: CN=Rocco L Brunelle/OU=AM/O=LLY

Subject: Recommendations for the HGJJ Study

As you are aware, we reviewed the interim analyses for the Zyprexa plus Sibutramine in weight loss study last Monday and decided to stop for futility. I called Walt Offen as discussed with him how to wrap up this study and when to share the details of the interim results with the team. Walt gave me two recent examples of two teams stopping their studies also for futility, redacted for sepsis. In both cases these teams decided to wrap up the study, clean the database, and then have a final lock before sharing the interim redacted This was done so that all the data could be cleaned prior to performing the final analysis and before performing additional exhaustive analyses which could possibly find something useful.

I suggest we follow this same process. That we wrap up the study, do not enter any new patients, finish cleaning all the data and then have a final data lock. After the final data lock we can rerun all the analyses that were performed at the interim and share with the team the interim results as well as the final results. Also we can then perform the additional analyses that Patrizia and Alan recommend.

For members on the HGJJ DAG and on the Assessment Committee, we can not share the exact study results until the final database lock.

Rocco