Hyperglycemia Literature Review

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1.1 Prevalence of Diabetes in the General Population

The Third National Health and Nutrition Examination Survey (N=18,825) reported that the estimated prevalence of diabetes mellitus (DM) in 1988-1994 was 7.8% for U.S. adults ≥20 years of age (5.1% diagnosed; 2.7% undiagnosed [fasting glucose ≥126 mg/dl]) (Harris et al 1998). This corresponds with 15.6 million people when extrapolated to the 1997 U.S. population. The prevalence of impaired fasting glucose (110 to <126 mg/dl), likely a strong risk factor for the development of DM, was 6.9%. Thus, the prevalence of DM and impaired fasting glucose combined is estimated to be 14.8%, or 29 million for 1997. A much lower estimated DM prevalence of 1.46% was recently reported from a multipractice primary care audit for the years 1993-1995 in England and Wales (N=1,475,512) (Khunti et al 1999).

1.2 Prevalence of Diabetes in Schizophrenia and Bipolar Disorder

Several studies have implicated schizophrenia as a potential risk factor for developing type II DM (DM-II) (Mukherjee 1999; Dixon et al 1998; Mukherjee et al 1996; McKee et al 1986; Keskiner et al 1973). These studies report the prevalence of DM-II in patients with schizophrenia to be approximately 2 to 4 times greater than in the general population. On the basis of current data, this amounts to a prevalence of some 14% to 28% among U.S. patients with schizophrenia. There is some disagreement on this issue, however, as Dvirskii et al. (1997) argues that DM-II in schizophrenia is observed less frequently than would be expected based on the prevalence in the general population. Interestingly, Thonnard-Neumann (1968) has found a greater prevalence of DM-II among patients with paranoid type of schizophrenia, even though they had fewer risk factors including less antipsychotic use, than patients with the nonparanoid type. Moreover, the later manifestations and complications of DM-II, such as cardiovascular disorders and diabetic retinopathy, were much less frequent among patients with schizophrenia and DM-II than among patients with primary DM-II. These studies suggest that the underlying mechanism of DM-II associated with schizophrenia may be different than that of primary DM-II.

It is of further interest that an increased prevalence of DM-II has also been reported in patients with bipolar disorder, 9.9%. In addition, the bipolar patients with comorbid DM-II had significantly more lifetime psychiatric hospitalizations than those without DM. Taken together, these results suggest a higher risk of DM-II among patients with such mental illnesses as schizophrenia and bipolar disorder.
The mechanism for the higher prevalence of DM-II in schizophrenia and bipolar disorder is not presently understood. The use of antipsychotic agents has been suggested; however, high incidences of insulin resistance and impaired glucose tolerance (IGT) had been noted in patients with schizophrenia even before the introduction of antipsychotic agents (Langfeldt 1952; Freeman 1946; Braceland et al 1945; Lorenz 1922).

1.3 Studies on the Effects of Antipsychotic Agents on Insulin and/or Blood Glucose in Animals and Normal Volunteers

To gain a better understanding of the possible relationship between the use of antipsychotic agents and hyperglycemia and/or DM-II, both animal and human studies have examined the effects of antipsychotic agents on carbohydrate metabolism. In rodents, phenothiazines (primarily chlorpromazine and fluphenazine) induced significant hyperglycemic responses with concomitant increases in liver glycogen, elevation of serum fatty acids, and hypokalemia (Bugajski and Lech 1979; Jori and Bianchetti 1966). In contrast, long-term administration of sulpiride to rats induced obesity that was not associated with a significant change in the area under the glucose curve, but was associated with a significant decrease in the area under the insulin curve (Baptista et al 1998). In this study, an increased insulin sensitivity was thought to cause the decreased insulin response in these sulpiride-treated rats. In cebus monkeys, haloperidol increased both glucose and insulin levels following a glucose tolerance test (Casey 1994). Interestingly, the atypical antipsychotic agent clozapine significantly decreased glucose and increased insulin in this non-human primate model. These findings suggest that haloperidol produces a state akin to DM-II, while

clozapine may improve glycemic control, which is contrary to many clinical reports (see below). A preclinical rat study suggests that the effects of antipsychotic agents on carbohydrate metabolism may be mediated through antagonism of serotonin 5-HT_{1A} and/or dopamine D_3 receptors (Uvnäs-Moberg et al 1996). A correlation between weight gain with sulpiride treatment and leptin, a molecule thought to regulate body fat stores and nutrient metabolism, and insulin levels has not been demonstrated in rats (Lacruz et al 2000).

The effects of typical antipsychotic agents on carbohydrate metabolism are similar for normal human volunteers as they are for non-human animals. In normal men, oral chlorpromazine had little or no effect on blood glucose levels or insulin secretion, while acute iv chlorpromazine produced hyperglycemia and inhibited glucose-stimulated insulin secretion both in normal men and in subjects with latent diabetes (Erle et al 1977; Erle et al 1975). Additionally, chlorpromazine decreased plasma insulin concentrations and increased fasting blood glucose in a patient with malignant insulinoma (Lambert et al 1972). By contrast, sulpiride did not change blood glucose, plasma insulin levels, hepatic insulin removal, and glucose utilization during basal conditions or after iv glucose administration in normal men (Hagen et al 1979). Thus, in general, it appears that insulin output in animals and normal volunteers may be reduced by the typical antipsychotic agents (see Table 1.1). However, this is a complex relationship that has been demonstrated to be dependent on dose, route of administration, time course of administration, and degree of glycemia. Most human studies in normal volunteers have employed low doses of antipsychotic agents and short durations of administration.

Table 1.1. The effects of typical antipsychotic agents on insulin and/or blood glucose

	Rodents/Non-human primates	Normal Humans
Glucose	↑, ↑, –, ↑	–, –, ↑iv, ↑I*
Insulin	↓, ↑	–, –, –, ↓iv, ↓I*

Abbreviations: ↑ increase; ↓ decrease; – no change; I* patients with insulinoma; iv intravenous

Note: This table does not distinguish between outcomes with normal or basal glycemic levels versus high glycemic levels (with oral or iv glucose challenge).

1.4 Reports on the Relationship between Typical Antipsychotic Agents and Hyperglycemia and/or Diabetes in Patients with Schizophrenia

For patients with schizophrenia treated with a variety of antipsychotic agents across a variety of chemical classes, increased blood glucose and decreased glucose tolerance can be observed. Statistically significant increases in fasting blood glucose have been observed with both fluphenazine and pimozide, but generally only after long-term treatment (Abuzzahab and Zimmerman 1998). In another study, 74% of patients with schizophrenia who were treated long-term with neuroleptics (primarily perazine) showed hyperglycemic reactions via the oral glucose tolerance test (Goncalves and Gruneberg 1997). However, 34.9% of those patients with abnormal glucose tolerance tests had fasting blood glucose levels greater than 100 mg/100 ml. Intravenous chlorpromazine causes a pronounced delay in the removal of glucose from the blood, following a single loading dose of glucose in patients (Charatan and Bartlett 1955). Reports have further suggested the induction of DM-II by chlorpromazine (≥200 mg/day) (Vukicevic and Zjacic-Rotkvic 1994; McKee et al 1986; Korenyi and Lowenstein 1968), the phenothiazines in general (Thonnard-Neumann 1968), loxapine (Tollefson and Lesar 1983), and amoxapine (Tollefson and Lesar 1983). The effects of typical antipsychotic therapy on blood glucose may be a function of dosage and duration of therapy. Finally, there may be an association between tardive dyskinesia (possibly a state of increased D_2 dopamine receptor number/sensitivity) and impaired glucose metabolism during antipsychotic treatment (Mukherjee et al 1989).

By contrast, other studies have been unable to demonstrate an association between DM-II and the use of antipsychotic agents. In one study, only 5 of 823 patients developed permanent hyperglycemia with

chlorpromazine therapy, and these patients had predisposing factors for DM-II (Schwarz and Munoz 1968). In another study, neither acute nor long-term chlorpromazine treatment impaired glucose tolerance in hospitalized patients with schizophrenia (Waitzkin 1970). DM-II has been observed in 4 of 8 patients (50%) who were not receiving neuroleptics compared to 7 of 87 patients (12.6%) who were receiving neuroleptics (Mukherjee et al 1996). Furthermore, no correlation was found between DM-II and age of onset or duration of schizophrenia. The authors suggest that it is unlikely that the high prevalence of DM-II in schizophrenia can be explained entirely as a secondary effect of pharmacological treatment. Diet and lack of exercise associated with institutionalization, brain changes associated with schizophrenia, or a common underlying and linked pathology of schizophrenia and DM-II are possible explanations. Clearly, interpretation of these findings is limited by different study methods including criteria selected for hyperglycemia or DM-II, as well as confounding factors such as age and body weight, duration of schizophrenia, and dose and duration of therapy, which may not have been accounted for or consistent across studies.

1.5 Influence of Weight Gain and/or Obesity on the Development of Hyperglycemia and/or Diabetes and Relationship to Antipsychotic Agents

Weight gain has been reported during treatment with nearly every antipsychotic drug on the market (molindone is an exception) (Ganguli 1999). Weight gain occurs during treatment no matter what the patient's age, sex, or race and is seen with both oral and depot drug formulations. The mechanism by which antipsychotic agents might cause weight gain is not presently understood. It has been estimated that approximately 50% of patients receiving chronic neuroleptics are affected by obesity (Baptista et al 1998). A strong positive association has been demonstrated between overall obesity and risk of DM-II (Carlsson et al 1998; Chan et al 1994). Furthermore, the magnitude of obesity (BMI ≥29), duration of obesity, early obesity, and continued weight gain after becoming obese are significant independent risk factors for DM-II (Resnick et al 1998; Chan et al 1994). Weight gain in non-obese (BMI=24.0-24.9 kg/m^2) individuals may be a risk factor for DM-II. Weight gain of 8.0 to 10.9 kg increased the relative risk of DM-II by approximately 3 times compared to women who gained less than 5.0 kg (Colditz et al 1995). Additionally, subjects who lost more than 5.0 kg decreased the risk for DM-II by 50% or more, independent of family history for the disease. A similar relationship was demonstrated by Ford et al. (1997), but the magnitude of risk estimates were consistently lower than that observed in the Colditz et al. study. In general, there was approximately a 4.5% increase in risk for DM-II for every kg increase in weight. In men, the rate of weight gain was also strongly and significantly related to the incidence of DM-II, whereas weight fluctuation did not appear to be associated with an increased incidence of DM-II in either gender (Hanson et al 1995). In contrast to these studies, results of a 10- to 16-year follow-up study in high- and low-risk women suggest that weight gain may only be predictive of DM-II when other high-risk factors are present (O'Sullivan 1982). Thus, the possibility exists that the increased incidence of hyperglycemia and/or DM-II in schizophrenia may be secondary to weight gain and/or obesity induced by antipsychotic agents.

Weight gain during treatment with the typical antipsychotic agents has not been adequately studied. In general, of the typical antipsychotic agents, haloperidol is thought to be associated with less weight gain than with other neuroleptic agents, such as fluphenazine and pipothiazine (Stanton 1995). A meta-analysis of weight change after 10 weeks of treatment demonstrated that among conventional agents, mean weight change ranged from a reduction of 0.39 kg with molindone to an increase of 3.19 kg with thioridazine (Allison et al 1999). In the clinical experience, some patients have shown marked weight gain during treatment with the atypical antipsychotic agents. A retrospective chart review of patients treated longer than 2 weeks demonstrated a significantly greater increase in weight during treatment with atypical agents than with typical agents, with young and non-obese patients demonstrating the highest weight increase, (Wetterling and Musigbrodt 1999). Although in rats the atypical antipsychotic agent clozapine did not result in increased BMI (Baptista et al 1993), in humans significant weight gain and increases in BMI have been demonstrated during both short- and long-term treatment with clozapine (Bai et al 1999; Bromel et al 1998; Frankenburg et al 1998; Bustillo et al 1996; Hummer et al 1995; Umbricht et al 1994; Lamberti et al 1992; Leadbetter et al 1992), and this weight gain is significantly greater than that observed with haloperidol (Bustillo et al 1996; Hummer et al 1995). By contrast, one study showed that the increase in

body weight caused by long-term (>6 months) clozapine treatment is comparable to that obtained following long-term classical antipsychotic treatment (Spivak et al 1999). It has been reported that over half of the patients on clozapine therapy experience significant weight gain which is, on average, an increase in weight of approximately 9% over baseline (Bustillo et al 1996; Umbricht et al 1994; Leadbetter et al 1992). Moreover, marked weight gain (>10% increase) may occur in up to 80% of the patients treated with clozapine (Bustillo et al 1996; Hummer et al 1995; Umbricht et al 1994; Leadbetter et al 1992). The results of one study suggest a relationship between improvement in psychopathology and weight gain (Leadbetter et al 1992); however, other studies have not confirmed such a relationship (Bustillo et al 1996; Hummer et al 1995; Umbricht et al 1994). Additional relationships between weight gain during clozapine treatment and gender, severity of illness, concomitant medications, and mean dose were not demonstrated by Hummer et al. (1995), but Leadbetter et al. (1992) observed a protective effect of concurrent lithium treatment against the weight gain effects of clozapine. It has further been demonstrated that underweight patients tend to gain more weight than do those with normal or above normal weight at baseline (Umbricht et al 1994). In another study in which 70% of patients gained an average of 7.5 kg following 12 months of clozapine treatment, marked weight gain (>15% increase) was associated with food intake early in treatment and having gained weight at 3 months (Briffa and Meehan 1998). Finally, the increase in body weight and body composition observed during clozapine and olanzapine treatment is accompanied by a significant elevation of serum leptin concentrations, which is thought to be caused by overeating (Kraus et al 1999; Bromel et al 1998).

Other atypical antipsychotic agents have also been observed to be temporally associated with an increase in weight (Kraus et al 1999; Wirshing et al 1999; Allison et al 1999; Osser et al 1999; Kelly et al 1998; Gupta et al 1998; Brecher and Geller 1997; Crockford et al 1997). Among newer antipsychotic agents, after 10 weeks of treatment mean weight increases were as follows: clozapine, 4.45 kg; olanzapine, 4.15 kg; sertindole, 2.92 kg; risperidone, 2.10 kg; and ziprasidone, 0.04 kg (Allison et al 1999). In a retrospective chart review (N=92) clozapine and olanzapine were associated with the most weight gain, risperidone was intermediate, and sertindole had less associated weight gain than haloperidol (Wirshing et al 1999). Moreover, weight gain with clozapine, but not olanzapine or risperidone, appeared to persist (as reflected by final weight) despite behavioral interventions (e.g., nutritional consultation, suggested exercise regimen). In addition, clozapine- and olanzapine-treated subjects appeared to gain weight over a prolonged period of time, whereas risperidone-and sertindole-treated subjects had a more limited period of weight gain. The authors conclude that the relative receptor affinities of the novel antipsychotics for the histamine H_1 receptor appear to be the most robust correlate of these clinical findings. In a comparison of weight change with risperidone versus conventional agents in adolescents, the risperidone-treated group gained significantly more body mass than did the conventional antipsychotic group (Kelly et al 1998). Among 25 inpatients treated with olanzapine for 12 weeks (mean dose=13.8±4.4 mg/day), a significant mean weight increase from baseline of 12 lb (5.4 kg) was noted (Osser et al 1999). A body mass index increase of 58% with olanzapine treatment has also been reported (Bryden and Kopala 1999). Weight gain during olanzapine treatment, like clozapine, has been suggested to be associated with an increase in leptin levels (Kraus et al 1999).

1.6 Clozapine and Hyperglycemia in Patients

Recent reports have described over 20 cases of hyperglycemia (including cases of diabetic ketoacidosis, DM-I, and/or DM-II) observed with patients on clozapine therapy (Colli et al 1999; Maule et al 1999; Mohan et al 1999; Ai et al 1998; Wirshing et al 1998; Thompson et al 1998; Dickson and Hogg 1998; Pierides 1997; Popli et al 1997; Weiden and Glazer 1997; Kostakoglu et al 1996; Peterson and Byrd 1996; Dassori et al 1995; Kamran et al 1994; Koval et al 1994; Ai et al 1998). Most of the cases had pre-existing DM-II or risk factors for diabetes, such as non-Caucasian ethnicity, family history, or overweight. In addition, many of the patients were taking concurrent medication, such that the concurrent medication or a drug combination with clozapine may have been responsible for impaired glucose metabolism, although cases with monotherapy have been reported. In many cases, discontinuation of clozapine resulted in resolution of hyperglycemia, and in one case, clozapine therapy was continued and the patient's insulin requirements decreased (Smith et al 1999). However, in other cases, rechallenge with clozapine resulted in reemergence of hyperglycemia that did not disappear after discontinuation (Brugman et al 2000; Colli et al 1999). Hyperglycemia with clozapine therapy has been controlled by a lowered dose, diabetic diet (Maule

et al 1999), and oral hyperglycemic agents (McDonnell and Ruderman 1999; Mohan et al 1999). Clozapine has also been successfully substituted with olanzapine (Ai et al 1998); however, in one case, hyperglycemia that resolved prior to clozapine discontinuation reappeared three years later when risperidone was initiated and did not resolve upon discontinuation of risperidone (Mohan et al 1999). Finally, in a case report series of five clozapine-treated adolescents, glycosylated hemoglobin (HbA_{1C}) levels, which are increased in poorly controlled diabetes, were within the normal range at 8 and 16 weeks of therapy (Zung et al 1999). In one clinic, the incidence of clinically significant changes in glucose tolerance with clozapine treatment (n=147) was about 2.7% (Popli et al 1997). In contrast, in another clinical study, 21.7% of the subjects treated with clozapine developed DM-II or impaired glucose tolerance compared to 9.5% of the subjects treated with depot injections of neuroleptics, but this difference was not statistically significant (Hagg et al 1998). In a recent retrospective chart review, 75% (18/24) of clozapine-treated patients and 55% (42/76) of olanzapine-treated patients experienced weight gain, and 43% (6/14) of clozapine-treated patients and 25% (3/12) of olanzapine-treated patients experienced treatment-emergent abnormal fasting glucose (Casey and Shepherd 1999). A recent five-year naturalistic study reported that 36.6% (30/82) of clozapine-treated patients were diagnosed with DM-II (Henderson et al 2000). Interestingly, weight gain, valproate use, and total daily dose of clozapine were not significant risk factors for developing DM-II. There was a significant mean increase in weight that continued until approximately 46 months after clozapine initiation. A study of 6 patients with schizophrenia found increased mean levels of blood glucose, insulin, and C-peptide, suggesting that the glucose intolerance observed during clozapine treatment is due to increased insulin resistance (Yazici et al 1998). Supporting this notion, insulin levels have been shown to be positively correlated with serum clozapine levels (n=13), but not typical antipsychotic levels (n=21) (Melkersson et al 1999). Insulin elevation was seen in the patients receiving clozapine more frequently than in the patients receiving classical antipsychotics and all patients but one were normoglycemic. It was concluded that, although the mechanism regarding the potential effect of clozapine on insulin secretion is unclear, clozapine may induce peripheral insulin resistance and subsequent increased insulin secretion from pancreatic beta cells. A review of the FDA's MedWatch surveillance program was completed to assess the clinical characteristics of clozapine in temporal association with DM (Koller et al 1999). This review concluded that further investigation and documentation are warranted. Finally, preliminary findings from an open-label, non-randomized, retrospective chart review (65 charts) report a decrease in weight and also an improvement in glycemic control after quetiapine was added to clozapine therapy (Reinstein et al 1999). The authors discussed the need for a double-blind, randomized, prospective study to further study the effects of this combination.

1.7 Risperidone and Hyperglycemia in Patients

There has been one case report to date of the development of diabetic ketoacidosis with risperidone (2 mg/day) (Croarkin et al 2000). This patient was a 42-year-old white male with a history of chronic major depression disorder with psychotic features and no family history of DM-II. He was treated with quetiapine and insulin. One case has been reported that describes the utilization of risperidone in a patient with pre-existing Type I DM (DM-I) (Melamed et al 1998). The patient's diabetes was usually controlled except when he failed to eat properly during acute exacerbations of his psychosis. Risperidone was utilized for 2 months with only slight improvement in his Positive and Negative Symptom Scale (PANSS) and no change on Clinical Global Impression (CGI). It was noted during a routine daily check that his serum glucose was normal.

1.8 Olanzapine and Hyperglycemia in Patients

Recent reports including a case series (n=7) that was originally presented as a poster (Sporn et al 1998) and subsequently published (Goldstein et al 1999) have described cases of hyperglycemia (including cases of diabetic ketoacidosis, DM-I and/or DM-II) observed with patients on olanzapine therapy in a total of 16 patients (Goldstein et al 1999; Gatta et al 1999; Ober et al 1999; Lindenmayer and Patel 1999; Hayek et al 1999; Zung et al 1999; Wirshing et al 1998; Fertig et al 1998). Twelve of the cases occurred in male patients, 12 were reported as being obese, and 4 were African-Americans. Further, in five cases the patient had a family history of DM (Goldstein et al 1999; Wirshing et al 1998) and in three cases the patient had pre-existing hypertension (Goldstein et al 1999; Lindenmayer and Patel 1999; Fertig et al 1998). In one case report, the hyperglycemia required insulin therapy, resolved after olanzapine was discontinued, and recurred upon rechallenge (Fertig et al 1998). Another case report involved a patient with a 4-year history

of diabetes (controlled by diet) and hypertension who was switched from thioridazine to olanzapine and experienced a 25% increase in weight (Ober et al 1999). A case presented in a poster presentation involved a 12.5-year-old patient that presented with diabetic ketoacidosis that was treated with insulin (Zung et al 1999). Olanzapine was discontinued with no decrease in insulin requirements. Olanzapine was re-started and the patient's blood glucose levels have been mostly in the normal range over the last 6 months with a decrease in daily insulin requirements. The authors concluded that the temporal association of developing DM-I with olanzapine was a coincidental finding. On the basis of these case studies it appears as though patients that may develop hyperglycemia in temporal association with olanzapine are patients that are typically at risk for DM-II based on race, obesity, or family history. It is unclear at this point whether or not the number of cases of olanzapine in temporal association with DM-II exceeds the expected incidence for the development of DM-II in patients with schizophrenia.

1.9 Quetiapine fumarate and Hyperglycemia in Patients

There is one case report of a 42-year-old white man without a family or personal history of DM, glucose intolerance, or hyperglycemia who was diagnosed with new-onset DM when quetiapine was added to his medication regimen. Following quetiapine discontinuation, his insulin requirements were noted to have "decreased markedly" (Sobel et al 1999). The previously mentioned chart review in which a decrease in weight and improvement in glycemic control was reported after quetiapine was added to clozapine therapy requires further investigation (Reinstein et al 1999).

1.10 Atypical Antipsychotics as a Group and Hyperglycemia in Patients

A poster presentation detailed a retrospective chart review (n=126) that was completed to identify patients treated with an atypical antipsychotic that were subsequently evaluated for diabetes and/or managed for diabetes (Wilson et al 1999). This naturalistic, retrospective study identified 14 patients on an atypical antipsychotic that subsequently had a study of blood glucose, glucose tolerance, or other evaluations of diabetes completed. New-onset, acute glucose intolerance was reported to have developed in 11 of the 14 patients after treatment with an atypical antipsychotic (clozapine, olanzapine, or quetiapine). Weight gain usually occurred during the first 6 weeks of treatment and was not related to changes in glucose tolerance. Six of the 11 patients that developed new-onset, acute glucose intolerance were treated with insulin therapy (4 received transient treatment) and 5 patients developed diabetic ketoacidosis.

1.11 References

Abuzzahab FS and Zimmerman RL (1998): Increase in fasting blood glucose in schizophrenic patients on neuroleptics (Abstract).

Ai D, Roper TA, and Riley JA (1998): Diabetic ketoacidosis and clozapine. *Postgrad Med* 74:493-494.

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC et al (1999): Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156:1686-1696.

Bai YM, Lin CC, Chen JY, and Lin CY (1999): Weight gain among patients on clozapine [letter]. *Psychiatric Serv* 50:704-705.

Baptista T, Contreras Q, Teneud L, Albornoz MA, Acosta A, Paez X et al (1998): Mechanism of the neuroleptic-induced obesity in female rats. *Prog Neuro-Psychopharm & Biological Psych* 22:187-198.

Baptista T, Lacruz A, and Hernandez L (1998): Glucose tolerance and serum insulin levels in an animal model of obesity induced by the antipsychotic drug, sulpiride. *Pharmacol Toxicol* 83:57-61.

Baptista T, Mata A, Teneud L, de Quijada M, Han H-W, and Hernandez L (1993): Effects of long-term administration of clozapine on body weight and food intake in rats. *Pharm Biochem Behav* 45:51-54.

Braceland RJ, Meduna LJ, and Vaichulis JA (1945): Delayed action of insulin in schizophrenia. *Am J Psychiatry* 102:108-110.

Brecher M and Geller W (1997): Weight gain with risperidone. *J Clin Psychopharmacol* 17:435-436.

Briffa D and Meehan T (1998): Weight changes during clozapine treatment. *Australian & New Zealand Journal of Psychiatry* 32:718-721.

Bromel T, Blum WF, Ziegler A, Schulz E, Bender M, Fleischhaker C et al (1998): Serum leptin levels increase rapidly after initiation of clozapine therapy. *Molecular Psychiatry* 3:76-80.

Brugman NJ, Cohen D, and de Vries RH (2000): Diabetes mellitus after treatment with clozapine [Dutch]. *Nederlands Tijdschrift voor Geneeskunde* 144:337-439.

Bryden KE and Kopala LC (1999): Body mass index increase of 58% associated with olanzapine [letter]. American Journal of Psychiatry. 156(11):1835-6, 1999. *Am J Psychiatry* 156:1835-1836.

Bugajski J and Lech J (1979): Effects of neuroleptics on blood glucose, free fatty acids and liver glycogen levels in the rat. *Pol J Pharmacol Pharm* 31:45-58.

Bustillo JR, Buchanan RW, Irish D, and Breier A (1996): Differential effects of clozapine on weight: a controlled study. *Am J Psychiatry* 153:817-819.

Carlsson S, Persson P-G, Alvarsson M, Efendic S, Norman A, Svanstrom L et al (1998): Weight history, glucose intolerance, and insulin levels in middle-aged Swedish men. *Am J Epidemiol* 148:539-545.

Casey DE (1994): Haloperidol and clozapine effects on glucose, insulin and extrapyramidal syndrome in nonhuman primates (Abstract). *Neuropsychopharmacol* 10:140S.

Casey DE and Shepherd P (5-20-1999): Weight Gain and Glucose Metabolism with Atypical Antipsychotics (poster) *American Psychiatric Association annual meeting.*

Cassidy R, Ahearn R, and Carroll BJ (1999): Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry* 156:1417-1420.

Chan JM, Rimm EB, Colditz GA, Stampfer MJ, and Willett WC (1994): Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17:961-969.

Charatan FBE and Bartlett NG (1955): The effect of chlorpromazine ("Largactil") on glucose tolerance. *J Mental Sci* 101:351-353.

Colditz GA, Willett WC, Rotnitzky A, and Manson JE (1995): Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Int Med* 122:481-486.

Colli A, Cocciolo M, Francobandiera F, Rogantin F, and Cattalini N (1999): Diabetic ketoacidosis associated with clozapine treatment [letter]. *Diabetes Care* 22:176-177.

Croarkin PE, Jacobs KM, and Bain BK (2000): Diabetic ketoacidosis associated with risperidone treatment? *Psychosomatics* 41:369-370.

Crockford DN, Fisher G, and Barker P (1997): Risperidone, weight gain, and bulimia nervosa [letter]. *Can J Psychiatry* 42:326-327.

Dassori AM, Miller AL, and Saldana D (1995): Schizophrenia among Hispanics: epidemiology, phenomenology, course, and outcome. *Schizophr Bull* 21:303-312.

Dickson RA and Hogg L (1998): Pregnancy of a patient treated with clozapine. *Psychiatr S* 49:1081-1083.

Dixon RB, Lehman AF, Postrado LF, and Delahanty JC (1998): Diabetes in schizophrenia.

Dvirskii AA (1997): Mutual modifying effect of schizophrenia and diabetes on their phenotypic manifestations (translated from Russian). *Tsitologiia I Genetika* 31:67-70.

Erle G, Basso M, Federspil G, Sicolo N, and Scandellari C (1977): Effect of chlorpromazine on blood glucose and plasma insulin in man. *Eur J Clin Pharmacol* 11:15-18.

Erle G, Basso M, Zaccaria C, DePalo C, and Zago E (1975): Effects of chlorpromazine (CPZ) on blood glucose and plasma insulin levels in healthy subjects and diabetic patients (Abstract). *Diabetologia* 11:340.

Fertig MK, Brooks VG, Shelton PS, and English CW (1998): Hyperglycemia associated with olanzapine. *J Clin Psychiatry* 59:687-689.

Ford ES, Williamson DF, and Liu S (1997): Weight change and diabetes incidence: findings from a national cohort of U.S. adults. *Am J Epidemiol* 146:214-222.

Frankenburg FM, Zanarini MC, Kando J, and Centorrino F (1998): Clozapine and body mass change. *Biol Psychiatry* 43:520-524.

Freeman H (1946): Resistance to insulin in mentally disturbed soldiers. *Arch Neurol Psychiatry* 56:74-78.

Ganguli R (1999): Weight gain associated with antipsychotic drugs. *J Clin Psychiatry* 60 (suppl 21):20-24.

Gatta B, Rigalleau V, and Gin H (1999): Diabetic ketoacidosis with olanzapine treatment. *Diabetes Care* 22:1002-1003.

Goldstein LE, Sporn J, Brown S, Kim H, Finkelstein J, Gaffey GK et al (1999): New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics* 40:438-443.

Goldstein LE, Sporn J, Brown S, Kim H, Finkelstein J, Gaffey GK, Sachs G, and Stern TA (1999): New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics*.

Goncalves N and Gruneberg F (1997): Oral glucose tolerance test, on one single occasion, in scizophrenics under long-term neuroleptic treatment (translated from German). *Pharmakopsych* 8:289-295.

Gupta S, Droney T, Al-Samarrai S, Keller P, and Frank B (1998): Olanzapine-induced weight gain. *Ann Clin Psychiatry* 10:39.

Hagen C, Pedersen PB, Jensen SB, Faber OK, and Jensen T (1979): The effect of sulpiride induced hyperprolactinemia on glucose tolerance and insulin secretion in normal subjects. *Clin Endocrinol* 10:55-60.

Hagg S, Joelsson L, Mjorndal T, Spigset O, Oja G, and Dahlqvist R (1998): Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. *J Clin Psychiatry* 59:294-299.

Hanson RL, Narayan KMV, McCance DR, Pettitt DJ, Jacobsson LTH, Bennett PH et al (1995): Rate of weight gain, weight fluctuation, and incidence of NIDDM. *Diabetes* 44:261-266.

Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR et al (1998): Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. *Diabetes Care* 21:518-524.

Hayek DV, Huttl V, Reiss J, Schweiger HD, and Fuessl HS (1999): Hyperglycemia and ketoacidosis under olanzapine (translated from German). *Nervenarzt* 70:836-837.

Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA et al (2000): Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry* 157:975-981.

Hummer M, Kemmler G, Kurz M, Kurzthaler I, berbauer H, and leischhacker WW (1995): Weight gain induced by clozapine. *Eur Neuropsychopharmacol* 5:437-440.

Jori A and Bianchetti A (1966): Effect of chlorpromazine and its metabolites on blood glucose and glucose tolerance. *Intl J Neurophamacol* 5:435-440.

Kamran A, Doraiswamy PM, Jane JL, Hammett EB, and Dunn L (1994): Severe hyperglycemia associated with high doses of clozapine. *Am J Psychiatry* 151:1395.

Kelly DL, Conley RR, Love RC, Horn DS, and Ushchak CM (1998): Weight gain in adolescents treated with risperidone and conventional antipsychotics over six months. *J Child Adolesc Psychopharmacol* 8:151-159.

Keskiner A, Toumi AE, and Bousquet T (1973): Psychotropic drugs, diabetes and chronic mental patients. *Psychosomatics* 16:176-181.

Khunti K, Goyder E, and Baker R (1999): Collation and comparison of multi-practice audit data: prevalence and treatment of known diabetes mellitus. *Br J Gen Practice* 49:375-379.

Koller E, Dubitsky G, Lutwak L, and Schneider B (1999): Clozapine-Associated Diabetes (poster presentation). *The Endocrine Society's 81st Annual Meeting (San Diego, CA).*

Korenyi C and Lowenstein B (1968): Chlorpromazine-induced diabetes. *Diseases of the Nervous System* 827-828.

Kostakoglu AE, Yazici KM, Erbas T, and Guvener N (1996): Ketoacidosis as a side-effect of clozapine: a case report. *Acta Psychiatr Scand* 93:217-218.

Koval MS, Rames LJ, and Christie S (1994): Diabetic ketoacidosis associated with clozapine treatment. *Am J Psychiatry* 151:1520-1521.

Kraus T, Haack M, Schuld A, Hinze-Selch D, Kuhn M, Uhr M, and Pollmacher T (1999): Body weight and leptin plasma levels during treatment with antipsychotic drugs. *Am J Psychiatry* 156:312-314.

Lacruz A, Baptista T, de Mendoza S, Mendoza-Guillen JM, and Hernandez L (2000): Antipsychotic drug-induced obesity in rats: correlation between leptin, insulin and body weight during sulpiride treatment. *Molecular Psychiatry* 5:70-76.

Lambert AE, Henquin JC, Frenkel A, and Hoet JJ (1972): Blood sugar and plasma immunoreactive insulin during the treatment of a malignant insulinoma with chlorpromazine and streptozotocin (Abstract). *Eur Soc Clin Invest* 2:293.

Lamberti JS, Bellnier T, and Schwarzkopf SB (1992): Weight gain among schizophrenic patients treated with clozapine. *Am J Psychiatry* 149:689-690.

Langfeldt G (1952): The insulin tolerance test in mental disorders. *Acta Psychiatr Scand* 80 (suppl):189-200.

Leadbetter R, Shutty M, Pavalonis D, Vieweg V, Higgins P, and Downs M (1992): Clozapine-induced weight gain: prevalence and clinical relevance. *Am J Psychiatry* 149:68-72.

Leadbetter R, Shutty M, Pavalonis D, Vieweg V, Higgins P, and Downs M (1992): Clozapine-induced weight gain: prevalence and clinical relevance. *Am J Psychiatry* 149:68-72.

Lindenmayer JP and Patel R (1999): Olanzapine-induced ketoacidosis with diabetes mellitus [letter]. *Am J Psychiatry* 156:1471.

Lorenz WF (1922): Sugar tolerance in dementia praecox and other mental disorders. *Arch Neurol Psychiatry* 8:184-196.

Maule S, Giannella R, Lanzio M, and Villari V (1999): Diabetic ketoacidosis with clozapine treatment. *Diabetes Nutrition and Metabolism* 12:187-188.

McDonnell ME and Ruderman NB (1999): Cutting the Gordian knot: Addition of metformin to insulin therapy in a patient with uncontrolled diabetes and schizophrenia. *Diabetes Care* 22:1912-1913.

McKee HA, D'Arcy PF, and Wilson PJK (1986): Diabetes and schizophrenia: a preliminary study. *J Clin Hosp Pharmacy* 11:297-299.

Melamed Y, Mazeh D, and Elizur A (1998): Risperidone treatment for a patient suffering from schizophrenia and IDDM [letter]. *Can J Psychiatry* 43:956.

Melkersson KI, Hulting AL, and Brismar KE (1999): Different Influences of Classical Antipsychotics and Clozapine on Glucose-Insulin Homeostasis in Patients With Schizophrenia or Related Psychoses. *J Clin Psych* 60:783-791.

Mohan D, Gordon H, Hindley N, and Barker A (1999): Schizophrenia and diabetes mellitus [letter]. *British Journal of Psychiatry* 180-181.

Mukherjee S (1999): High prevalence of type II diabetes in schizophrenic patients (Abstract).

Mukherjee S, Decina P, Bocola V, Saraceni F, and Scapicchio PL (1996): Diabetes mellitus in schizophrenic patients. *Compr Psychiatry* 37:68-73.

Mukherjee S, Roth SD, Sandyk R, and Schnur DB (1989): Persistent tardive dyskinesia and neuroleptic effects on glucose tolerance. *Psychiatry Res* 29:17-27.

O'Sullivan JB (1982): Body weight and subsequent diabetes mellitus. *JAMA* 248:949-952.

Ober SK, Hudak R, and Rusterholtz A (1999): Hyperglycemia and olanzapine. *Am J Psychiatry* 156:970.

Ober SK, Hudak R, and Rusterholtz A (1999): Hyperglycemia and olanzapine. *American Journal of Psychiatry* 156:970.

Osser DN, Najarian DM, and Dufresne RL (1999): Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry* 60:767-770.

Peterson GA and Byrd SL (1996): Diabetic ketoacidosis from clozapine and lithium cotreatment. *Am J Psychiatry* 153:737-738.

Pierides M (1997): Clozapine monotherapy and ketoacidosis. *Br J Psychiatry* 171:90-91.

Popli AP, Konicki PE, Jurjus GJ, Fuller MA, and Jaskiw GE (1997): Clozapine associated diabetes mellitus. *J Clin Psychiatry* 58:108-111.

Reinstein MJ, Sirotovskaya LA, Jones LE, and et al (1999): Effect of clozapine-quetiapine combination therapy on weight and glycaemic control: preliminary findings. *Clin.Drug Invest.* 18:99-104.

Resnick HE, Valsania P, Halter JB, and Lin X (1998): Does additional weight gain increase diabetes risk in obese adults? (Abstract). A148.

Schwarz L and Munoz R (1968): Blood sugar levels in patients treated with chlorpromazine. *Am J Psychiatry* 125:253-255.

Smith H, Kenney-Herbert J, and Knowles L (1999): Clozapine-induced diabetic ketoacidosis [letter]. *Austr & New Zealand J Psych* 33:120-121.

Sobel M, Jaggers ED, and Franz MA (1999): New-onset diabetes mellitus associated with the initiation of quetiapine treatment. *Journal of Clinical Psychiatry* 60:556-557.

Spivak B, Musin E, Mester R, Gonen N, Talmon Y, Guy N et al (1999): The effect of long-term antipsychotic treatment on the body weight of patients suffering from chronic schizophrenia: clozapine versus classical antipsychotic agents. *Int Clin Psychopharmacol* 14:229-232.

Sporn J, Goldstein L, Brown S, and et al (1998): Hyperglycemia associated with olanzapine (abstract). (presented as a poster, May 30 - June 4, Toronto, Canada. *Annual Meeting of the American Psychiatric Association.*

Stanton J (1995): Weight gain associated with neuroleptic medication: a review. *Schizophr Bull* 21:463-472.

Thompson J, Chengappa KNR, Good CB, Baker RW, and et al (1998): Hepatitis, hyperglycemia, pleural effusion, eosinophilia, hematuria and proteinuria occurring early in clozapine treatment. *Int.Clin.Psychopharmacol.* 13:95-98.

Thonnard-Neumann E (1968): Phenothiazines and diabetes in hospitalized women. *Am J Psychiatry* 124:138-142.

Thonnard-Neumann E (1968): Phenothiazines and diabetes in hospitalized women. *Am J Psychiatry* 124:138-142.

Tollefson G and Lesar T (1983): Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 44:347-348.

Umbricht DSG, Pollack S, and Kane JM (1994): Clozapine and weight gain. *J Clin Psychiatry* 55:157-160.

Uvnäs-Moberg K, Ahlenius S, Alster P, and Hillegaart V (1996): Effects of selective serotonin and dopamine agonists on plasma levels of glucose, insulin and glucagon in the rat. *Neuroendocrinol* 63:269-274.

Vukicevic Z and Zjacic-Rotkvic V (1994): Chlorpromazine in etiology and treatment prognosis of refractory diabetic ketoacidosis (translated from Czech). *Pharmaca* 32:325-330.

Waitzkin L (1970): Glucose tolerance in man during chlorpromazine therapy. *Diabetes* 19:186-188.

Weiden P and Glazer W (1997): Assessment and treatment selection for "revolving door" inpatients with schizophrenia. *Psychiatr Q* 68:377-392.

Wetterling T and Musigbrodt HE (1999): Weight gain: side effect of atypical neuroleptics? *J Clin Psychiatry* 19:316-321.

Wilson DR, D'Souza L, and Sarkar N (1999): New-onset diabetes and ketoacidosis with atypical antipsychotics. *US Psychiatric and Mental Health Congress (Poster Presentation, Atlanta, Georgia)*.

Wirshing DA, Spellberg BJ, Erhart SM, and Wirshing WC (1998): Novel antipsychotics and new onset diabetes. *Biol Psychiatry* 44:778-783.

Wirshing DA, Wirshing WC, Kysar L, Berisford MA, Goldstein D, Pashdag J et al (1999): Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 60:358-363.

Yazici KM, Erbas T, and Yazici AH (1998): The effect of clozapine on glucose metabolism. *Exp Clin Endocrinol Diabetes* 106:475-477.

Zung A, Blumenson R, Kupchik M, and Zadik Z (1999): Are the atypical antipsychotic drugs diabetogenic? *Hormone Research* 51:102.