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Investigation of the Metabolic Effects of Antipsychotics

By

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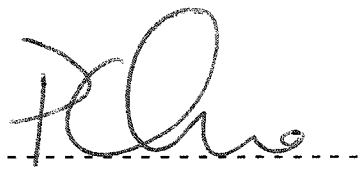

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Abstract

The purpose of this study was to investigate the metabolic effects of different antipsychotic (atypical and conventional) drugs, and to elucidate the relationships between psychiatric disorders and diabetes. The research was a prospective incidence study of metabolic parameters (plasma glucose, insulin, lipids, and uric acid, together with weight and blood pressure) in subjects with schizophrenia being treated with antipsychotic monotherapy for at least 3 months. Demographic information and treatment history were obtained together with laboratory and physical assessments from subjects receiving psychiatric care in outpatient and inpatient programs of Alberta Hospital Edmonton. Clozapine and olanzapine were associated with greater body weight, as well as more adverse changes in insulin, glucose and lipid regulation than risperidone and conventional antipsychotics. These differential liabilities may be significant in the presence of pre-existing factors for diabetes mellitus. It is recommended that blood pressure and weight should be routinely monitored, with fasting lipid profile and oral glucose tolerance test also suggested, in at-risk subjects.

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DEDICATION

This thesis is dedicated to my parents, Stanley and Therese Chue, for their unconditional support and encouragement throughout my life, and especially to my wife, Jocelyn Chue, without whom none of this would have been possible.

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ABBREVIATIONS

ANOVA	Analysis of variance
AAP	Atypical antipsychotic
AIMS	Abnormal involuntary movements scale
cAMP	Adenosine monophosphate
ATP	Adenosine triphosphate
BMI	Body mass index
CAD	Coronary artery disease
CAP	Conventional antipsychotic
CI	Confidence interval
m-CPBG	1- (m-Chlorophenyl)-biguanide HCl
m-CPP	m-Chlorophenylpiperazine
CYP	Cytochrome P450
D	Dopamine
DOI	1- (2,5-Dimethoxy-4-iodophenyl)-2-aminopropane
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DMX	Dorsal motor nucleus of the vagus
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
FSIVGTT	Frequently sampled intravenous glucose tolerance test
GABA	γ-Aminobutyric acid
GH	Growth hormone

G6PD ..... Glucose-6-phosphate dehydrogenase

GLUT ..... Glucose transport

GS ..... Glycogen synthase

H ..... Histamine

HBA_{1C} ..... Glycosylated hemoglobin

HDL-C ..... High density cholesterol

HOMA-IR ..... Homeostasis model assessment of insulin resistance

HPA ..... Hypothalamic-pituitary-adrenocortical axis

HR ..... Hazards ratio

5-HT 5-Hydroxytryptamine

5-HTP 5-Hydroxytryptophan

IDD ..... Insulin dependent

IBW ..... Ideal body weight

IGF ..... Insulin growth-like factor

IGFBP-1 ..... Insulin growth-like factor binding protein-1

IGT ..... Impaired glucose tolerance

IFG ..... Impaired fasting glucose

IR ..... Insulin resistance

K_i ..... Dissociation constant

LDL-C ..... Low density cholesterol

M ..... Muscarinic

MAOIs ..... Monoamine oxidase inhibitors

MI ..... Myocardial infarction

MOPS ..... 3-[N-Morpholino]propanesulfonic acid

n ..... Number of samples

NA ..... Noradrenaline

NAD ..... Nicotinamide adenine dinucleotide

NADH ..... Nicotinamide adenine dinucleotide (reduced)

NaSSA ..... Norepinephrine and selective serotonin antidepressant

NIDD ..... Non insulin dependent

NR ..... Not reported

ns ..... Not significant

OGTT ..... Oral glucose tolerance test

7-OH-DPAT ..... 7-Hydroxy-2-(di-n-propylamino)-tetralin

8-OH-DPAT ..... 8-Hydroxy-2-(di-n-propylamino)-tetralin

OR ..... Odds ratio

P ..... Probability

PCOS ..... Polycystic ovarian syndrome

PEG ..... Polyethylene glycol

PMP ..... 1-(2-Pyrimidinyl)-piperazine

PVN ..... Paraventricular nucleus

RIMA ..... Reversible inhibitor of monamine oxidase A

s^2 ..... Variance

SDRI ..... Selective dopamine reuptake inhibitor

SEM ..... Standard error of the means

SNRI ..... Serotonin and norepinephrine reuptake inhibitor

SSRIs ..... Selective serotonin reuptake inhibitors

STZ ..... Streptozotocin

T_3 ..... Triiodothyronine

TCAs ..... Tricyclic antidepressants

TFMPP ..... N- (3-Trifluoromethylphenyl)-piperazine HCL

TCHOL ..... Total cholesterol

TGs ..... Triglycerides

TOOS ..... N-Ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline

TSH ..... Thyroid stimulating hormone

VLDL ..... Very low density lipoprotein

V_{max}pgu ..... Maximal peripheral glucose uptake

Chapter 1

Rationale, Objectives and Hypothesis

1.1 Rationale for the study

Psychiatric disorders have been reported to be associated with a number of physical disorders and an increased prevalence of metabolic abnormalities. Psychotropic drugs used in the treatment of psychiatric disorders may also result in various metabolic disturbances associated with impaired glucose and lipid metabolism, including diabetes mellitus (DM). This area has not been systematically studied from the point of view of either the literature or the effects of specific classes of psychotropic drugs.

1.2 Objectives

The purpose of this study was to systematically investigate the metabolic effects of conventional (CAPs) and atypical (AAPs) antipsychotics on patients with schizophrenia as well as to comprehensively and critically examine the literature on psychotropic drugs and DM.

1.3 Research hypothesis

Increasing clinical experience with the AAPs has shown that the side effect burden is different to that of the CAPs, with a decreased liability for neurological side effects but an apparent increased liability for weight gain, impaired glucose tolerance (IGT) and DM, as well as hyperlipidemia. It is postulated that because of their neurotransmitter receptor profile, the AAPs differ in their propensity for inducing these side effects, with clozapine and olanzapine being associated with a greater liability compared to quetiapine, risperidone and ziprasidone.

1.4 Relevance and clinical significance

Patients with schizophrenia are at greater risk of cardiovascular morbidity and mortality, as well as DM, than the general population. It is important to determine if these risks are increased by the use of particular psychotropic drugs and which metabolic parameters are most likely to be affected. This clearly has great importance in the outcome of such disorders as schizophrenia where treatment is of potentially lifelong duration. The results of the study may enhance the knowledge required to select appropriate AAP therapy in individuals with schizophrenia and improve clinical monitoring of the baseline parameters that may change with longer-term antipsychotic use.

Chapter 2

Review of the literature

2.1 Introduction

Diabetes mellitus (DM) is a heterogeneous set of metabolic disorders characterized by hyperglycemia and a complex, multifactorial etiology leading to defective insulin secretion, insulin action, or both. It is a common, chronic, potentially incurable illness that is classified as a public health disorder by virtue of high disease burden (Meltzer et al., 1998). There has been a six-fold increase in prevalence over the last 35 years, with dietary and lifestyle changes associated with obesity and inactivity postulated as predisposing factors (Harris et al., 1987). Approximately 7% of these cases are classified as type 1 DM (formerly type I, IDD or insulin dependent diabetes) and the remainder as type 2 DM (formerly type II, NIDD or non-insulin-dependent diabetes). For every diagnosed case of type 2 DM, it is estimated that there is at least one undiagnosed case (Meltzer et al., 1998). In addition to the low detection rate, previous diagnostic criteria lacked sensitivity and correlated poorly with the diagnostic threshold determined by the oral glucose tolerance test (OGTT). The current criteria encompass 3 categories; impaired fasting glucose (IFG) defined by fasting plasma glucose (FPG) values of 6.1 - 7.0 mmol/L, impaired glucose tolerance (IGT) defined by OGTT values 7.8 – 11.0 mmol/L, and DM defined by OGTT values > 11.1 mmol/L (Table 1). The category of IFG was introduced to identify an intermediate stage of abnormal glucose homeostasis associated with a higher risk for the development of DM and cardiovascular disease (Meltzer et al., 1998). Type 2 DM not uncommonly goes undetected for many years because the hyperglycemia develops gradually and ketoacidotic presentations are rare; thus, the classical symptoms of DM may not be sufficiently severe to be noticed.

Nonetheless, such patients are at risk of developing the macrovascular and microvascular complications associated with DM, and it has been reported that at least 50% of type 2 diabetics have established macrovascular disease (Groop, 1999). On average, a period of 6 years elapses before the diagnosis is made, by which time 20% of individuals have retinopathy. (Stern, 1999).

Category	Fasting Plasma Glucose (FPG) mmol/L	PG 1 h after 75-g glucose load; mmol/L	PG 2 h after 75 g (OGTT) mmol/L
Impaired fasting glucose (IFG)	6.1 – 6.9	Not Applicable	Not Applicable
Impaired glucose tolerance (IGT)	< 7.0	Not Applicable	7.8 – 11.0
Diabetes mellitus (DM)	≥ 7.0	Not Applicable	≥ 11.1
Gestational diabetes mellitus (GDM)	≥ 5.3	≥ 10.6	≥ 8.9

Table 1: Diagnostic criteria for diabetes mellitus

DM represents an enormous and growing health problem contributing to significant rates of disability, morbidity and mortality for persons suffering from this disorder (Schmidt and Stern, 2000). Life expectancy for patients with DM is on average 7 to 10 years shorter than for people without DM, and 67% will die through cardiovascular disease. It is also the major cause of new cases of blindness and renal disease in adults (Meltzer et al., 1998). Diabetics compared to non-diabetics are twice as likely to die of coronary artery disease (in females this is further multiplied by a factor of two), four times more likely to suffer from peripheral vascular disease, and twice as likely to have a stroke (again in females this is further multiplied by a factor of two) (Ginsberg, 1999). Diabetics are also at a greater risk of QT prolongation, which has recently been associated with adult sudden death syndrome as well as with potentially fatal arrhythmias such as Torsades des Pointes (Welch and Chue, 2000). Furthermore, since QT prolongation is also associated with certain psychotropic drugs, these medications should be used with particular caution in the diabetic population. The myocardial infarction (MI) risk for a type 2 diabetic is equivalent to that of a non-diabetic with a positive history of previous infarction. This illustrates the significant elevation of risk directly attributable to DM. After a MI diabetic patients have a poorer outcome with a fourfold increase in risk for the development of congestive cardiac failure and a greater likelihood of both repeat infarction and arrthymia. Neurological impairment is particularly evident over the long term with over 60% of diabetic patients developing neuropathy, which may include mono- and polyneuropathies, as well as autonomic neuropathies including erectile dysfunction, urinary incontinence, gastroparesis and nocturnal diarrhea (Schmidt and Stern, 2000).

In summary, the increased medical morbidity of DM has significant implications in terms of potentially increased side effects and complications associated with all aspects of therapy, both psychiatric and physical.

2.2 Relationship between type 2 diabetes mellitus, obesity and insulin resistance

Insulin resistance (IR) (Syndrome X, Metabolic or Reaven's Syndrome) refers to an association of resistance to insulin-mediated glucose disposal together with a cluster of cardiovascular risk factors consisting of obesity, hypertension, dyslipidemia, glucose intolerance and type 2 DM (Reaven, 1988; Opara and Levine, 1997). In addition, metabolic disturbances including coagulopathies, hyperuricemia and polycystic ovarian syndrome (PCOS) have all been associated with IR. In type 2 DM the fundamental metabolic disturbance may range from predominant IR with relative insulin deficiency, to a predominantly insulin secretory defect with IR; 90% of type 2 diabetics are insulin resistant (Bonora et al., 1999). Insulin levels are normal or elevated (fasting level > 15μU/ml). Defects leading to IR may occur at several levels: pre-receptor (abnormal insulin), receptor (decreased receptor number or affinity), glucose transporter (decreased GLUT4 molecules) or post-receptor (abnormal signal transduction or phosphorylation). Insulin resistance is a common disorder influenced by such factors as increasing age, smoking, physical inactivity, family history of DM and gestational DM, a variety of drugs (both psychotropic and non-psychotropic) and obesity (Granberry and Froncesda, 1999). Most patients with type 2 DM are obese, and obesity itself causes some degree of IR; insulin sensitivity declines by up to 40% when an individual is 40% over ideal body weight (IBW) (DeFronzo and Ferannini, 1999).

Excess body fat in the upper body (android pattern) is a better predictor of IR than excess fat in the lower body (gynecoid pattern).

Obesity may be evaluated by the body mass index (BMI - calculated as the ratio of weight in kg divided by the height in m^2) of > 27.3 for females and > 27.8 for males. However even patients who are not obese according to BMI criteria may have an increased percentage of intra-abdominal fat indicated by a waist circumference of > 80cm for females and > 94cm for males or waist/hip ratios > 0.9 for females and > 1.0 for males (Table 2).

			Disease Risk Relative to Normal Weight and Waist Circumference	
	BMI (kg/m^2)	**Obesity Class**	**Men ≤ 100 cm (≤ 40 in) Women ≤ 90 cm (≤ 35 in)**	**> 100 cm (> 40 in) > 90 cm (> 35 in)**
Underweight	<18.5		-	-
Normal	18.5 – 24.9		-	-
Overweight	25.0 – 29.9		Increased	High
Obesity	30.0 – 34.9	I	High	Very High
	35.0 – 39.9	II	Very High	Very High
Extreme Overweight	≥ 40	III	Extremely High	Extremely High

Table 2: Classification of overweight and obesity by BMI, waist circumference and associated disease risk

2.3 Relationship between diabetes, psychiatric disorders and psychotropic drugs

The relationship between DM and psychiatric disorders is complex and involves interactions at the neurobiological level that affect the course, management and prognosis of both (Nicoletti et al., 1996). In addition, there are specific effects of psychiatric medications on glycemic control, risk of diabetes, potential weight gain, and development of metabolic and endocrine syndromes such as IR, PCOS and dyslipidemia. While many psychotropic medications affect blood glucose levels, the extent of these effects can be highly significant clinically, with impact on both the psychiatric disorder and DM, and although there have been previous reviews (Mirouze et al., 1971), this area has not been recently and systematically evaluated. There also exist potential drug-drug interactions between medications used to treat DM and psychotropic drugs, and these can be exacerbated by higher rates of liver cirrhosis in diabetics. Understanding the relationship between disturbances of glycemic control and psychiatric disorders has been confounded by studies which have included heterogeneous patient populations, allowed multiple concomitant medications, and employed non-standardized criteria for the diagnosis of DM. A few studies have reported on the prevalence of psychiatric disorders in DM (Bieder et al., 1972) and specifically depression (Goodnick et al., 1995). In a study of outpatients attending a diabetic clinic, diabetic patients with psychiatric illness had significantly more medical complications than those without and perceived their illness as more disabling (Waring et al., 1978). These patients had significantly worse diabetic symptoms and more frequent problems of diabetic control compared to non-psychiatric patients.

Other studies have demonstrated that symptoms such as decreased energy, fatigue, irritability, anxiety and mood lability are common in diabetics (Surridge et al., 1984). Nonetheless, despite this extensive overlap, there is a remarkable paucity of literature, and this present review attempts to summarize the available data and to recommend rational treatment strategies based upon the empirical evidence available.

2.4 Relationship between diabetes and depression

The overall prevalence of major depression in patients with DM is estimated to be 3 times that of the general population (25% vs. 7%), with a point prevalence of approximately 1 in 5 and a lifetime prevalence of 1 in 3 (Gavard et al., 1993). Prevalence rates of major depressive disorder diagnosed by structured diagnostic interview, in diabetic populations, have been found to range from 8.5% to 27.3% in 4 controlled studies, and from 11.0% to 19.9% in 5 uncontrolled studies (Gavard et al., 1993). However, there remains a significant under-diagnosis of depression and a consequent underutilization of antidepressants in patients with DM. In a study of 3445 Medicaid clinic patients, only 2.6% were receiving antidepressant therapy for the treatment of diagnosed depression (Sclar et al., 1999). Despite this, the treatment of depression in diabetics has been shown to improve glycemic control independent of weight change or improved compliance. Depressed patients demonstrate improved glucose tolerance, enhanced insulin secretion and diminished insulin sensitivity on the OGTT and frequently sampled intravenous glucose tolerance test (FSIVGTT) (Okamura et al., 1999). These abnormalities resolved after recovery from depression independent of body weight changes.

The presence of depression has a negative impact on the management and prognosis of DM. Depressed diabetics have an 8-fold greater relapse rate than the depressed but physically healthy population (Lustman et al., 1988). Direct correlations have also been shown between the severity of depression, diabetic symptoms and glucose levels which are not merely attributable to the presence of chronic disease (Lustman et al., 1986). The likelihood that there is a direct neurobiological relationship between DM and depression is suggested by many studies in which depression has been directly linked with glucose dysregulation (Lustman et al., 1986; 1988). The overall increase in glycosylated hemoglobin (HbA_{1c}) directly attributable to depression has been estimated to be 1.8%. Studies have shown that hyperglycemia itself can result in changes in hypothalamic-pituitary-adrenocortical axis (HPA) activity and altered 5-hydroxytrytamine (5HT) sensitivity in streptozotocin-induced (STZ) rats. These findings have implications for a greater vulnerability of diabetics to stress and potential depression (Lustman et al., 1983). Depression is also an independent risk factor for cardiovascular disease. For example, the effect of both depression and DM is illustrated by a 10 year follow up study of depressed vs. non-depressed diabetics which found a 3-fold greater incidence of coronary artery disease (CAD) in depressed diabetics (Carney et al., 1994).

Depression is also associated with other factors that can affect diabetes such as obesity and treatment non-compliance. Depressed diabetics comply 2-fold less with their diabetic medications than non-depressed diabetics, and 52.4% of obese type 2 DM patients with a history of depression compared to 22.2% without such a history did not complete a weight control program (Marcus et al., 1992).

2.4.1 Effects of antidepressants on diabetes

From both animal models and clinical data in man, there is clear evidence of very different effects on glucose metabolism dependent upon class of antidepressant. Selective serotonin reuptake (SSRI) antidepressants have been reported to produce a dose-dependent decrease in PG of up to 20%, monoamine oxidase inhibitor (MAOI) antidepressants produce decreases of 35%, while tricyclic (TCA) antidepressants increase PG by up to 150% (Wilson and Furman, 1982). The specific effects of a wide range of antidepressants are reviewed in detail.

2.4.2 Monoamine oxidase inhibitor antidepressants

The MAOI antidepressants comprise both nonhydrazines (tranylcypromine, pargyline) and hydrazines (isocarboxazid, phenelzine, iproniazid, nialamide). Early animal studies showed a preventive action of nialamide and tranylcypromine on experimental diabetes in rats (Mordujovich et al., 1966; Buschiazzo et al., 1967). In man, it was noted that the therapeutic effect of MAOIs was accompanied by a significant decrease in PG or OGTT values (Van Praag and Leijinst, 1963, 1964, 1965a, 1965b; Grabowska 1971; Leak and Dormandy, 1961; Cooper & Keddie, 1964; Wickstrom and Petterson, 1964). Furthermore not only were these hypoglycemic effects less pronounced in patients with refractory depressive symptoms, they tended to coincide with the onset of hypotension generally during the third and fourth weeks of treatment and also persisted for 2 to 3 weeks after discontinuation (Wickstrom and Petterson, 1964; Parodi, 1967). Other studies suggested that the hydrazine MAOIs potentiated and prolonged insulin-induced hypoglycemia more than nonhydrazine MAOIs (Cooper and Ashcroft, 1966;

Kopin et al., 1965; Cooper & Keddie, 1964). This was therefore postulated to be related primarily to the hydrazine structure and not to MAO inhibition (Bresler et al., 1968; Aleyssanine and Lee, 1972; Aleyssanine and Gardiner, 1975; Ismahan et al., 1978; Clissiounis, 1979; Potter et al., 1969). Intraperitoneal injection of tranylcypromine in mice produced an elevation of insulin secretion followed by significant hypoglycemia (Bressler et al., 1968). Tranylcypromine was found to be over 30 times more potent than tolbutamide, and this effect was not observed with any of the other MAOIs tested. Furthermore, the effect was blocked by pre-treatment with a β-adrenergic receptor blocker, and augmented by pre-treatment with an α-adrenergic receptor blocker, suggestive of a stimulatory effect on pancreatic insulin secretion possibly mediated by β-adrenergic receptor stimulation. This is supported by findings that β-adrenergic receptor agonists in man, such as isoproterenol, stimulate insulin secretion and β-adrenergic blockers inhibit this response (Porte,1967). Furthermore, epinephrine and norepinephrine are potent inhibitors of insulin secretion in man, and this effect is mediated via an α-adrenergic mechanism. In summary, it appears that the MAOIs potentiate hypoglycemia, likely through effects on gluconeogenesis via combined α- and β-adrenergic mechanisms. Whilst the non-hydrazine MAOIs possess some hypoglycemic effects (Parodi, 1967; Van Praag and Leijnst, 1965b), these appear to be significantly less than those of the hydrazine MAOIs. Hydrazines are converted through blockade of acylcarnitine translocase to hydrazones that have less MAOI effect but greater hypoglycemic action (Bressler and Johnson, 1992; Haeckel & Oellerich, 1979), and there was some early interest in developing these compounds as oral hypoglycemics. Similarly,

whilst it was suggested that MAOIs could be used successfully in the treatment of depressed diabetic patients, particularly those refractory to sulfonylureas or insulin (Wickstrom and Petterson et al., 1964), the concomitant use of an MAOI with diabetic therapy is generally not recommended because of the potential risk of hypoglycemia (Cooper, 1966). In addition, MAOIs are not only associated with weight gain (Rabkin et al., 1984), but the necessity of rigid adherence to a tyramine-free diet may impact negatively on diabetic and weight reducing diets as well as being difficult to follow for patients with significant depression. Other potential risks include the fact that seizures have been reported in a diabetic patient on MAOIs (Albareda et al., 1999). There are no data concerning reversible inhibitors of MAO A (RIMAs) such as moclobemide in terms of effects on glycemic control. Unlike irreversible MAOIs, moclobemide is not associated with weight gain and does not require a special diet. In summary, MAOIs have been used in the treatment of depression in DM but clinical use is limited by the dietary requirements, weight gain and potential hypoglycemia. As a consequence irreversible MAOIs are probably not recommended as first line agents although a RIMA may be a reasonable alternative choice given the lack of any demonstrable deleterious effects.

2.4.3 Tricyclic antidepressants

TCAs, particularly secondary amines, possess activity in terms of noradrenergic reuptake inhibition. It has been suggested that TCAs may produce hyperglycemia by potentiating the actions of catecholamines. Although TCAs have been associated with hypoglycemia when used alone or in conjunction with sulfonylureas (Sherman and Borneman, 1988; True et al., 1987), their hyperglycemic actions are

suggested by several lines of evidence. Early animal studies demonstrated that adrenaline and noradrenaline in rabbit pancreas completely inhibited glucose-mediated insulin release (Aleyassine and Lee, 1972). Adrenaline's effects on insulin secretion in rats are mediated via α-and β-adrenergic receptors in pancreatic islets, with α-stimulation being inhibitory and β- adrenergic stimulation resulting in a rise in cAMP concentrations *in vitro* and an increase in insulin secretion *in vivo* (Turtle and Kipnis, 1967; Turtle et al., 1967; Sussman and Vaughan, 1967).

Results from human studies of the effects of TCAs show considerable variation, with short-term studies indicating hypoglycemic effects, whilst data from longer-term administration suggest hyperglycemic effects. In a study comparing the effect of imipramine versus placebo in 3 diabetics (2 of whom were depressed), PG levels fell significantly during imipramine treatment and increased during the placebo period, with a general increase in hyperglycemia over the study period (Kaplan et al., 1960). An additional 2 patients showed an improvement in glycosuria over several days on impramine. Similarly profound hypoglycemia was observed with the acute addition of a TCA to maintenance sulfonylurea therapy (True et al., 1987). In this study doxepin with tolazamide, and nortriptyline with chlorpropamide, over 7 –11, days produced reductions in PG of greater than 50%. However, effective pharmacotherapy for the treatment of depression usually involves longer-term administration and negative effects on glycemic control are seen with longer-term treatment. Eight weeks of clomipramine treatment was found to lead to hyperglycemia with an increase in PG from 120mg/dL to 300-400mg/dL

(Katz et al., 1991). Thus, while TCAs have been shown to cause hyperglycemia laboratory and short-term clinical studies, their effects on glycemic control in depressed and non-depressed diabetics appear to be different. In a randomized, double-blind, placebo controlled trial of 68 diabetics with poor glycemic control, 28 of whom had DSM-IIIR depression, nortriptyline at therapeutic levels (50-150 ng/ml) was compared to placebo over 8 weeks (Lustman et al., 1988). Path analysis showed that the direct effect of the TCA was to worsen glycemic control, but improvement in depression had an independent positive effect on $HbA_{1C.}$. The findings were not related to weight change or improved compliance.

Studies in rats have shown differential metabolism of amitriptyline in hepatocytes from STZ-induced diabetic rats compared to non-diabetic rats (Coudore et al., 1997). Amitriptyline was less completely metabolized, with greater glucuronidation of metabolites, especially for Z-hydroxynortriptyline in the diabetic animals. Although these effects have not been explored in man, there may be a potential effect in diabetics if similar mechanisms operate, leading to a reduced conversion of amitriptyline (tertiary amine) to nortriptyline (secondary amine). Nortriptyline possesses more norepinephrine reuptake activity and less α_1- and α_2- adrenergic antagonism and this could conceivably have a greater adverse effect on glycemic control. Imipramine metabolism has been studied in both type 1 (STZ-induced insulin-deficient) and type 2 (genetically insulin-resistant) DM in mice (Rouer et al., 1987). In both types of DM, the formation of imipramine N-oxide is increased, but in type 1 DM, the formation of desmethyl- and 2-

hydroxyimipramine is additionally increased through the activity of flavin monooxygenase. Again, this has implications for the metabolism of imipramine in human diabetic subjects.

The hypothesis that depressed diabetic patients possess resistance to TCAs has been investigated in animal studies, but the underlying mechanisms are complex and remain unclear. Using the learned helplessness model in STZ-induced diabetic rats, it has been shown that clomipramine or imipramine prevented escape deficits in non-diabetic, but not diabetic, rats (Massol et al., 1989). However, operant escape responding was made possible in the diabetic rats by either increasing the duration of antidepressant therapy, insulin therapy for 1 week or supplementation of antidepressant therapy with triidothyronine (T_3). Clenbuterol, a central β-adrenergic agonist, also prevented escape deficits in non-diabetic rats, but not diabetic, rats and showed reversal only with insulin therapy. It was hypothesized by the authors that thyroid-mediated alterations of central noradrenergic function might be a critical factor in the resistance to antidepressants in experimental diabetes. The possibility of a central β-adrenergic mechanism was further explored in 2 psychopharmacological tests; namely the reversal of apomorphine-induced hypothermia, and hypoactivity induced by clenbuterol (Massol, et al., 1989). At day 15 after STZ or vehicle treatment, imipramine antagonized the apomorphine-induced hypothermia in diabetic and non-diabetic mice while clenbuterol produced hypoactivity in both groups. At days 30 and 45, the ability of the three TCAs studied, to reverse apomorphine-induced hypothermia diappeared at the same time that clenbuterol lost its

ability to induce hypomobility in the diabetic mice; these impaired responses were reversed by insulin treatment. The authors suggested that a central β-adrenergic desensitization similar to that seen peripherally may be occurring in DM. The possibility that a thyroid hormone deficiency may be involved was also tested. Decreased T_3 plasma levels were found in diabetic mice at the same time as impaired pharmacological responses, and T_3 supplementation restored these responses. It has also been suggested that a central GABAergic dysfunction may play a role in antidepressant resistance since a specific and marked decrease in GABA-B receptor density was observed (with no change in GABA-A receptor density) in the cortex of STZ-diabetic rats (Martin et al., 1988). It does not appear that a serotonergic dysfunction is involved in antidepressant resistance since no differences were found in the ability of 3 SSRIs to reverse performance deficits in the learned-helplessness paradigm between STZ-diabetic and non-diabetic rats (Massol et al., 1989). In summary, these findings appear to suggest the possibility of a central noradrenergic mechanism that may account for an impaired response to TCAs in depressed diabetic patients.

The TCAs are associated with weight gain, and specifically carbohydrate craving, which impacts negatively on adherence to a controlled caloric diet (Paykel et al., 1973; Nakra et al., 1977; Harris et al., 1984; Berken et al., 1984; Fernstrom et al., 1987; Stein et al., 1985). Carbohydrate or sweet cravings have been reported to increase by 34 to 200% with TCAs in studies in non-diabetic populations (Fernstrom et al., 1987; Stein et al., 1985; Paykel et al., 1973), and it has been shown that in normal controls weight gain

associated with amitriptyline was not related to changes in OGTT but to increased appetite (Nakra et al., 1977). Amitriptyline and fluphenazine have been used to successfully treat diabetic cachexia (Gade et al., 1980). TCAs are also associated with impaired concentration and memory through antimuscarinic side effects and sedation. This may be particularly significant in further compromising cognitive function in elderly diabetics as well as having implications for a diabetic to follow a diet and adhere to a complex medication regimen. Additive negative effects on cognition may also increase the risk of accidental toxicity, which is particularly significant in the case of the TCAs given their narrow therapeutic range. Furthermore, medical complications of DM such as cardiovascular disease, autonomic dysfunction, impotence and retinopathy may all be adversely affected by TCAs and can be further exacerbated by concomitant medications (Rubinow, 1982). TCAs are considerably more cardiotoxic than SSRIs, with the relative risk of myocardial infarction being 2.2 in patients on TCAs and 0.8 in patients on SSRIs compared with subjects not receiving any antidepressants (Cohen et al., 2000). In view of the cardiovascular complications that occur with DM, there is thus the theoretical risk of a significant increase in the potential for myocardial infarction and arrthymias to occur with the use of TCAs in diabetic patients.

TCAs may be more effective than other classes of antidepressants in treating diabetic neuropathic pain syndromes, but the role of psychotropic drugs in the management of diabetic neuropathy is beyond the scope of this article. Of note, pain has been shown to be a common presenting symptom of depression in diabetics and it has

been suggested that painful diabetic neuropathy may represent a depressive equivalent. In one study, 59 patients referred primarily for painful neuropathy of the lower limbs, were all found to be significantly depressed on psychiatric assessment. Subsequent double blind treatment with imipramine or amitriptyline resulted in complete resolution of pain symptoms and relief of depression (Turkington, 1980).

2.4.4 Selective serotonin re-uptake inhibitor antidepressants

The SSRIs, notably fluoxetine, are associated with hypoglycemia in both case reports and clinical studies (Deeg and Lipkin, 1996; Fernandez et al., 1996; Lear and Burden, 1992). Thus, SSRIs may offer particular advantages, together with a more favorable side effect profile, for the treatment of depression in patients with DM given the potential positive effects on glycemic control (Zumoff, 1979).

In studies investigating the effects of serotonin on plasma glucose *in vivo*, pre-treatment with a serotonin precursor, 5-hydroxytrytophan (5-HTP), significantly decreased the effect of sulfonylurea stimulated insulin release in normal mice and in the presence of nialamide, whilst 5-HTP alone significantly reduced both PG and plasma insulin (Lundquist et al.,1971). Similarly pre-incubation of rabbit pancreas with 5-HTP *in-vitro* increased β-cell serotonin content and blocked glucose-stimulated insulin secretion, suggestive of serotonin's action in reducing PG independent of insulin secretion (Feldman, 1975). The hypoglycemic response induced by 5-HTP in the presence of nialamide was not associated with an elevation in plasma insulin, and was prevented by cyproheptadine, a serotonin antagonist (Furman, 1974). High dose 5-HTP produced hypoglycemia in fasted mice but only in those where significant elevation in

plasma insulin levels was possible (Furman, 1980). These findings suggest the importance of a direct effect of serotonin on glucose metabolism.

In terms of clinical studies, sertraline at a dose of 50 mg/day in a 10-week open study of 28 type 2 DM patients with DSM-IIIR major depression produced a significant improvement in depression rating scores, together with a fall in platelet 5-HT content (baseline concentrations correlated with clinical response), a reduction of HbA_{1c} levels, and improved dietary compliance (Goodnick et al., 1997). Similarly, in 60 patients with DM (26 with type 1, 34 with type 2) and major depression in a 8 week randomized placebo-controlled double-blind trial, who were treated with fluoxetine up to 40mg/day, significantly greater improvement in depression was seen in patients treated with fluoxetine compared to those receiving placebo, and a greater reduction in HbA_{1C} was observed in the fluoxetine group (Lustman et al., 1998). Both of these studies demonstrate that successful treatment of depression with SSRIs can also improve glycemic control.

Weight reduction is essential in the management of most type 2 diabetics, but this therapeutic goal is frequently difficult to obtain. The effects of SSRIs on short and longer-term diabetic management in non-depressed patients has been examined in the following studies. In a double-blind parallel study, 82 moderately obese (BMI = 30-39 kg/m^2) non-depressed type 2 diabetic patients were given either placebo or fluoxetine 60mg daily, in addition to their usual anti-diabetic treatment, for 8 weeks (Daubresse et al., 1996). At baseline, both groups had similar weight excess, metabolic control and serum lipid values. In comparison with placebo, the fluoxetine-treated patients lost more

weight and had lower FPG at 3 and 8 weeks. HbA_{1c} decreased from 8.5% to 7.7% and mean triglyceride (TG) levels were also reduced in the fluoxetine group after 8 weeks. Fasting C-peptide did not change in either group, but PPI decreased and the insulin/C-peptide molar ratio decreased significantly in the fluoxetine group after 3 and 8 weeks. It was concluded that the addition of fluoxetine to oral hypoglycemics might be beneficial in obese non-depressed type 2 diabetics, at least on a short-term basis. In a 12-month double-blind trial in 19 obese non-depressed type 2 patients, fluoxetine 60 mg daily compared to placebo produced a significant fall in median body weight after 3 months (3.8 kg), 6 months (6.5 kg), 9 months (7.1 kg) and at 1 year (5.8 kg) (O'Kane et al., 1994). Median FPG and HbA_{1c} levels fell significantly after 3 months (1.9 mmol/L and 1.7%, respectively) and 6 months (1.8 mmol/L and 1.7%) but neither showed a significant difference from placebo after 9 or 12 months. There were no significant changes in TCHOL levels in the year, but patients on fluoxetine showed a significant fall in TGs (0.5 mmol/L) after 3 months therapy but not thereafter. Compared to placebo there was a significant fall in median energy intake on fluoxetine after 3 months (257 kcal day-1) and 6 months (199 kcal day-1), but this difference was not significant at 9 or 12 months. There was also a significant fall in carbohydrate intake after 3 months (30 g /day) and 6 months (23 g/day) on fluoxetine.

Fluoxetine was further investigated in obese non-depressed type 2 diabetics in which 48 male and female subjects were randomized to receive either fluoxetine 60 mg or placebo once-daily in a double-blind fashion for 24 weeks together with dietary instruction (Gray et al., 1992). Subjects treated with fluoxetine achieved a maximum 8 kg

greater weight loss on average than the placebo-treated subjects. At the end of active treatment, fluoxetine-treated subjects had significantly lower HbA_{1c} levels than the placebo-treated group (9.72 vs. 10.76%). In addition, fluoxetine-treated subjects showed a greater decrease in total daily insulin dose than placebo-treated subjects (44.5 vs. 20.1%). Insulin resistance contributes to the metabolic defects in type 2 diabetes and anorectic agents such as fluoxetine have been shown to improve insulin action in type 2 DM, irrespective of weight reduction. In a double-blind placebo-controlled crossover study, hepatic and peripheral insulin action was monitored by the sequential hyperinsulinemic euglycemic clamp technique with infusion of 3-^{3}H-glucose in 8 obese type 2 diabetics and in 8 obese non-diabetics, matched for age, sex and BMI (Potter at al., 1992). Body weight was kept constant. After 14 days of fluoxetine, 60 mg daily, in diabetics half-maximal peripheral glucose uptake was achieved at a lower insulin level than after placebo (ED_{50}pgu 180.5 ± 25.8 vs 225.3 ± 39.9 mU/l, $P < 0.05$), but not in non-diabetics (140 ± 15.3 vs 135.3 ± 22.2 mU/l, n.s.); maximal peripheral glucose uptake (V_{max}pgu) did not change significantly. Basal hepatic glucose production was reduced after fluoxetine in diabetics (9.45 vs 10.37 μmol/kg/min), and in non-diabetics (8.57 vs 9.16 μmol/kg/min), although the difference was only significant in non-diabetics ($p < 0.05$). Multivariate analysis did not show any differences in the effect of fluoxetine between diabetics and non-diabetics. When non-diabetics and diabetics were considered together, only the most insulin-resistant individuals demonstrated a decrease in ED_{50}pgu.

Similarly, only the individuals with the greatest hepatic IR demonstrated a

decrease in insulin level at which hepatic glucose production is completely suppressed.

To further study the effect of fluoxetine specifically on insulin sensitivity independent of its action on body weight, a randomized, double-blind, placebo-controlled trial utilizing measurement of insulin-mediated glucose disposal by the 2-step euglycemic hyperinsulinemic clamp technique was carried out in 12 obese type 2 patients, before and after 4 weeks of treatment with either placebo or fluoxetine (60 mg/day) (Maheux et al., 1997). Compared to placebo, fluoxetine increased glucose disposal by 2.4-fold, insulin sensitivity index by 2.7-fold and glucose metabolic clearance rate by 2.9-fold, suggestive of improvement in insulin-mediated glucose disposal in these patients independent of weight (which remained stable with no change in dietary intake). To study fluoxetine's long-term metabolic effects, 40 obese patients with either type 2 DM or IGT, were included in a 12-month, randomized, placebo-controlled study. Patients were assigned to receive either 60 mg fluoxetine or placebo daily in conjunction with a 5.0-MJ/day diet (> 50% carbohydrate) (Breum et al., 1995). Both groups showed a significant weight loss, with a nadir after 6 months (without group differences). Fifteen patients from the fluoxetine group and 14 from the placebo group completed the 12-month study without weight loss differences. Glycemic regulation improved along with the weight loss, but with a larger decline in plasma C-peptide and FPG in the fluoxetine group. Total skeletal muscle glycogen synthase (GS) activity increased by 31% in the fluoxetine group and by 17% in the placebo group after 6 months of treatment, but was still less than the activity in normal weight controls. After adjustment for FPG, insulin, weight loss, and diabetic

state, a positive effect of fluoxetine on the total GS activity remained (accounting for 27% of the variation). The waist to hip ratio was reduced in placebo subjects as compared with fluoxetine subjects. Fat-free mass showed a trend for greater reduction in the fluoxetine group as compared with placebo subjects. Overall, the results of this study suggest that fluoxetine improved insulin sensitivity beyond the effect mediated through weight loss, possibly by an effect on GS activity in skeletal muscle tissue. In all these studies, high dose fluoxetine led to improvements in weight and HbA_{1C} levels in the long term in non-depressed diabetic patients.

Treatment of the elderly diabetic population is complicated by age-related changes in pharmacodynamics and pharmacokinetics of drugs as well as through an increased prevalence of physical co-morbidity and use of concomitant medications, leading to greater susceptibility to adverse effects. Fluoxetine (60mg/day), was compared to placebo in obese, non-depressed type 2 diabetic patients over 60 years of age in a randomized, double-blind, parallel study in order to establish the safety and efficacy of fluoxetine in this population (Connolly et al., 1995). Subjects were diet controlled with an $HbA_{1c} < 14\%$ (reference range 6-9%) and BMI > 29 kg/m^2. Improved glycemic control was demonstrated in the fluoxetine group compared with placebo, with initial HbA_{1c} levels of 8.0% vs 8.7% (NS) falling at 4 months by 0.9% and at 6 months by 0.9%, although no sustained improvement in FPG was demonstrated. Those taking fluoxetine also had a median weight loss of 2.6 kg at 3 months and 3.9 kg at 6 months, compared with weight loss in the placebo group of 0.1 kg and 0.0 kg at 3 and 6 months, respectively.

The effects of SSRIs on weight are not clear. In general, acute treatment studies with SSRIs in depressed, but non-diabetic, patients are associated with weight loss. Despite the commonality of effect on 5-HT uptake, the structural heterogeneity of the SSRI class implies pharmacokinetic and pharmacodynamic differences. A double blind study over 6 months found intra-class differences in weight gain with paroxetine showing a greater increase than sertraline or fluoxetine (Fava, 2000). The exact mechanism underpinning the role of 5-HT in weight control remains to be established, but it does appear to regulate the dietary intake of carbohydrate versus protein such that an increase in 5-HT in the medial hypothalamus results in decreased carbohydrate intake (Tecott et al., 1995). Interestingly, there is a case report on the effective treatment of bulimia with fluoxetine in a patient with type 1 DM (Ramirez et al., 1990). In general, weight gain with SSRIs is less than with TCAs, and a recent study comparing weight gain with amitriptyline and nortriptyline to paroxetine found that weight gain was greater with the TCAs and appeared to involve activation of the tumour necrosis factor-α system (TNF-α) and not changes in leptin (Hinze-Selch et al., 2000).

From the evidence to date it can be seen that SSRIs can help both mood and diabetic control in depressed diabetics and may even benefit non-depressed diabetic patients. In general, SSRIs are well tolerated with few serious adverse effects. Nonetheless, SSRIs can be associated with effects on hepatic cytochrome P450 (CYP) isoenzyme systems through direct enzyme inhibition in a dose-dependent fashion. This may potentially lead to interactions with concomitant medications prescribed in the

treatment of DM. Hypoglycemia postulated to be related to the inhibition of CYP enzymes, has been reported in a patient with schizoaffective disorder with type 2 diabetes treated with sertraline, risperidone and glyburide (Takhar et al., 1999). Glycemic control normalised within 10 days of discontinuing the sertraline. Sexual dysfunction is associated with serious medical illnesses such as DM, psychiatric disorders (particularly depression) and the use of psychotropic drugs. Of the antidepressants, SSRIs are reported to produce 1.6 times more sexual dysfunction than TCAs, and this may be a particularly troublesome adverse effect in the diabetic population, who already have higher rates of sexual dysfunction due to chronic disease and impaired cardiovascular and autonomic function. Rare adverse effects associated with SSRIs in diabetic patients have been described in pediatric populations. Growth failure following the use of high dose fluoxetine in a pediatric patient with type 1 DM has been reported (Frank and Navron, 1999) as has a loss of hypoglycemia awareness in an adolescent with type 1 DM on fluoxetine (Sawka et al., 2000).

2.4.5 Trazodone and nefazodone

There are limited data concerning the effects of trazodone and nefazodone in diabetic patients. Nefazodone's actions include blockade of 5-HT_2 and 5-HT_1 receptors as well as weaker blockade of α_1- and α_2-adrenoreceptors. For nefazodone, there are reports of rare induction of both hyperglycemia and hypoglycemia (CPS Product Monograph). The role of the common metabolite of nefazodone and trazodone, m-chlorophenylpiperazine (mCPP) may be relevant in these contradictory effects. One case report describes a 54-year old female with type 1 DM whose insulin requirements fell

markedly with the use of nefazodone to treat a major depressive episode (Warnock and Biggs, 1997). Dietary compliance, exercise and weight control all showed improvement. Nefazodone, like the SSRIs, tends not to cause the same degree of weight gain or carbohydrate craving commonly associated with the TCAs; weight gain has been reported to be less than with the SSRIs. While nefazodone may well be a reasonable alternative to the SSRIs, it is a potent CYP 3A4 inhibitor and this may result in drug-drug interactions with concomitant medications which are metabolized by this route and prescribed in diabetic patients. Recent reports of its hepatoxicity may further limit its use.

Trazodone posesses a similar profile to nefazodone but is a more potent blocker of 5-HT_2 and α_1-adrenoreceptors. Trazodone has also been used in the treatment of diabetic neuropathy. In addition, it is commonly used as an adjunct in the treatment of side effects such as insomnia and sexual dysfunction associated with other antidepressants. There are no reports of glycemic dysregulation with trazodone in diabetic populations, and it would appear that it can be used safely in these patients.

2.4.6 Venlafaxine

Venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI) structurally similar to β-phenylethylamine, is associated with activation and weight loss. There are rare reports of both hyperglycemia and hypoglycemia (CPS Product Monograph). While venlafaxine may well be a reasonable alternative to the SSRIs, particularly given its weight loss properties, dose-dependent hypertension and increased serum cholesterol, are reported and appropriate monitoring is recommended.

2.4.7 Mirtazapine, Mianserin, Maprotiline

Mirtazapine, a norepinephrine and selective serotonin antidepressant (NaSSA), is a tetracyclic related structurally to mianserin. Its principal mode of action is the blockade of α_2-autoreceptors and α_2-heteroreceptors as well as some 5-HT_2 and H_1-receptor antagonism. Mianserin possesses greater α_1 antagonism than mirtazapine, and while both mirtazapine and mianserin are associated with greater weight gain than SSRIs, there have been no reports concerning disturbance of glycemic control with mirtazapine. Mianserin has beeen associated in one case report with blood glucose dysregulation (Wolter-Henseler, 1996). Maprotiline, another tetracyclic compound with primarily norepinephric reuptake activity, has been reported to cause hypo- and hyperglycemia (CPS Product Monograph). There are two case reports of hypoglycemia in diabetic patients (Isotani and Kameoka, 1999; Zogno et al., 1994). In view of these variable effects, at this time the heterocyclic antidepressants remain second line agents to the SSRIs for use in diabetic patients.

2.4.8 Bupropion

Bupropion, an aminoketone, is a selective, but weak, dopamine reuptake inhibitor (SDRI), further metabolised to hydroxybupropion, an active metabolite which is in itself a weak noradrenergic reuptake inhibitor (although concentrated some twentyfold in the plasma compared to the parent drug). There are reports of hypoglycemia, hyperglycemia and glycosuria, consistent with the actions of both the parent and metabolite on dopamine and noradrenaline (CPS Product Monograph). Bupropion is structurally related to an anorectic agent, diethylpropion, and is therefore associated with weight loss as well as

psychomotor stimulation. It can precipitate seizures in a dose-dependent fashion, and the seizure threshold is lower in diabetics taking oral hypoglycemics. Consequently, dosing should be carefully supervised in this population. A 10 week study comparing bupropion to placebo in diabetic men with sexual dysfunction showed a trend towards improved sexual function without adverse effects on diabetic control (Rowland et al., 1997). Thus, the possible role of bupropion in the treatment of diabetic patients who are also depressed remains uncertain.

2.4.9 Amoxapine

Amoxapine, although a noradrenergic reuptake inhibiting TCA, shares a structural similarity with the antipsychotic loxapine, as well as being a weak dopamine antagonist. Amoxapine and loxapine have been related to hyperglycemia, possibly through the action of a common active metabolite, 7- hydroxyamoxapine (Tollefson and Lesar, 1983). Thus, amoxapine cannot be recommended for use in diabetic patients.

2.5 Relationship between diabetes and anxiety

Anxiety symptoms are common in diabetics (Surridge et al., 1984) and have been related to fluctuations in glucose levels. The presence of an anxiety disorder is associated with poorer glucose control and increased reports of diabetic symptoms (Lustman, 1988).

2.5.1 Effect of anxiolytic and hypnotic drugs on diabetes

A variety of compounds of both structural and functional diversity have been used clinically as anxiolytics (and to a certain extent as hypnotics). These include benzodiazepines and buspirone, and less commonly antihistamines, barbiturates and

carbamic acid derivatives. There are few data concerning the effect of these compounds on glycemic control. Phenobarbital and meprobamate have been shown to be essentially inactive (Sternbach et al., 1964; Von Optiz, 1962) and there is one case report of hyperglycemia with diphenhydramine.

2.5.2 Benzodiazepines

In studies in rats, chlordiazepoxide produced significant, though temporary, increases in PG (correlated with dose and degree of sedation) and diazepam produced slight increases (Rutishauser et al., 1963: Sternbach et al., 1964). One case is reported of an insulin-dependent woman who experienced significant hyperglycemia with chordiazepoxide, but other diabetic patients were unaffected (Zumoff & Hellman, 1977). A double-blind, placebo-controlled study with alprazolam (up to 2 mg/day) in 58 patients with poor glycemic control, 16 of whom had symptomatic generalised anxiety disorder, found a statistically significant reduction in HbA_{1c} with alprazolam compared to placebo (-1.1 vs 0.3%, $P = 0.04$). There was no correlation with a reduction in anxiety rating scale scores or improved compliance, thus, it was concluded that this was an intrinsic effect of the drug (Lustman et al, 1995). In view of the large number of clinical situations in which diabetic patients have received benzodiazepines, and yet the paucity of any reports, it is probably safe to conclude that benzodiazepines do not have significant effects on glycemic control.

2.5.3 Buspirone

$5\text{-}HT_{1A}$ receptor agonists such as 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and buspirone produce an increase in plasma glucose levels and a decrease in

plasma insulin levels (Chaouloff et al., 1990a; Chaouloff et al., 1990b). This effect is suggested to be due to sympathoadrenal activation and is blocked by hexamethonium and idazoxan (α_2-antagonist); the decrease in insulin may be mediated via activation of α_2-adrenergic receptors on pancreatic β-cells through adrenaline secretion (Chaouloff et al., 1987; Chaouloff et al., 1990d). Consistent with this, others have shown that 8-OH-DPAT in rats produced a statistically significant decrease in plasma insulin levels, an increase in glucose (antagonized by pre-treatment with the 5-HT_{1A} agonist, pindolol,), and no change in glucagon levels (Uvnas-Moberg et al., 1996). The only effect observed after buspirone treatment was a small increase in plasma glucose levels, and it has been suggested that the mechanism may involve oxytocin via vagal stimulation, resulting in lowered plasma insulin levels. In rats buspirone inhibits tolbutamide-induced hypoglycemia, an effect likely mediated through 5-HT_{1A} receptors and involving adrenaline, not insulin, release (Sugimoto et al., 1995).

Other studies have presented contrasting data which suggest agonism of 5-HT_{1A} receptors causes hypoglycemia (Baudrie and Chaouloff, 1991), but buspirone also possesses antagonistic and agonistic activity at the D_2 receptor and its active metabolite 1-(2-pyrimidinyl)-piperazine (PMP) is a non-selective 5-HT_1 agonist, 5-HT_2 antagonist and α_2-antagonist. As a consequence, the expected hyperglycemic effect of buspirone may be modified by these additional influences. Despite the findings in animal studies, clinical studies have not found marked effects of buspirone on glucose levels in man. No differences were found in PG between male subjects on either placebo or buspirone after exercise (Marvin et al., 1997). To summarize these complex data, pure 5-HT_{1A} receptor

agonism appears to result in elevation of PG. However most psychotropic drugs acting at 5-HT_{1A} receptors are partial agonists (buspirone, pindolol, ziprasidone), and have multiple actions at other receptor sites that may mitigate potential hyperglycemic effects. Because of these actions it is probably safe to use buspirone in the treatment of anxiety in diabetic patients.

2.5.4 Beta-blockers

Pancreatic islets contain α_2-and β_2-adrenergic receptors, and α_2-receptor stimulation inhibits insulin release in contrast to stimulation of β_2-receptor (and vagal muscarinic receptors) that enhances insulin release (Ferner, 1992; Chan and Cockram 1991). However, changes in glucose tolerance resulting from pancreatic effects are offset by effects on hepatic glucose production, which is increased by β_2-stimulation and decreased by α_2-stimulation while glucose synthesis is reduced by β_2-stimulation and increased by α_2-stimulation. The overall result of stimulation or inhibition of these adrenergic receptors can be either hyperglycaemia or hypoglycaemia. Thus, while β-blockers might be expected to reduce glucose tolerance by inhibiting insulin release, this effect is not clearly demonstrated in diabetic patients (Ferner, 1992). Drug dose, β_1 versus β_2 selectivity and duration of treatment may be relevant since hyperglycemic effects are not observed with long-term administration. Slightly higher rates of IGTT in β-blocker-treated patients have been noted (Houston, 1986), with one case report of hyperosmolar coma (Podolsky, 1973), but severe hyperglycemia has been described only with β-blockers in combination with diuretics and other hypertensives (Mammarella et al., 1988).

However, β-blockers decrease hypoglycemic awareness, delay recovery from hypoglycemia and mask the symptoms of acute hypoglycemia in diabetics (Chan et al., 1996).

2.5.5 Hypnotics

There are, to my knowledge, no published data on chloral hydrate, ethchlorvynol, hydroxyzine, zopiclone or zaleplon with respect to disturbances of glycemic control.

2.6 Relationship between bipolar disorder and diabetes

In reviewing the relationship between bipolar disorder and DM, limitations need to be recognized. The first is that despite the fact that both disorders are common, there is relatively little research into any possible relationships between the two. The second is that the data (similar to the situation with major depressive disorder and schizophrenia), are confounded by the retrospective nature of most of the studies, with the diagnostic criteria for bipolar disorder changing considerably over time making inter-study comparisons problematic; in addition, the methodology for diagnosing DM has also changed. Nonetheless, there is some suggestive information both about the possible increased risk of DM and about the possible effects of medications used in bipolar disorder (Lustman et al., 1986). There are two major studies both of which examine retrospective data, but which suggest that there is significantly increased risk of bipolar patients also having DM. The first found that 20 patients (9.8%) of 203 with DSM-II bipolar disorder also had a diagnosis of DM (Lilliker, 1980); the author also estimated the incidence of diabetes as 1.8% in the general population based upon age-corrected National Health Survey data. In 13 of these patients, DM was diagnosed after the bipolar

disorder. Interestingly, the author stated that most of these patients had not been treated with lithium (although the exact percentage is not clarified), but patients did receive antipsychotics (APs), which may have increased their risk. A second, larger, study examined 345 DSM-III bipolar patients who were hospitalized with a diagnosis of manic or mixed type (Cassidy et al., 1999). The authors found that 9.9% of these patients also had a co-morbid diagnosis of DM at the time of admission, however, medication usage is not reported in this population. They compared this to age- and sex-matched mean US rates of 3.5% found in other epidemiological research (Harris et al, 1987). It should be noted that in contrast to these reports, a study to determine the effects of lithium in 460 bipolar patients found only 1 patient with glucosuria at baseline (Vestergaard and Schou, 1987). However, other factors may have influenced the data, co-morbidity was not specifically examined, patients with DM may have been excluded from receiving lithium, and lithium has an insulinomimetic effect. In terms of possible mechanisms by which this co-morbidity could occur, several possibilities are suggested (Cassidy et al., 1999). These include overlapping genetic causes, possibly linked to the tyrosine hydroxylase-INS-insulin-like growth factor II gene cluster on the short arm of chromosome 11 (Todd et al, 1989; Faas et al, 1994), small intraparenchymal cerebrovascular disease and focal infarction in DM that may cause intra-cranial lesions leading to bipolar disorder (Aronson and Aronson, 1973; Dupont et al, 1990), increased glucorticoid release during mania, increasing the risk of DM either through increased glucocorticoid secretion or via joint disturbances of the hypothalamic pituitary adrenal (HPA) axis (National Diabetes Data Group, 1979; Carroll, 1979; Cookson et al, 1985), or finally that both diseases may affect

similar regions of the brain. In addition to these hypotheses, it has also been suggested that common alterations in fatty-acid and phospholipid metabolism may underlie both disorders (Horrobin and Bennett, 1999). Another possibility to account for the increase in co-morbidity is that the medications used in the treatment of bipolar disorder increase the risk of diabetes, either directly or indirectly, for example through weight gain. However, from the evidence to date it is not likely to be due to lithium or other mood stabilizer treatment, although it could conceivably be due to AP use. Clearly, more research in this area is required.

2.6.1 Effect of mood stabilizer drugs on diabetes

The range of compounds used as mood stabilizers in the treatment of affective disorders includes the monovalent cations such as lithium, anticonvulsants, calcium channel (Ca^{2+}) antagonists, and, more recently, atypical antipsychotics (AAPs). The heterogeneity of the drugs is reflected in quite diverse effects on glucose regulation. These effects are confounded by the weight gain observed with most of these compounds, with the exception of topiramate, and the frequent use of concomitant medications.

2.6.2 Lithium

Lithium was used in the treatment of DM before insulin became available and well before its use in psychiatry (Weiss, 1924). However, lithium's effects on glucose metabolism are complex and contradictory. Administration of lithium to rats has been shown to lead to hyperglycemia in some studies (Shah et al., 1980) or improvement in

glucose regulation in others (Vendsborg , 1979; Mannisto et al.,1972; Hu et al., 1997b). In man, similar contradictory results have been reported, including an improvement in GTT (Vendesborg and Rafaelsen, 1973; Vendesborg, 1979; Van der Velde & Gordon, 1969, Hunt, 1987; Saran, 1982; Mellerup and Plenge, 1974; Mannisto et al., 1972), no effect (Heninger et al.,1970; Vendesborg and Prytz, 1976) or an impairment in GTT (Waziri and Nelson, 1978; Shopsin et al., 1972; Muller-Oerlinghausen et al., 1978; Champeyroux et al., 1978; Derot et al., 1978; Kamei et al., 1984). The variability in results likely reflects differences in duration of treatment, concomitant medications, and study methodology including psychiatric diagnosis and DM diagnostic criteria. Some early case reports suggested an increased risk of developing DM and its complications including fatal diabetic ketoacidosis (DKA) (Johnson, 1977; Wazari and Nelson, 1978; Kondziela et al., 1985). Abnormal glucose tolerance in patients given lithium in the short-term was also reported (Vendesborg and Rafaelsen, 1973; Purgyi, 1972) as well as recurrence on rechallenge (Craig et al., 1977). Although a study comparing 22 lithium-treated patients with 21 matched controls found a significant lowering of FPG after 1 year of treatment, a rise to normal values after 3 years was observed (Agbayewa, 1982); in a later study no effect of lithium on glycosylated hemoglobin was found (Agbayewa, 1986).

A number of larger studies also appeared to suggest that there was an increased risk, as suggested by the results of GTT tests in 49 patients on long-term lithium treatment. However the authors noted that weight gain may have contributed to these findings and furthermore baseline diabetic status of patients before starting lithium

treatment was unknown (Muller-Oerlinghausen et al., 1978). It should also be noted that none of the studies controlled for factors likely to influence the incidence of DM, including concomitant medications such as APs, weight gain (Baptista et al., 1995) and age. More than 50% of bipolar patients aged over 40 (n=50) receiving lithium had abnormal GTTs (Van der Velde and Gordon, 1969). In contrast to above findings, other reports have described an improvement in GTT (Shopsin et al, 1972; Huntsinger, 1987), or hypoglycemia in patients treated with lithium (Shah et al., 1980). These findings were in keeping with an earlier study by the same group that found no effect of lithium on OGTT (Vendesborg and Prytz, 1976). A case report is described in which a bipolar patient with DM was given lithium with consequent improvement in their DM to the point where they no longer needed any treatment (Saran, 1982). Plasma glucose response to a 50g carbohydrate breakfast over 3 hrs in 6 type 2 diabetics before and after 1 week of treatment was measured and a significant reduction in PG noted with no change in plasma insulin (Jones et al, 1983). Lithium decreased FPG and 1 hr post-prandial glucose in 38 diabetics, with the most significant decreases occurring in patients treated with oral hypoglycemics or insulin while diabetics controlled with diet alone showed the smallest decreases (Hu et al., 1997a). In the largest study to date, of 460 lithium-treated patients who had fasting PG levels done before lithium treatment was started and were followed up with repeated assessments of FPG from 6 months (all patients) to 6 years (15 patients) after initiation of lithium, the authors concluded that there was no evidence that lithium was diabetogenic even though patients gained on average 4.3 kg (Vestergaard and Schou, 1987).

From animal studies, lithium appears to exert insulin-like effects on glucose metabolism *in vivo*, possibly through 2 separate mechanisms: a direct liver effect via the activation of GS and simultaneous inactivation of glycogen phosphorylase in both healthy and diabetic rats as well as modulation of insulin and other hormones related to glucose homeostasis, including glucagon (Mellerup and Thomsen 1970). Lithium's hypoglycemic effects appear to result from increased insulin sensitivity rather than a direct action on insulin secretion, and this is supported by observations of an insulinomimetic effect on intracellular second messenger systems as well as a potential effect on intracellular active glucose transport and insulin receptors (Hu et al., 1997b). In summary, lithium appears to act in man to reduce PG levels, but its use in diabetics should be tempered by the risk of weight gain and renal impairment. In the presence of nephrogenic diabetes insipidus, the extracellular volume depletion can result in excessive reabsorption of glucose from the renal tubules, and both DKA and hyperosmolar nonketotic coma have been reported (Chan and Cockram, 1991; Azam et al., 1998).

2.6.3 Anticonvulsants

In terms of other drugs used in bipolar disorder there is a single case report describing DKA 6 weeks after the introduction of carbamazepine to an epileptic patient. This resolved on discontinuation of treatment, and recurred when carbamazepine was reintroduced. Interestingly, this patient was subsequently given sodium valproate, which did not cause any change in PG (Obembe, 1991). Valproate was originally linked to the development of IR, obesity and PCOS, in women with seizure disorder (Isojarvi et al.,

1998), and more recently in women with bipolar disorder (McIntyre et al., in press). Valproate can also interfere with urinary ketone analysis. In contrast there have been no case reports or other studies suggesting that lamotrigine, gabapentin, tiagabine or topiramate can increase the risk of DM, and indeed many of these drugs, including carbamazepine, are used in the treatment of diabetic neuropathic pain.

2.6.4 Calcium-channel antagonists

Insulin secretion is dependent on the entry of calcium into β-cells, and Ca^{2+} antagonists have been shown to inhibit insulin release (Ferner, 1992). However, clinical studies with therapeutic doses of calcium-channel antagonists have generally failed to show any important effects on insulin secretion or glucose tolerance in diabetics or non-diabetics (Chan and Cookram, 1991). There are a number of case reports of hyperglycemia with verapamil at therapeutic doses and following overdose, but nifedipine and diltiazem have rarely been associated with changes in glycemic control (Giugliano et al., 1980; Roth et al., 1989; McMillan et al., 1988).

2.7 Relationship between diabetes and schizophrenia

Early observations dating back to 1919 (Kooy, 1919; Lorenz, 1922), and subsequently in the 1940s (Braceland et al., 1945; Holmgren and Wohlfhart, 1944) and in the 1950s (Shattock, 1950; Simon & Garvey, 1951; Henneman et al., 1954; Freeman and Zabarenko, 1949), reported a greater prevalence of abnormalities of glucose regulation in patients with schizophrenia and other psychoses than in the general population, well before the advent of APs. Abnormal OGTTs were reported in up to two thirds of

schizophrenics, particularly in acute or catatonic states (Aldrich, 1948; Freeman and Almadjan,1950, Freeman, 1946; Lorenz, 1922). Insulin resistance was identified as a frequent finding in schizophrenic patients, and the consequent disturbance of insulin tolerance tests was described as or "hypoglycemia unresponsiveness". Psychiatrists administering insulin shock therapy to schizophrenic patients found they required doses of insulin up to 1,000 i.u. to induce hypoglycemia and it was claimed that impaired GTT and the finding of an "anti-insulin hyperglycemic factor" were characteristic of oneirophrenia (Meduna, 1950). Later investigators (Mayer-Gross, 1951; Braceland et al., 1945) did not find such a link with this particular diagnostic sub-type, but noted that such "hyperglycemic factors" occurred up to three-fold more often in schizophrenic patients. However many of these early studies showing a range of prevalence of diabetes from 11.7% to 30.4% compared relatively small numbers of patients prior to standardized diagnostic criteria for DM and schizophrenia (Balter, 1961; Waitzkin, 1966a; Waitzkin, 1966b ; Freeman, 1950; Langfeldt, 1952; Lingjaerde, 1956; Winkelmayer, 1966; Lilliker, 1980). More recent studies have shown an overall prevalence of DM in schizophrenic populations ranging from 8.8% to 15.8% (Keskiner et al., 1973; Ward, 1972; Dynes, 1969; McKee et al., 1986; Brambilla et al., 1975; Tabata et al., 1987; Mukherjee et al.,1996). By comparison , in the general population the prevalence of DM for US adults over 20 years of age was estimated to be 7.8% (Harris et al., 1998); higher incidences are reported with increased age, female gender and in those of African-American, Hispanic or Native American descent (Cowie and Eberhart, 1996).

2.7.1 Effects of antipsychotics on diabetes

Subsequent to the introduction of the first AP, chlorpromazine, the prevalence of type 2 DM reportedly increased from 4.2 % to 17.4 % in a cohort of hospitalized women with schizophrenia (Thonnard-Neumann, 1968). Others have found that unmedicated schizophrenic patients had lower PG values than those on thioridazine or chlorpromazine (Efron and Balter, 1966). However, other reports have been unable to demonstrate an association between DM and the use of APs (Mukherjee et al.,1996; Keskiner et al., 1973) and specifically with chlorpromazine (Schwarz and Munoz, 1968). In general, these studies were flawed by small sample size, poor inter-study comparative data particularly with respect to high potency versus low potency conventional antipsychotics (CAPs), and lack of standardized diagnostic criteria. A study which examined 95 schizophrenic patients in Italy found the prevalence of DM to be 0% in patients less than 50 years, 12.9% in patients 50 to 59 years old, 18.9% in patients 60 to 69 years old and 16.7% in patients over 70 years (Mukherjee et al., 1996). There were no significant gender differences, with 14% of men and 20% of women being diagnosed with DM, but it was significantly more common in AP-free patients than in patients on APs after controlling for age, sex and cumulative duration of AP treatment. These results exceeded rates of DM in the US general population of 1.3% in persons 18 to 44 years old, 6.2% in persons 45 to 64 years old, and 10.4% in persons over 65 years old (Kenny et al., 1995) as well as in the Italian population (Bruno, 1992). The negative association with respect to AP treatment is interesting, but it is important to note that there were no data on which APs were prescribed, concomitant medications or diagnostic stringency.

More recent studies have attempted to more clearly define the epidemiology related to the different antipsychotics, including the AAPs. However much of the data presented is based upon retrospective case reports, reviews, cross-sectional analyses or prescription data. There are relatively few large scale prospective incidence studies employing rigorous fasting data and adequately controlling for diagnosis and acuity, duration of treatment on drug when tested, previous medication, particularly if associated with weight gain or metabolic changes, age, sex, smoking status, family history of diabetes, ethnicity and concomitant drugs. Thus, it must be recognized that because of the limitations in the data it is not yet possible to draw definitive conclusions, although it will be seen that certain consistent trends are becoming increasingly apparent. The mechanisms by which APs are associated with new-onset DM are also not yet clearly elucidated. The etiology is complex and likely to be multifactorial, with different factors of importance for different drugs additionally influenced by the relationship between DM and schizophrenia itself superimposed on the risk factors for DM. The effects on glucose regulation appear to be related to particular patterns of CNS receptor blockade and direct metabolic effects on systemic organs as well as indirect effects via weight gain. Chemical structure as with the MAOIs, may possibly play a role since olanzapine (a thienobenzodiazepine) and clozapine (a dibenzodiazepine) share some similarity of structure and have similar effects on glucose metabolism and weight; however, it is not clear whether this is a more important factor than receptor antagonism profiles (which are also similar). Clearly, much more research needs to be done in this area.

The complexity of this area is highlighted in the results of a study in rats given a

D_2 agonist (bromocriptine), a D_2/D_3 agonist (quinpirole), or a D_3 agonist (7-hydroxy-2-(di-n-propylamino)tetralin, 7-OH-DPAT) (Uvnas-Moberg et al., 1994). Administration of 7-OH-DPAT produced a decrease in plasma insulin and an increase in glucose levels, which were blocked by pre-treatment with a D_2/D_3 antagonist (raclopride); quinpirole caused an increase in glucose only and bromocriptine, a D_2 antagonist, had no effect. The role of adrenaline was hypothesized to be important in mobilizing blood sugar from the liver since the plasma levels of glucagon remained constant in these experiments. According to Saller & Kreamer, 1991, sympathoadrenal activation results in an increase in PG levels that is mediated by D_2 receptors. In contrast to the results from Uvnas-Moberg et al., 1994, bromocriptine when given with SKF 38393, a D_1 agonist, has been shown to normalize hyperphagia, body fat, hyperglycemia, and hyperlipidemia in ob/ob mice (Scislowski et al., 1999; Bina & Cincotta, 2000). It is suggested that sympatholytic dopamine agonists may act via the hypothalamic–neuroendocrine axis to correct autonomic control of pancreatic islet function (Jetton et al., 2001). In man, bromocriptine compared to placebo, significantly reduced FPG and HbA_{1C} as well as enhancing maximally stimulate insulin-mediated glucose disposal in a 16 week double-blind study in 22 obese, type 2 diabetics (Pijl et al., 2000). Thus, alteration in glucose homeostasis may well be a function of the action of APs on dopamine receptors, in the presence of the abnormal neural substrates found in psychiatric syndromes. It has been proposed that glucose regulation is mediated via D_3 and 5-HT_{1A} receptors separately, but with a putative common mechanism involving oxytocin (Uvnas-Moberg et al., 1994). Oxytocinergic neurons of the paraventricular nucleus (PVN) of the hypothalamus project to the dorsal motor nucleus of the vagus (DMX) (Buijus, 1983) and local application of oxytocin into

the DMX lowers insulin via a vagal mechanism (Siaud et al., 1991). 7-OH-DPAT increases oxytocin levels and stimulation of 5-HT_{1A} and 5-HT_2/5-HT_{1C} receptors induces oxytocin release in male rats (Bagdy and Kadogeras, 1993). The possibility that these drugs may affect glucose homeostasis directly through their impact on serotonin receptors has been suggested (Wirsching et al., 1998). However, the data in this area are complex and contradictory. No significant effects on plasma insulin, glucagon or glucose were seen in rats after treatment with the selective agonist N-(3-trifluoromethylphenyl) piperazine HCl (TFMPP), the 5-$HT_{2A/2C}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) or the 5-HT_3 agonist 1-(m-chlorophenyl)-biguanide HCl (m-CPBG) (Uvnas-Moberg et al., 1996). However, DOI has been shown to induce hyperglycemia via central inhibition of insulin release, and a peripherally acting 5-HT $_{2A/C}$ agonist (α-methyl-5-HT) also produced hyperglyemia (Chaouloff et al., 1990a). The effect of DOI was significantly blocked by ketanserin (an 5-HT $_{2A/2C}$ /α_1 antagonist) (Chaouloff et al., 1990a; Yamada et al., 1995). Ritanserin (5-HT_{1C}/5-HT $_{2A/B/C}$ antagonist) also blocked, to a lesser extent, DOI-induced hyperglycemia (Chaouloff et al., 1990a) although it did not demonstrate any effects on glucose regulation when administered alone (Wozniak and Linnoila., 1991). Idazoxan (an α_2 antagonist) significantly blocked hyperglycemia induced by DOI, but a selective β antagonist (ICI 118.551) had no effect (Chaouloff et al., 1990a). From studies with 8-OH-DPAT described in the section on buspirone, it is suggested that insulin release is mediated through central serotonergic activity separately via 5-HT_{1A} and 5-HT_2 receptors. To summarize these very complex and sometimes contradictory data it is hypothesized that APs possessing a profile of antagonism at 5-HT_2, HT_{1A}, α_2, and D_2/D_3 receptors may be less likely to be associated with hyper-glycemia.

It has been suggested that IR and hyperglycemia are associated with hyperprolactinemia, and that prolactin's diabetogenic properties result from the impairment of insulin's antilipolytic action (Foss et al., 1995; Sorenson and Brelje 1997; Johnston et al 1980; Tourniarire et al., 1974; Landgraf et al., 1977). However, other studies have concluded that under physiological conditions prolactin does not appear to play an important role in the regulation of glucose in man (Vigas et al., 1993; Skouby et al., 1986). In support of this, high potency conventional antipsychotics such as haloperidol and AAPs such as risperidone and amisulpiride, are associated with hyperprolactinemia but do not appear to be more frequently associated with DM. In contrast, low potency CAPSs such as chlorpromazine and AAPs such as clozapine and olanzapine have little effect on prolactin but are more frequently associated with DM.

Finally, another possible mechanism may involve specific glucose transport (GLUT) proteins which are responsible for maintaining cellular levels of glucose. The brain expresses two forms of these proteins, GLUT1 and GLUT3. Clozapine and fluphenazine induced a 100%-300% increase in GLUT3 and a 100% increase in GLUT1 (Dwyer et al., 1999). In contrast, haloperidol reduced the levels of GLUT1 and GLUT3 and only marginally inhibited 2-deoxyglucose uptake into PC12 cells (a neuronal cell line) compared to clozapine and fluphenazine. The differential effects of the APs are speculated to impact on cerebral metabolism and pharmacological mode of action.

There have been no controlled studies comparing the incidence of DM in different diagnostic groups, although weight gain with psychotropic drugs may be influenced by diagnosis. The consequences of disturbed glycemic control and potential development of

DM have significant clinical implications for many patients, but particularly those suffering from schizophrenia, ranging from the increased morbidity and mortality from cardiovascular causes, DKA and neuropsychiatric consequences. This may include not only a greater risk of depression but also tardive dyskinesia and cognitive impairment. Hyperglycemic rats have been shown to have a significantly higher incidence and severity of abnormal perioral movements, which were correlated with blood glucose levels (Sandyk, 1990; Sandyk et al., 1991). In patients with schizophrenia, the relationship is complex, with the risk of TD possibly increased in those patients with DM (Woermer et al., 1993) as well as the presence of TD being associated with a two to fourfold increased rate of DM (Mukherjee et al.,1985, Mukherjee et al.,1996, Mukherjee et al.,1989; Schultz et al.,1999). A study of 21 schizophrenics found a significant positive correlation between Abnormal Involuntary Movement Rating Scale (AIMS) ratings and hyperglycemia (Schultz et al.,1999). Whilst the risk may be small in comparison to the other risk factors, it is unclear as to how this may translate in the long term for APs with the greatest propensity for DM-induction. The presence of DM may also result in the impaired use of glucose for CNS cognitive functions, potentially exacerbating the deficits in schizophrenia and increasing the difficulty of disease control (Newcomer & Craft, 1999). In addition to this, recent studies suggest that DM, IR, hyperinsulinemia and hypertension are all independent risk factors for dementia, with the presence of DM particularly linked to early dementia (Gregg et al., 2000; Knopman et al., 2001).

Antipsychotics have been associated with drug-induced pancreatitis, and this may lead to secondary changes in glucose levels. A brief review of the literature revealed 2 reports with olanzapine, 3 reports with clozapine (Martin, 1992; Jubert et al., 1995; Frankenburg and Kando, 1992) and 1 report with risperidone (Berent et al., 1997). Another proposed mechanism of action of olanzapine-induced DM is direct damage to pancreatic islet cells (Goldstein et al., 1999). Diabetics also suffer higher rates of cirrhosis, and alterations in drug metabolism may be associated with increased susceptibility to side effects, toxicity and drug-drug interactions, leading to decreased effectiveness of medications. Many APs are associated with transient and clinically insignificant changes in liver function tests, but the consequences of psychotropic drug-related liver function abnormalities have not been systematically studied in diabetic populations. Elevation of hepatic transaminases are reported in up to 8% of olanzapine-treated patients (CPS), allergic hepatitis has been described with chlorpromazine (CPS), and toxic hepatitis has been associated with clozapine treatment (Kellner et al., 1993).

2.7.2 Conventional antipsychotics

Certain CAPs, particularly of the phenothiazine class, have been associated with DM. Abnormal GTTs were observed in 40%, 35% and 15% of patients on chlorpromazine, perphenazine and clopenthixol, respectively (Amdisen et al., 1964). Overall, chlorpromazine has been reported to be the most diabetogenic and haloperidol the least diabetogenic of all the CAPs; thioridazine appeared less diabetogenic than chlorpromazine or perphenazine (Amdisen et al., 1964; Thonnard-Neumann, 1968). Sulpiride-induced IGT was noted in normal subjects after 8 days at full dose, but no

change in carbohydrate homeostasis was reported for haloperidol. Studies in rats have demonstrated marked increases in PG with chlorprothixene (Von Optiz, 1962). Cautious interpretation of animal data is required, particularly when extrapolating findings to man, as demonstrated by differences in animal models. Chlorporomazine-induced hyperglycemia in the mouse, hamster and rat showed significant differences in the magnitude of response, hypothesized to be due to differences in basal metabolic rate (Norman and Hiestrand, 1995). Similarly, early studies in primates found that following IVGTT challenge, hyperglycemia and hyperinsulinemia were observed with haloperidol, but not with clozapine, which is in contrast to later clinical data in humans (Casey, 1994). From all the data, it would appear that chemical class and associated similarities of receptor profile appear to be determinants of potential effects on glucose regulation.

2.7.3 Chlorpromazine

Chlorpromazine has been reported to alter glucose-insulin homeostasis (Arnesson, 1964; Thonnard-Neumann, 1968; Proakis 1971; Amdisen, 1964), producing hyperglycemia in animal studies (Mennear and Miya, 1970; Wannarka et al., 1993; Ammon et al., 1971; Amnon et al., 1973; Jori and Carrara, 1966; Bhide et al., 1965; Norman and Hiestand, 1955; Bonaccorsi et al., 1964; Rutishauser, 1963; Von Optiz, 1962) as well as inducing hyperglycemia in healthy volunteers, schizophrenic patients and in patients with latent DM (Erle et al.,1977; Dagli, 1984; Charactan and Bartlett, 1955; Hiles, 1956; Waitzkin, 1970; Gerich et al., 1971; Jori et al., 1964; Ryall, 1956).

A number of studies have reported that chlorpromazine increased PG levels and inhibited insulin secretion in hypoglycemic patients, and it has been used to prevent

hypoglycemia in patients with malignant insulinoma (Lambert et al., 1972; Federspil et al., 1974; Scandellari et al., 1976). Chlorpromazine produces a hyperglycemic response possibly through inhibition of insulin release from Langerhans' islets via decreased activity in the β-cells of the pentose-phosphate shunt (Ammon et al., 1971; Amnon et al., 1973); small doses of chlorpromazine inhibit emiocytosis, but high doses increase the number of autophagosomes in pancreatic β-cells (Orci et al., 1972). Chlorpromazine also increases adrenaline release from the adrenals *in vitro* (Weil-Malherbe, 1963) and increases urinary excretion of catecholamines *in vivo* (Johnson, 1964). Furthermore, chlorpromazine impairs the uptake of catecholamines (Herting, et al., 1961) and blocks α- adrenergic receptors (Jori and Carrara, 1966). Thus, the hyperglycemic response to chlorpromazine may be in part due to release of catecholamines by adrenal stimulation (Carlson and Hillarp., 1961; Von Opitz, 1962; Bhide, et al., 1965; Mennear and Maya, 1970; Erle et al., 1977; Saller and Kreamer, 1991).

In contrast to the above studies, it has been shown by (Hasselblatt et al., 1958; Christy et al; 1957) that chlorpromazine produced a mild hypoglycemia and did not block insulin-induced hypoglycemia although it did block tolbutamide-induced hypoglycemia. Similarly, other researchers concluded that there was no evidence that phenothiazines, and specifically chlorpromazine, significantly affected PG levels (Schwartz & Munoz, 1968; Efron and Balter, 1966). However drug dose and duration may play a role, as with the TCAs, and in one of these studies patients received a mean dose of chlorpromazine of 400 mg/day for only 3 weeks (Schwartz and Munoz, 1968). These apparent discrepancies are further highlighted in the following study in which the effects of chlorpromazine on

PG and insulin levels during both acute and chronic administration (the latter being only 7 days) were investigated in three groups of normal subjects and in one group of patients with latent DM (Erle et al., 1977). Treatment with chlorpromazine at 75 mg/day for 7 days did not alter the plasma insulin response after oral glucose; nor did treatment with chlorpromazine at 50 mg/day for 7 days affect the glucose assimilation rate or insulin response to glucose injection. Infusion of chlorpromazine (50 mg in 60 min) only slightly increased the basal blood glucose level but had no significant effect on basal plasma insulin. The insulin/glucose ratio after the end of the infusion was significantly higher than during the period of infusion of the drug in the normal subjects whereas in latent diabetic patients chlorpromazine infusion significantly diminished the insulin/glucose ratio during an IVGTT. The authors concluded that, whereas prolonged treatment with low doses of chlorpromazine did not modify glucose tolerance and glucose-stimulated pancreatic response, higher acute doses of the drug may induce hyperglycemia and can inhibit insulin secretion both in normals and in patients with latent DM. However, it should be noted that the doses used and duration of administration, particularly for the chronic treatment phase (7 days), are not reflective of the doses used in clinical practice (up to 1200mg/day) often for periods of many years given the chronicity of most psychotic disorders. Thus, in a clinical setting 15 out of 16 schizophrenic patients receiving high dose chlorpromazine had type 2 DM (Mckee et al., 1986).

2.7.4 Loxapine

Loxapine and amoxapine are similar structurally (both are dibenzoxazepines), and both of these drugs have been associated with disturbances of glycemic control. Thus, in

a case of nonketotic hyperglycemic coma associated with loxapine, drug discontinuation led to a return of normal FPG. Later challenge with amoxapine was also associated with acute hyperglycemia. Their common metabolite, 7-OH-amoxapine, was implicated (Tollefson and Lesar, 1983).

2.7.5 Atypical antipsychotics

There are increasing data describing a hierarchy of liability of diabetic association with the AAPs. However, most of these studies are either in the form of retrospective cohort and chart reviews (Wilson et al., 1999b; Zoler, 1999; Sernyak et al., 2001), or analyses of prescription data (Caro et al., 2000; Mahmoud et al., 2000; Cavazzoni et al., 2001; Moisan et al., 2001). As a consequence of the methodology, these studies likely underestimate the true prevalence of DM, particularly early changes, since they depend upon the diagnosis of DM either having been made or treatment initiated. Furthermore, any real differences between the APs may be confounded by lack of control for such factors as baseline weight and change, ethnicity, family history, treatment duration and history, diagnosis and phase of illness, smoking status, and concomitant medications. Prospective incidence studies also rarely control for these factors. These problems are coupled with the inherent difficulties in obtaining accurate fasting bloodwork. There are a few studies looking at metabolic changes and IR factors following patients from baseline (Cohn et al., 2001) or following switches from 1 AP to another (Glick et al., 2001, Fryburg et al., 2000).

A number of chart review studies have looked at the differences between AAPs. The charts on 408 patients with schizophrenia in the primary care clinic of a

schizophrenia treatment and research center were reviewed. Fifty-eight patients (13%) had been diagnosed with type 2 DM: 16 of 85 on clozapine (16%), 4 of 92 on fluphenazine (4%), 4 of 60 on haloperidol (6.6%), 5 of 44 on olanzapine (11%), 4 of 59 on risperidone (6%) and 5 of 68 patients on other antipsychotics (7.3%) (Zoler, 1999). In a naturalistic retrospective chart review of 126 patients receiving an AAP in an academically affiliated state hospital over a 30-month period, baseline FPG levels were available for 21 patients, and 14 patients subsequently completed a diabetic evaluation (Wilson et al., 1999a). New-onset acute IGT was reported to have developed in 11 of the 14 patients treated with clozapine, olanzapine or quetiapine. Six of the 11 patients required insulin therapy (4 received transient treatment) and 5 patients developed DKA. Of these 5 patients, 2 (a 49-year old African-American male and a 31-year old African-American female) were on olanzapine, 2 were on clozapine and 1 on quetiapine. Mean and median time to onset of DKA was 81 and 33 days respectively. Changes in GTT were not related to weight gain and generally occurred in the first 6 weeks of treatment. Mean and median weight gains in patients with new onset DM were 7.27 and 3.64 kg, respectively.

Clozapine was compared to olanzapine in a retrospective chart review of patients treated with either drug for 4 months or more (Casey, 1999). Mean length of treatment was 3.6 years on clozapine (n=29) and 1.4 years on olanzapine (n=136). Changes in weight, BMI and FPG were measured. Six of 16 patients on clozapine (38%) with normal pre-treatment FPG developed elevations of FPG during treatment. Seven of 39 patients on olanzapine (18%) with normal pre-treatment FPG developed elevations of FPG during

treatment. Sixty-nine percent of patients on clozapine and 50% of patients on olanzapine showed weight gain of more than 7% above baseline. BMI increased from 25.53 to 29.35 (16%) in patients on clozapine and from 28.08 to 30.80 (9.7%) in patients on olanzapine. For both drugs, neither weight gain nor BMI change correlated with age, gender, dose, duration of treatment or starting weight. Glucose elevations were not correlated with weight gain.

The frequency of DM across age groups and different APs was examined using a multiple logistic regression analysis over a 4-month period and odds ratios calculated (OR; CI=95% confidence interval) (Sernyak et al., 2001). Of the 30,819 veterans studied, 12,695 received CAPs, and 18,124 received AAPs: clozapine (n=935), olanzapine (n=8,772) quetiapine (n=773), or risperidone: (n=7,944). A higher percentage of the AAP cohort compared with the CAP cohort 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 DM. By medication prescribed, risk of DM was also increased for clozapine (OR = 1.251; 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). Patients on AAPs were more likely to be female, have other psychiatric diagnoses, be African-American, not be on veteran support and have fewer hospitalizations. Some patients on AAPs also received CAPs in the same period but were only included in the AAP group for analysis (94% of patients remained on the same drug through the 4 months of study). Sample sizes were disparate and there were no data on concomitant medications.

A number of prescription claims-based studies have looked at the differences between AAPs. Claims data for 7933 patients diagnosed with psychotic disorders within health plans in the US were analyzed (Mahmoud et al., 2000). The frequency of new onset type 2 DM in untreated patients and among patients treated with risperidone, olanzapine, clozapine, high potency and low potency CAPs was compared using episodes of treatment as the basis of observation. Logistic regression models developed to compare the ORs of reporting DM based on 12 months of exposure determined the values to be 2.44 (±2.10) for olanzapine, 6.72 (±4.71) for clozapine, 1.99 (±1.95) for high potency CAPs, 3.21 (±2.27) for low potency CAPs and 0.79 (±2.39) for risperidone. Older age, observation period length and greater use of non-antipsychotic psychotropic medications were also significant predictors of DM. Although this study controlled for concomitant (non-antipsychotic) medications, patients could be on multiple APs and diabetic risk was ascribed to both drugs; only 17.2% of patients had a diagnosis of schizophrenia. Patients were assessed at different time points and the data extrapolated to 12 months. Among patients receiving clozapine, schizophrenia was the commonest diagnosis (57%) and the duration of AP treatment was the longest (9.4 ±5.5 months). Concurrent use of other APs was greater in the olanzapine group and the daily dose of olanzapine was higher than that of the other APs; dose was a predictor of DM for olanzapine only.

Another study examined a prescription claims database (PCS) identifying patients on antipsychotic monotherapy who also received prescriptions for anti-diabetic agents (Cavazzoni et al., 2001). The hazard ratios (HR; CI=95% confidence interval) calculated

using a Cox proportional hazard regression model were (3.5; 3.1-3.90) for the CAPs cohort (n=19,782) and (3.1;2.9-3.4) for the AAPs cohort (n=38,969), compared to the general PCS population. Hazard ratios for the individual APs were: quetiapine (1.7; 1.2-2.4) (n=4,186), olanzapine (3.0;2.6-3.5) (n=13,863), haloperidol (3.1;2.6-3.7) (n=8,476), clozapine (3.3;1.4-8.0) (n=277), risperidone (3.4;3.1-3.80) (n=20,633), and thioridazine (4.2;3.2-5.5) (n=3,133). There was no statistically significant difference in risk of developing DM between the atypical and conventional cohorts (HR=0.966; CI=0.8-1.1; p=0.6) or between olanzapine and risperidone cohorts; the risperidone cohort compared to the haloperidol cohort was associated with an increased risk (HR=1.2; CI=1.0-1.5; p=0.04). However, in this database there was no information with respect to diagnosis and the general population cohort was comprised of healthy non-psychotic individuals. The average duration of treatment for an AAP (except clozapine) was 90 days, and although age and gender were controlled, the mean age for the atypical cohort was 60 years and for the conventional cohort was 64 years. Thus not only were sample sizes disparate, but the data are confounded by diagnostic issues and potentially by an age and treatment duration effect.

To assess the risk of DM among patients treated with olanzapine or risperidone, two cohorts totaling 33,945 patients were identified from the Quebec Medicare (RAM-Q) database. One cohort consisted of patients who had received at least one prescription of olanzapine (n=19,153) and the other cohort consisted of patients who had received at least one prescription of risperidone but not olanzapine (n=14,792). In the olanzapine cohort 336 patients (1.8%) developed DM compared to 220 (1.5%) in the risperidone

cohort, but after correction for age and gender differences, the hazard ratio was calculated to be 1.22 or 20% (CI=1.02-1.45). After further adjusting for the duration of olanzapine exposure, the first 3 months of olanzapine treatment were associated with the highest risk of DM (91%) (HR=1.91). These differences appeared to be greater in females, where women taking olanzapine had a 31% higher risk of developing DM compared to women on risperidone. Women taking olanzapine had a 68% higher risk of developing DM compared to men on olanzapine. Diagnosis was controlled for, but as with all of the prescription claims-based studies, there were no data on baseline BMI and weight change. A re-analysis of the data applying a proportional hazards model to calculate the age- and sex-adjusted incidence ratio found that there was only a slightly higher risk of developing DM for those exposed to olanzapine (n=12,945), than for those exposed to risperidone (n=15,197) (Moisan et al., 2001).

Other studies have looked at the direct effect of APs on insulin and glucose metabolism. The effect of an oral 50g dextrose challenge on PG and insulin levels was examined in patients with schizophrenia (n=32) treated with risperidone, olanzapine or clozapine and in healthy controls (n=31) (Newcomer et al., 1999a). Although PG varied significantly across treatment groups, at baseline and at 75 min after glucose challenge, both clozapine and olanzapine patients had higher PG levels at baseline compared to controls (P=0.002 and P=0.007 respectively) and to risperidone patients (P=0.0.5 and P=00.02 respectively). At 75 min after glucose load, clozapine and olanzapine patients had higher PG levels than controls; clozapine patients also had higher insulin levels than

controls, but this was not statistically significant. Although the oral dextrose challenge was lower than the 75g used in a standard OGTT, the trends are not only consistent with most data in this area, but it is likely that the differences shown with olanzapine and clozapine would have been even greater with the larger dextrose dose. The authors further investigated the potential for different APs to influence glucose regulation independent of differences in adiposity (Newcomer et al., 1999b). Modified OGTTs were performed in schizophrenic patients (n=48) receiving clozapine, olanzapine, risperidone or CAPs, and untreated healthy controls (n=31) matched for age and adiposity. Subjects with DM were excluded. Blood samples were obtained at 0 (fasting), 15, 45, and 75 min post glucose load. Significant time x treatment group interactions for PG ($F_{(12,222)}$=4.89, $p<0.001$) and insulin ($F_{(12,171)}$=2.10, p=0.02) were found. Effects of treatment group on PG were significant at all time points, with olanzapine-treated patients having significant glucose elevations at all time points (1.0-1.5 S.D.), in comparison to controls as well as patients receiving CAPs. Clozapine-treated patients had significant glucose elevations at fasting and 75 min (1-1.5 S.D.) compared to controls and patients receiving CAPs. Risperidone-treated patients had similar elevations in fasting and post-load glucose levels, but only in comparison to healthy controls. The authors postulated that clinically significant hyperglycemia could occur during AP treatment independent of adiposity due to IR effects. In a review of AP adverse effects, a series of patients was described whose PG levels were measured before and after treatment with various APs; a statistically

significant increase in PG was observed in patients treated with olanzapine (n=39), clozapine (n=39) and haloperidol (n=41 (Wirshing, 2001). No changes were observed with risperidone or fluphenazine. These data together with other studies focusing specifically on the effects of the atypicals on glucose metabolism suggest that clozapine and olanzapine are associated with specific and early IGT associated with hyperinsulinemia.

In contrast to the previous studies, an analysis was conducted of random blood glucose data pooled from 78 clinical trials (Beasley et al., 2000). The incidences and estimated time-to-event rates (Kaplan-Meier analyses) were calculated for treatment-emergent potential impaired glucose intolerance (160mg/dl) and potential diabetes (200mg/dl) in patients without indicators of hyperglycemia at baseline, and for treatment with olanzapine (n=4,574), clozapine (=200), risperidone (n=267), haloperidol (n=888) or placebo (n=445). The estimated rates of treatment-emergent IGT or DM (from 2.7%-15.4% over 0.5 to 2 years) were higher than expected for all treatment groups and placebo. Time-to-event time was not different between olanzapine, risperidone, haloperidol or placebo, but was significantly greater with olanzapine compared to clozapine. Risk factors included age, an increase in adiposity during treatment and maximum absolute body weight. However, random PG estimation is of very limited value in terms of prediction of potential DM since it is an insensitive measure affected by many factors and shows no correlation with IGT or DM, and is thus not part of the standardized diagnostic criteria for the diagnosis of DM.

2.7.6 Clozapine

There have been case reports dating back to 1994 in the psychiatric literature linking clozapine with hyperglycemia, *de novo* DM, DKA, worsening of previously controlled DM and increased risk of gestational diabetes (Ai et al., 1998; Colli et al., 1999; Smith et al., 1999; Pierides, 1997; Peterson and Byrd, 1996: Koval et al., 1994; Maule et al., 1999; Popli et al., 1997; Kamran et al., 1994; Koren et al., 1997; Kostakoglu et al., 1996; Wirshing et al., 1998; Thompson et al., 1998; Hauptmann et al., 1999; Mohan et al., 1999; Dickson and Hogg, 1998; Waldman and Safferman, 1993, 1999; Smith et al., 1999; Wu et al., 2000). Furthermore, a number of these case reports describe resolution or improvement of DM on reduction or discontinuation of clozapine and recurrence of DM when rechallenged with the drug (Koval et al., 1994; Maule et al., 1999; Brugman et al., 2000; Wu et al., 2000). The published case reports are summarized in Table 1 and are dicussed in other reviews (Leibzeit et al., 2001, Wirshing et al., 1998; Mir & Taylor, 2001). In summary, more cases have been reported for males and non-Caucasians (African American, Afro-Caribbean, Oriental), and most, but not all patients had experienced significant weight gain. Time of onset of DM after clozapine initiation varied from 4 days to 2 years and dose of clozapine ranged from 100 mg to 900mg/day.

Table 3: Summary of case reports of clozapine-induced diabetes

Author	Concomitant Medications	Dose at time of DM onset	Age/race/sex	Obesity/Weight Change	Personal History	Family History	Time to onset of DM
Ai et al., 1998	None	300 mg	30/B/M	NR	HbA_{1C} 11%	Negative	5 months
Kamran et al., 1994	Ranitidine, benztropine	900 mg	41/B/M	NR	Negative	NR	2 months
Koval et al., 1994	Lithium, benztropine	250mg	34/B/F	NR	Negative	Type 1 DM	6 weeks
Kostakoglu et al., 1996	NR	350 mg	42/NR/M	Obese	Negative	Type 2 DM	4 weeks
Peterson & Byrd, 1996	Lithium,verapamil, bethanechol	500 mg	46/B/M	NR	Hypertension	DM (type NR)	5 weeks
Koren et al., 1997		NR	37/C/M	NR	Negative	Negative	11 weeks
Colli et al., 1999	Carbamazepine	200 mg	31/C/M	BMI=29/1 kg	Negative	Negative	3 months
Mohan et al., 1999	None	325 mg	30/B/M	NR	Negative	Negative	3 months
Hauptmann et al., 1999		NR (low dose)	57/NR/F	NR	Negative	NR	
Popli et al., 1997	Ephedrine	425 mg	32/B/M	11% over IBW/4 kg increase over 5 weeks	Negative	Type 1 & 2 DM	8 weeks
Popli et al., 1997	Risperidone (taper) Hydrochlorthiazide Lithium	450 mg	44/B/M	42% over IBW/1.4 kg increase over 5 weeks	Hypertension	Negative	5 weeks
Popli et al., 1997	Glyburide	200 mg	51/C/M	No change	Type 2 DM	NR	2 weeks
Popli et al., 1997	Lisinopril, glyburide	900 mg	51/B/M	NR/No Change	Type 2 DM Hypertension	NR	4 months
Wehring et al., 2000	Prazosin, H2 blockers,prednisone	900 mg	45/NR/M	53% over IBW, 23kg in 6 years	Negative	Negative	17 months
Wehring et al., 2000	Metoprolol, lisinopril, nitroglycerin, fludrocortisone	NR	54/NR/M	7% over IBW, 19 kg in 7 years	Hyperglycemia	Negative	4 years
Wirshing et al., 1998		150 mg	47/B/M	9% over IBW/11 kg (11%) increase over 8 weeks	IGT	Negative	2 months
Wirshing et al., 1998		400 mg	32/B/M	No obesity/26 kg (37%) increase over 18 months	Negative	Negative	18 months
Wirshing et al., 1998		100 mg	43/B/M	13% over IBW/3 kg (4%) increase over 20 weeks	Negative	Type 2 DM	6 months
Wirshing et al., 1998		200 mg	41/B/M	38% over IBW/ No weight change from baseline	Negative	Negative	5 weeks

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(Cont'd from previous page) Table 3: Summary of case reports of clozapine-induced diabetes

Author	Concomitant Medications	Dose at time of DM onset	Age/race/sex	Obesity/Weight Change	Personal History	Family History	Time to onset of DM
Thompson et al., 1998		120 mg	48/C/M	NR	NR	NR	Unclear
Smith et al., 1999		NR	40/B/M	NR	Negative	Negative	6 days
Pierides, 1997		300 mg	50/C/M	NR	NR	NR	10 days
Maule et al., 1999		400 mg	50/C/F	NR	Negative	Negative	1 month
Lu & Yu, 1997			24/O/F				1 week
Wu et al., 2000		125 mg	25/C/M	NR	NR	NR	12 months
Brugman et al., 2000	Perphenazine		40/C/M	NR	NR	NR	

NR, not reported; B, Black; C, Caucasian; O, Oriental; M, male; F, female; IBW, ideal body weight

Ethnicity is a risk factor for IR and may therefore be relevant in terms of predisposition to AP-associated DM. In a study of 23 individuals of mixed and Curacao descent on clozapine in the Netherlands, hyperglycemia was detected in 10 patients and DM in 2 patients (Ramaekers et al., 2000). In 16 patients, PG had been checked before the initiation of treatment and thus, the authors recommended routine determination of PG levels before and after treatment with clozapine particularly in mixed populations with subjects of African origin. This is especially important since this ethnic group may be more at risk of TD as for suffering more DM and obesity. Similarly, in a case of a 25-year old Chinese male who demonstrated hyperglycemia, hypertriglyceridemia and periodic paralysis repeatedly when challenged with doses of clozapine above 150 mg/day, these symptoms either disappeared on discontinuation or ameliorated with dose reduction (Wu et al., 2000). However, mental state deteriorated with dose reduction and the patient was eventually stabilized on a combination of haloperidol (20 mg/day) and clozapine (25 mg/day) with normalization of metabolic parameters. In contrast, in a 58-year old male with type 2 DM on clozapine (600 mg/day) and benperidol (30 mg/day), the PG peaks of 135- 140 mg/dl coincided with a reduction in his movement disorder (Poersch et al. 1996). Pregnancy is associated with gestational DM, and a case report is described of a 28-year old woman with a history of hyperglycemia who required oral hypoglycemics after commencing clozapine and later went on to require insulin during pregnancy; delivery was complicated by shoulder dystocia (Dickson and Hogg, 1998). This raises the issue of the likelihood of increased prevalence of gestational DM and its complications, particularly in female patients whose fertility may be restored by prolactin-sparing but possibly more diabetogenic APs.

The treatment refractory and aggressive patients in which clozapine is used may also be important. Irritability is a reported psychiatric aspect of diabetes, and a relationship between latent DM and treatment resistance as well as variation in paranoid symptom severity with glycemic control has been reported (Surridge et al., 1984). In the case of a 30-year old black male who experienced DKA on clozapine, CAPs were only effective in controlling his violent behavior after his DM was stabilized with oral hypoglycemics (Mohan et al., 1999). Other studies examining the association of DM with clozapine have looked at a direct effect on insulin action as well as indirectly through weight gain. In 45 patients with schizophrenia being treated with clozapine, 7 cases with DM and 3 cases with IFG were identified; 49% of the sample met the criteria for obesity (BMI>30) (Goldman et al. 1999). Total glucose intolerance (DM and IFG) was statistically associated with obesity, but not with age, race or family history of diabetes. In contrast, an analysis of claims data from a state Medicaid program (1990-8) of 3,638 patients with schizophrenia did not identify any significant differences in overall outcome rates for DM, hyperlipidemia or hypertension between clozapine-treated and CAP-treated groups. However, a sub-analysis of younger patients (20-34 years) did find that clozapine was significantly associated within increased rates of DM and hyperlipidemia but not hypertension.

A comparison of 63 patients treated with clozapine with 67 patients treated with CAPs (haloperidol, zuclopenthixol, fluphenazine, perphenazine) was conducted in Sweden (Hagg et al., 1998). Random PG tests were followed by an OGTT; none of the patients had evidence of DM before treatment. Of the patients treated with clozapine, 21

(33%) had hyperglycemia defined as PG>6.6mmol/L and 13 (22%) patients were classified as having DM or IGT. Of the patients treated with CAPs, 13 (19%) had hyperglycemia and 6 (10%) patients were classified as having DM or IGT. The findings were not statistically significant due to the small sample size. Subjects in the clozapine group were significantly younger, had a shorter duration of disease and had been treated for a shorter period than subjects in the control group, but the two groups did not differ with respect to body weight, BMI, or prevalence of DM in first degree relatives. Females were more often diagnosed with DM or IGT when treated with clozapine than when treated with CAPs. Although not statistically significant, the concentration of the metabolite, desmethylclozapine, was higher in patients with hyperglycemia. The influence of duration of treatment was shown in a 5-year naturalistic study of 102 outpatients with schizophrenia or schizoaffective disorder (Henderson et al., 2000). Thirty patients of 82 completing the study (36%) were diagnosed with DM. Weight gain, gender, concomitant use of valproate, and total daily dose of clozapine were not significant risk factors for developing DM. However, weight gain was characteristic of patients who developed type 1 DM. Eleven patients were excluded from the study because of either a known history of DM (n=5) or a FPG greater or equal to 140 ng/ml (n=6). Of the 5 patients with a known history, 2 were on insulin and 3 on oral hypoglycemics. Both the insulin-treated patients required an almost two-fold increase in insulin requirements, and 2 of the patients on oral agents went on to require insulin after clozapine initiation.

Age was significantly correlated with the development of DM. Although the small number of non-Caucasian patients precluded an analysis based on ethnicity, two of the African-American and two of three Hispanic patients had abnormal FPG and required treatment. The lack of dose effect is interesting and may be related to the poor correlation between dose and serum level with clozapine (serum levels of clozapine or desmethylclozapine were not measured in this study). This was further investigated in 28 patients treated with CAPs and 13 patients treated with clozapine (Melkersson, et al., 1999). It was found that FPI levels correlated positively with serum concentrations of clozapine, whereas no correlation was found between FPI and serum concentrations of perphenazine or zuclopenthixol. Correlations with clozapine were also noted insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein (IGFBP-1). The normal PG levels in the clozapine group support the theory that clozapine induces concentration-dependent IR with secondary increased insulin secretion. In addition, lower growth hormone (GH) secretion in clozapine group was detected. This impaired GH secretion together with the clozapine-induced IR was suggested to be one of the mechanisms behind weight gain during clozapine therapy; thus, clozapine may also be associated with DM indirectly through weight gain. It has also been suggested that clozapine-induced suppression of Ca^{2+}-dependent K^{+} efflux may be responsible for reduced insulin secretion by β-pancreatic islet cells, leading to hyperglycemia (Koren et al., 1997). Another study examined PG, insulin and C-peptide levels in 3 female and 3 male clozapine-treated patients (titrated to 450 mg/day from 12.5 mg/day in 6 weeks),

with negative family history of DM and who were not on any concomitant medications (Yazici et al., 1998). Clozapine increased concentrations of PG, insulin and C-peptide concentrations in this study compared to baseline at second and third assessment points when patients were on doses of 200mg /day (third week) and 450mg/day (sixth week). The authors concluded that clozapine's effect on glucose regulation was due to the development of IR.

2.7.7 Olanzapine

With olanzapine, there has been an increasing number of case reports since 1996 linking it with hyperglycemia, *de novo* DM, DKA, worsening of previously controlled DM and increased risk of gestational diabetes (Wirshing et al., 1998; Gatta et al., 1999; Ober et al., 1999; Fertig et al., 1998; Lindenmayer and Patel, 1999; Goldstein et al., 1999; Zung et al., 1999; Von Hayek et al., 1999). In addition, Eli Lilly Pharmaceuticals have 330 case reports on file relating to type 1 and type 2 DM and DKA (Eli Lilly Pharmaceuticals; personal communication). Similar to clozapine, a number of these case reports describe resolution or improvement of DM on reduction or discontinuation of olanzapine and recurrence of DM when rechallenged with the drug (Goldstein et al., 1999; Fertig et al., 1998; Bonnano et al., 2001). The published case reports are summarized in Table 2 and are dicussed in other reviews (Leibzeit et al., 2001, Wirshing et al., 1998; Mir and Taylor, 2001). Again , similar to case reports with clozapine, there were more males and most, but not all patients had experienced significant weight gain. However there were more Caucasians than non-Caucasians, but this may reflect the difference in use of olanzapine compared to clozapine.Time of onset of DM after

olanzapine initiation varied from 8 days to 2 years and dose of olanzapine ranged from 5 mg to 30mg/day. Confounding factors such as concomitant medications and smoking history were not recorded for most cases. Two of these cases were associated with a fatal outcome; the first in a 24-year old female after 15 days of olanzapine treatment (Hayek et al., 1999), and the second was in a 31-year old male re-initiated on olanzapine for a 3 week period (Meatherall and Younes, 2002).

Table 4: Summary of case reports of olanzapine-induced diabetes

Author	Concomitant medications	Dose at time of DM onset (mg/day)	Age/race/sex	Obesity/ Weight Change / BMI (kg/m^2)	Personal History	Family History	Time to DM onset
Wirshing et al., 1998		250	38/B/M	Obese, 42% over IBW 14 lbs (5%) increase over 12 weeks	Negative	Negative	3 months
Wirshing et al., 1998		25	56/C/M	Obese, 27% over IBW No weight change from baseline	Negative	Negative	3 months
Goldstein et al., 1999			42/C/F		Negative	Type 2 DM	24 weeks
Goldstein et al., 1999			40/C/F	4.5-6.8 kg increase	Negative	Negative	17 months
Goldstein et al., 1999			41/C/F	NR	Negative	Negative	20 weeks
Goldstein et al., 1999			47/C/M	13.6 kg increase	Negative	Type 2 DM	5 weeks
Goldstein et al., 1999			43/C/M	11.4 kg increase	Negative	Negative	24 weeks
Goldstein et al., 1999			39/C/M	2.7 kg decrease	Negative	Type 2 DM	14 weeks
Goldstein et al., 1999			38/C/M	No change	Negative	Type 2 DM	12 weeks
Ober et al.,1999			45/B/M	25% increase	Type 2 DM	NR	Unclear
Fertig et al., 1998			32/B/M	NR	Negative	Negative	6 weeks
Hayek et al., 1999			25/C/F	NR	Negative	NR	3 months
Hayek et al., 1999 [1]		20	24/C/NR	BMI=22.3	Negative	NR	15 days
Hayek et al., 1999	Metoprolol, benzafibrate	20	19/C/F	BMI=26 s	Borderline GTT	Negative	3 months
Lindenmayer & Patel, 1999			50/B/M	9.5 kg increase	Negative	Negative	8 months
Gatta et al., 1999			31/C/M	4 kg decrease	Negative	Negative	3 months
Bonanno et al., 2001 [2]	Mirtazapine, sodium divalproex	10	31/B/M	12 kg increase, BMI=32	Negative	DM (type unknown)	18 weeks
Bonanno et al., 2001 [3]	Sodium divalproex, propanolol	15	44/C/M	BMI=26	Negative	DM (type unknown)	4 months
Meatherall & Younes, 2001	None	20	31/NR/M	BMI=29	Negative	NR	3 weeks
Littrell et al., (in press) [4]	None	15	40/C/F	35 kg increase during pregnancy	Negative	Positive	26 weeks
Muench & Carey, 2001	Venlafaxine, sodium valproate, atorvastatin, propanolol	20	38/C/M	BMI=36.7, 14 kg increase	Negative	Negative	12 months
Bettinger et al., 2000	Fluoxetine	10	54/B/F	13 kg increase	Type 2 DM	NR	12 days
Meyer, 2001	NR	NR	28/B/M	BMI=34	NR	NR	3.5 months
Meyer, 2001	NR	NR	44/C/M	BMI=39	NR	NR	6.5 months
Meyer, 2001	NR	NR	39/C/M	BMI=36	NR	NR	19.5 months
Roefaro & Mukherjee,	Gabapentin, venlafaxine, lansoprazole, isosorbide	25	51/C/M	7% over IBW	Negative	NR	6.5 months

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(cont'd from previous page) Table 4: Summary of case reports of olanzapine-induced diabetes

Author	Concomitant medications	Dose at time of DM onset (mg/day)	Age/race/sex	Obesity/ Weight Change / BMI (kg/m^2)	Personal History	Family History	Time to DM onset
Kropp et al.,	Cloprednole	2.5	79/C/W	BMI=21	IGT	NR	6 weeks
Rigalleau et al., 2000	NR	20	55/NR/M	BMI=28 (7 kg decrease)	Negative	Type 2 DM	4 months
Rigalleau et al., 2000	NR	NR	41/NR/M	BMI=40 (4 kg decrease)	Negative	Negative	3 months
Domon & Webber	Sodium valproate, buspirone	20	15/B/M	BMI=34	Negative	Type 2 DM	12 months
Chue, (in press)	None	20	26/B/M	14 kg increase	Negative	Type 2 DM	12 months
Paizis et al., 1999			/M	No change			4 weeks

NR, not reported; B, Black; C, Caucasian; O, Oriental; M, male; F, female; IBW, ideal body weight

[1,3] Patients died

[2] Exacerbation on re-challenge despite 18 kg weight loss (BMI= 25 kg/m^2)

[4] Gestational DM

As with clozapine, there appear to be risk factors for the development of DM with olanzapine that overlap with the risk factors for IR, as evidenced primarily in the case reports data. In a study of 47 patients from 2 clinical trials investigating the efficacy of olanzapine in medication-refractory schizophrenia, 5 patients (10%) had elevations of PG from baseline, of which 3 patients (6.4%) met the criteria for DM (these 3 patients all had a personal or family history of DM) (Lindenmayer et al., 2001). A subsample data set of 34 patients had statistically higher maximum glucose values during treatment with olanzapine, although generally not in the clinically significant range (with the exception of the 5 cases identified) and unrelated to olanzapine dose (which ranged from 20 to 40 mg/day) or clinically significant weight gain (mean = 3.8 ± 9.3 kg). There was a trend for black and Hispanic patients to have a greater rise in glucose than white or Asian patients (although ethnicity was apparently determined by surname). The authors concluded that the risk of hyperglycemia with olanzapine was comparable to expected prevalence rates in US adults over 20 years of age. However, it should be noted that this study was not primarily designed to evaluate hyperglycemia with olanzapine and, thus, glucose evaluations were not necessarily fasting and concomitant medications, including lithium, were allowed.

2.7.8 Risperidone

There are overall fewer reports linking risperidone to DM. Risperidone has been reported to not exacerbate DM in one patient with pre-existing type 1 DM (Melamed, 1998). A study involving the evaluation of HbA_{1C} after 6-9 months treatment with

risperidone in a Veterans Administration Medical Center showed no significant changes except in patients with pre-existing DM (n=4), in whom there was a significant increase in HbA1c and an increase in oral hypoglycemics (Brescan, 1997). A case is reported of a white HIV-positive male on risperidone, fluoxetine and trazodone with negative family history admitted in DKA (Croarkin et al., 2000). He was eventually discharged on quetiapine and insulin. It is unlikely that the concomitant medications played a role, with the possible exception of the trazodone, but asymptomatic HIV illness may have been a factor since this has been reported in itself to result in hyperglycemia (Hardy et al., 2001). In the treatment of psychosis with risperidone in 11 geriatric patients, 2 patients were reported to have developed type 2 DM (Madhusoodanan et al., 1995). In contrast, a report on the use of risperidone in elderly patients with chronic psychosis and medical illnesses, including 3 with DM did not find that any of the patients showed any worsening of the medical problems (Sajatovic et al., 1996). Similarly, a study on the use of geriatric patients with chronic psychoses and concurrent medical illnesses including 3 with DM, found no exacerbation of DM with risperidone (Joshi & Joshi, 1996).

2.7.9 Quetiapine

There have been 2 case reports to date concerning quetiapine (Sobel et al., 1999; Procyshyn et al., 2000). In the first, a 42-year old white male with no prior history except for hypertriglyceridemia, developed new-onset DM following one month of quetiapine (200mg/day). This resolved with fluids and insulin and the discontinuation of quetiapine. Concomitant medications included lithium, gabapentin and venlafaxine. In the second, a

30-year old man of Ethiopean descent (BMI=32.3) developed DM after 16.5 weeks of treatment which responded to discontinuation of quetiapine and insulin. However, he was also receiving fluphenazine, loxapine and sodium valproate during this period. In an open label, non-randomized trial, 65 patients on clozapine monotherapy all of whom who had gained weight (mean weight gain 6.5 kg), including 13 that had developed DM, were started on quetiapine (Reinstein, et al., 1999). These patients were subsequently followed for 10 months with evaluations of weight and glucose control. The dose of clozapine was reduced during combination therapy with satisfactory control of the schizophrenia. Interestingly, metabolic status improved, as shown by a reduction in weight in all patients (0.45 kg - 18.6 kg, mean= 4.2 kg) and PG in 20%. Three of the patients eventually required no intervention for their DM. The authors concluded that the combination produced satisfactory control of the underlying psychiatric condition, and that quetiapine allowed lowering of the clozapine dose and improvement in weight and glucose control. However, some individual changes in weight were very small and the effect of reduction in clozapine and consequent lowering of serum levels cannot be discounted.

2.7.10 Ziprasidone

Data concerning ziprasidone are limited, but random PG levels in clinical trials were not different from those observed with risperidone, haloperidol or placebo (FDA Briefing Document). In a double-blind trial, 269 acute in-patients were randomized to ziprasidone or olanzapine for 6 weeks (Glick et al., 2000). Weight, FI, HOMA-IR, TCHOL and TGs all increased with olanzapine compared to ziprasidone. Three 6 week randomized open label trials evaluated outcome in stable patients with schizophrenia

following a switch from CAPs (n=93), olanzapine (n=88) or risperidone (n=41) to ziprasidone (40-160mg/day) (Daniel et al., 2000). A significant improvement in TCHOL and TGs was noted in patients switched from olanzapine and risperidone ($P \leq 0.05$). For patients switched from olanzapine, a significant reduction in weight (mean change=1.6 kg) and BMI was observed ($P \leq 0.05$). A similar open label study of 37 patients found significant reduction in TCHOL ($P < 0.001$) and TG levels ($P=0.018$), independent of changes in BMI (Kingsbury et al., 2001). Thus far in mostly clinical trial populations, it would appear that ziprasidone has minimal clinical effects on glucose regulation.

2.7.11 Effects of antipsychotics on weight gain

Treatment with many psychotropic drugs is associated with weight gain and the development of drug-induced obesity (Baptista et al., 1995). Furthermore, it has been estimated that for every 1Kg increase in body weight above normal, the risk of DM increases by 4.5% (Kawachi, 1999; Colditz et al., 1995). The risk of DM associated with weight gain between the ages of 40 and 60 is greater with females (relative risk 1.7), compared to men (relative risk 1.4) (Holbrook et al., 1989). The principal health risks relate to cardiovascular disease and hypertension, and even modest increases in weight (4-10%) are strongly correlated with cardiovascular disease and non-fatal MI in men (Rosengren et al., 1999). Furthermore, smoking significantly compounded the mortality risk in this group. With respect to the APs, there are a number of recent reviews of this area indicating that of the CAPs, the phenothiazines (particularly thioridazine) are associated with the greatest weight gain (Allison et al., 1999; Wirshing et al., 1999). With respect to the AAPs, olanzapine and clozapine are associated with the greatest weight

gain. However, many studies of short duration do not necessarily capture these data since the rate or trajectory of weight gain and time of reaching a steady weight or weight plateau are very different between the drugs, e.g., 48 months with clozapine (Henderson et al., 2000). Thus, early assessments of weight gain may be misleading since the full extent of weight change may not be seen until after many months of treatment. The mechanisms of weight gain are as complex and manifold as the mechanisms postulated to be related to DM, and although there is some overlap, particularly at the level of IR and leptin, the data also suggest some different and contradictory mechanisms. Dysregulation of metabolism, satiety and activity levels acting through central (hypothalamic) and peripheral (gastrointestinal) mechanisms have been proposed. Atypical antipsychotics are antagonistic at 5-HT_{2A} and 5-HT_{2C} receptors, which have been shown to increase food intake (Tecott et al., 1995); agonists at these receptors such as fenfluramine and mCPP promote weight loss. Antagonism of histamine H_1 receptors increases food intake, and weight gain is prominent with anti-histaminic drugs such as the TCAs, clozapine and olanzapine; all of these agents are also associated with increased DM liability. The relationships of the histaminergic system are complex, but it appears that histamine stimulates noradrenaline release, and thus plays a role in the neuroregulation of not only prolactin (Willems et al, 2000), but also of intranuclear oytocin (Bealer & Crowley, 1999), which has been shown to be important in the etiology of drug-induced DM (Uvnas-Moberg et al., 1994).

Leptin is a hormone synthesized by adipocytes and signals the size of the adipose depot to the brain in a complex feedback fashion. Serum levels are correlated with BMI and percent body fat as well as fasting and overeating prior to alterations in fat mass or bodyweight. An increase in serum leptin levels has been reported in clozapine-treated patients, with even low doses of clozapine leading to a doubling of leptin levels in 8 out of 12 patients in the first 2 weeks of treatment (maximal relative increase over baseline was 536%) (Bromel et al., 1998). Another study found leptin levels to be elevated in 26% of patients on fluphenazine or zuclopenthixol, 21% of patients on clozapine and 57% of patients on olanzapine (Kraus et al., 1999). Furthermore, olanzapine-treated patients had significantly higher insulin levels despite no difference in BMI, suggestive of a direct effect on insulin secretion. The normally existing gender difference in leptin levels (females having higher circulating levels than males) was not found in the olanzapine or clozapine groups, which was felt by the authors to reflect alteration of leptin regulation.

2.7.12 Effects of antipsychotics on lipids

These changes in lipid metabolism seen with IR have been noted with respect to the APs and in general with those APs most commonly associated with weight gain and DM. Clozapine has been associated with an increase in TG levels, with reversal on switching to risperidone (Ghaeli et al., 1996). Marked elevation of TG has been reported in male patients on clozapine compared to male patients on haloperidol; the difference was much less marked in female patients (Gaulin et al., 1999). It was hypothesized that this was due to a direct effect on lipoprotein lipase. Of note, hyperinsulinemia also downregulates this enzyme which is involved in LDL-C metabolism and leads to an

increase in TG. A 6 week study comparing risperidone to clozapine following treatment with fluphenazine in 20 patients found TCHOL, TGs and PG were all significantly increased with clozapine compared to baseline fluphenazine (Su et al., 1996). Clozapine's effects on TCHOL and PG were also significant compared to risperidone. Significant weight gain was noted in both clozapine responders and non-responders and risperidone responders.

The data suggestive of differences between AAPs was further suggested in the preliminary analysis of the results of the metabolic profile of 44 patients (Bouchard et al., 2001). The authors found 32% of the olanzapine-treated patients were characterized by the development of an atherogenic triad (hyperinsulinemia, elevated apolipoprotein-B and LDL-C) compared to 5% of risperidone-treated patients occurring in 18 months (± 8 months). Thirteen cases of severe hypertriglyceridemia (>600mg/dl) associated with olanzapine and quetiapine treatment, including 5 cases with serum TG levels >1000mg/dl (4 olanzapine and 1 quetiapine) were reported (Meyer, 2001). Severe hypertriglyceridemia (>600mg/dl) occurred within 8 months of commencing therapy in 6 of the 11 olanzapine cases and in both quetiapine cases. Three olanzapine patients developed new onset DM after 3.5, 6.5 and 19.5 months respectively. The mean weight gain for all 11 patients was 6.49%. No statistical correlation was found between percent weight gain and percent TG increase. Given the short time frame of study, it is apparent that there are early and significant changes in glucose and lipid metabolism with certain APs, which may also be independent of weight.

It appears that there are differences in the potential for AAPs to adversely affect lipid metabolism, with links suggested through changes in leptin and IR. A number of the studies reported, in fact, allowed concomitant use of lipid lowering agents, which may have had an influence on lowering the incidence of DM when co- prescribed with certain APs. However, it has also been suggested that alterations in serum lipids may impact on the plasma distribution of APs and have some relevance in their therapeutic actions, particularly for clozapine and olanzapine (Procyshyn et al., 2001; Osser et al., 1999).

2.8 Summary

In summary, it is clear that many psychotropic drugs have a significant impact both directly and indirectly upon different facets of DM, which in turn may have either a positive or negative effect on the course and outcome of both the psychiatric disorder and DM. Traditionally, psychiatric disorders and physical diseases have been perceived as separate both in terms of etiology and treatment, yet it appears that this division is an artificial one, and in fact these illnesses overlap to a much greater degree than commonly thought.

The data presented in this review highlight not only the necessity for further research but also the potential benefit of collaboration between medical specialists to provide optimal care for patients suffering chronic, debilitating physical and psychiatric disease through a current, comprehensive, scientific and holistic approach.

Chapter 3

Subjects and Methods

3.1 Study design

The original sample from a pilot study (Prior et al., 1998) was expanded to include a larger number of patients treated with clozapine, olanzapine, risperidone, quetiapine or CAPs (oral/depot) as monotherapy for a minimum of 3 months. Patients on combination AP therapy were excluded. The CAPs included haloperidol, fluphenazine, flupenthixol, and zuclopenthixol. Any other concomitant drugs were reviewed and discontinued during the period of investigation if it was deemed that there was a likely significant effect on metabolic indices.

Fasting plasma insulin, FPG and fasting lipids (TCHOL, TG, HDL-C and LDL-C) were obtained. A full OGTT was performed (2hr PG after 75g oral glucose load in fasted state), but if the FPG was above 7.8 mmol/L then the OGTT was not completed since the criterion for DM was met. The homeostasis model assessment index of insulin resistance (HOMA-IR) was calculated {HOMA-IR = [FPG x FPI] ÷ 22.5). The TCHOL/HDL-C ratio was calculated. Blood pressure, weight and height were measured, and BMI was calculated (BMI= kg/m^2). Uric acid levels were obtained. In accordance with the standard protocol for fasting glucose and lipid studies, patients were not permitted to eat, chew, smoke, or swallow anything except water for 12 hours (no alcohol for 24 hours) before investigations.

3.2 Sample

The majority of patients were selected from the writer's outpatient program. In addition, patients on AP monotherapy were identified through the Alberta Hospital Edmonton pharmacy database, and their attending physician was contacted. Demographic

details, treatment information, laboratory investigations, height and weight measurements are generally captured routinely as part of the hospital standard patient assessment. Clinicians were asked to provide the information anonymously for analysis and to complete any investigations if these data were missing.

The data collection questionnaire is shown in Table 5. Only in- and outpatients (18-65 yrs) with a stable DSM-IV diagnosis of chronic schizophrenia were investigated. Patients with concomitant serious physical illness, specifically HIV infection, were excluded since this is in itself associated with hyperglycemia (Hardy et al., 2001). Details of age, duration of illness, ethnicity, family history of DM, smoking status and concomitant medications as well as previous AP and reasons for change to current AP, were obtained. If weight gain or any evidence of DM were determined to be the reason for the switch to the current AP, these patients were excluded.

Initials	
Date of Birth	
Family History of Diabetes	
Ethnic Status	
Psychiatric Diagnosis	
Duration of Schizophrenia	
Sex	
Smoker	
Current antipsychotic and start date Concomitant medications	
Previous antipsychotic medication (most recent) and reason for change to current	
Height	

Table 5: Metabolic assessment data collection questionnaire (part 1)

	Target Values	Date	Date	Date	Date	Date
Weight						
Blood Pressure	130/80					
Fasting Insulin	<15 mu/L					
Fasting Glucose	<6.1 mmol/L					
GTT (2hr)	<7.8 mmol/L					
Uric Acid	<295 µmol/L					
Cholesterol	<4.6 mmol/L					
Triglyceride	<2.0 mmol/L					
HDL-C	>0.9 mmol/L					
LDL-C	<2.5 mmol/L					
Chol/HDL	<4					
BMI (Kg/m^2)	<24.9					
HOMA-IR (Insulin x Glucose/22.5)						

Table 5: Metabolic assessment data collection questionnaire (part 2)

3.3 Data collection

Blood samples, except for plasma insulin, were analyzed by Dynacare Kasper Medical Laboratory Services using a Bayer Advia 1650 Clinical Chemistry Analyzer. Plasma insulin was measured by Capital Health Laboratory Services.

a) Analysis of Triglycerides

TGs are converted to glycerol and free fatty acids by lipoprotein lipase. The glycerol is then converted to glycerol-3-phosphate by glycerol kinase in the presence of glycerol-3-phosphate-oxidase to form hydrogen peroxide. A colored complex is formed from hydrogen peroxide, 4-aminophenazone and 4-chlorophenol under the catalytic influence of peroxidase. The absorbance of the complex is measured as an endpoint reaction at 505 nm.

b) Analysis of Cholesterol

The cholesterol esters are hydrolyzed by cholesterol esterase to cholesterol and free fatty acids. The cholesterol is converted to cholesterol-3-one by cholesterol oxidase in the presence of oxygen to form hydrogen peroxide. A colored complex is formed from hydrogen peroxide, 4-aminophenazone, and phenol under the catalytic influence of peroxidase. The absorbance of the complex is measured as an endpoint reaction at 505 nm.

c) Analysis of HDL-Cholesterol

The direct HDL method is based on the procedure of Suguichi and measures HDL-C in serum, without prior separation, using polyethylene glycol (PEG) modified enzymes and sulfated α-cyclodextrin. Reagent 1 (sulfated α-cyclodextrin buffer) is preincubated with the sample leading to the formation of water soluble complexes with LDL, VLDL

and chylomicrons. These complexes are resistant to PEG modified enzymes. Reagent 2 which contains 4-Morpholinepropanesulfonic acid buffer, PEG cholesterol peroxidase and PEG cholesterol esterase is then added. The concentration of HDL-C is determined enzymatically by the addition of cholesterol esterase and cholesterol oxidase, which have been coupled with PEG to the amino groups. The intensity of quinone imine dye produced is proportional to the cholesterol concentration, which is measured at 596 nm.

d) Analysis of LDL-Cholesterol

The LDL-C concentration was calculated by Friedwald's formula where LDL-C (S.I. units) = {TCHOL – [HDL-C + (TG x 0.46)]}, but if TGs were above 4.52 mmol/L then a valid LDL-C could not be determined.

e) Analysis of Glucose

The Glucose Hexokinase II enzymatic method involves a two-component reagent and is based on the method by Stein utilizing hexokinase and glucose-6-phosphate dehydrogenase (G6PDH) enzymes. Sample is added to Reagent 1, which contains buffered adenosine triphosphate (ATP), sodium azide (NaN_3) and nicotinamide adenine dinucleotide (NAD). Absorbance readings of the sample in Reagent 1 are taken and are used to correct for interfering substances in the sample. The Reagent 2 mix contains Reagent 1 in addition to G6PDH and hexokinase (both from microbial sources). The glucose is phosphorylated by ATP in the presence of hexokinase, and the glucose-6-phosphate that forms is oxidized in the presence of G6PDH, causing the reduction of NAD to nicotinamide adenine dinucleotide reduced (NADH). The absorbance of NADH is measured as an endpoint reaction at 340 nm. The difference between the absorbance in Reagent 1 and Reagent 2 is proportional to the glucose concentration.

f) Analysis of Uric Acid

The uric acid method is based on the Fossati enzymatic reaction using uricase with a Trinder-like endpoint. Reagent 1 contains N-ethyl-N-(2-Hydroxy-3-sulfopropyl)-3-methylaniline (TOOS) and NaN_3. Reagent 2 contains 4-Aminophenazone, peroxidase, uricase and NaN_3. The uric acid is converted by uricase to allantoin and hydrogen peroxide. A colored complex is formed from hydrogen peroxide, 4-aminophenazone, and TOOS under the catalytic influence of peroxidase. The absorbance of the complex is measured as an endpoint reaction at 545 nm.

g) Analysis of Insulin

Insulin was measured on the Roche Eleosys 2010 instrument. In this assay, patient samples are incubated with a biotinylated TSH antibody and a ruthenium-labeled TSH antibody. The resulting immune complexes are separated by addition of strepavidan-coated paramagnetic microparticles and passage over a magnet. Tripropylamine is then added and the chemiluminescent reaction electrically stimulated to produce light. The amount of light produced is proportional to the concentration of insulin in the sample.

3.4 Statistical methods

An interim analysis was conducted on the available data based on a total of 85 evaluable patients. Given the very small numbers of quetiapine, ziprasidone, and amisulpiride monotherapy patients (n=8), these were not included in this analysis. Although the data were not completely normal in distribution, it was hypothesized that data from a larger sample size would approach normal, thus an analysis of variance (ANOVA) was completed (after initial non-parametric analysis). The small sample sizes and moderate degree of skew in some groups decreased the sensitivity of the ANOVA,

but trends were evident in the present data, with statistical significance being found for 2 measures. It is likely that statistically significant group differences may be observed with larger sample sizes and further research with larger sample sizes is ongoing. Medians were calculated as the measure of central tendency for the data sets given the large variation. The variances of the samples (s^2), the variances of the means (VM), and the standard error of the means (SEM) are displayed in Table 7. The percentage of patients within each treatment group with values above the threshold values was also determined.

The ANOVA was done on all 4 cohorts (clozapine, olanzapine, risperidone, CAPs) for each of the various parameters (FPG, TGs, etc.). The ANOVA showed statistically significant differences between cohorts for FPG ($P < 0.05$) and TGs ($P < 0.01$), and statistical significance was almost reached for HOMA-IR ($P = 0.0566$). To further distinguish which cohorts were significantly statistically different from each other, the Tukey-Kramer formula for multiple comparisons test was administered. This test is used when the numbers in each cohort are different. Thus, a Tukey-Kramer test was performed on HOMA-IR, since this variable had almost reached statistical significance. After applying the formula, a statistically significant difference was found between clozapine and CAPs ($P < 0.05$). Some cohort distributions were observed to be slightly skewed, however the ANOVA is moderately robust to non-normal data (although data that are not normally distributed violate one of the assumptions of ANOVA). The data were not log transformed because the data were not sufficiently non-normal, and thus applying log transformation would not have changed the results. In addition, with more patients, the data set may well approach a normal distribution and the power of the analysis will be increased. If the skew continues to be present after the additional data have been obtained, a log transformation will be applied.

3.5 Ethics approval

Permission to conduct this study was given by Dr. Pierre Flor-Henry, Chair of the Research Ethics Committee and Medical Director, Adult Psychiatry Program of Alberta Hospital, Edmonton.

Chapter 4

Results

4.1 Patient demographics

Patient demographics are summarized in Table 6. The cohort sizes were comparable with the exception of the clozapine cohort which was approximately double that of the other cohorts. Mean age was 40.6 years, mean duration of illness was 14.8 years, and mean duration of antipsychotic therapy at the time of testing was 3.3 years. The olanzapine cohort had the lowest percentage of males (67%) and the fewest smokers (44%). The clozapine and olanzapine cohorts had the highest proportion of patients with a positive family history of DM (32% and 33% respectively) compared to the risperidone (13%) and CAP (18%) cohorts. The risperidone cohort had the lowest percentage of Caucasians (69%).

4.2 Diabetic indices

The results of the effects of the antipsychotics on fasting insulin are summarized in Figure 1. Despite an apparent difference between AAP and CAP cohorts, statistical significance was not demonstrated given the very large variance in this data set. Olanzapine was associated with the highest insulin values while FPG values were lowest in the CAPs cohort (Figure 2). For FPG, the only statistically significant difference was found between the clozapine and CAPs cohorts ($P < 0.05$). Application of the Tukey Kramer formula to calculations of HOMA-IR demonstrated a statistically significant difference between clozapine and CAPs cohorts ($P < 0.05$). The greatest percentages of patients with hyperinsulinemia (Figure 3) and DM (Figure 4) were those treated with clozapine.

4.3 Obesity indices

All patients were obese, as defined by a BMI > 24.9, with olanzapine patients

showing the highest BMIs (Figure 5). Similarly, the greatest percentage of patients with obesity was in the olanzapine cohort (Figure 6).

4.4 Lipid indices

Total cholesterol (Figure 7) and TGs (Figure 8) were highest in the clozapine cohort. For TGs, the only statistically significant difference was found between the clozapine and CAPs cohorts ($P < 0.01$). The percentage of patients with hyperlipidemia was also greatest in the clozapine cohort (Figure 9).

4.5 Uric acid

The clozapine cohort had the highest uric acid levels (Figure 10), but no statistically significant differences were found.

Antipsychotic	Clozapine	Olanzapine	Risperidone	Conventional
Number of patients	34	18	16	17
Mean age (yrs)	41.8	41.5	38.9	40.0
Male	26	12	12	13
Mean duration of treatment (yrs)	3.5	3.0	2.2	4.6
Mean duration of illness (yrs)	14	17.5	17.7	10.0
Smokers	20	8	10	10
Family history of DM	11	6	2	3
Caucasian	29	14	11	13
Black	2	1	3	1
Asian	2	2	1	2
East Indian	0	1	1	1
Native	1	0	0	0

Table 6: Patient demographics

		BMI			FPI			FPG		
	n	s^2	VM	SEM	s^2	VM	SEM	s^2	VM	SEM
Clozapine	34	27.78	0.817	0.904	79.99	2.353	1.534	6.58	0.194	0.440
Olanzapine	18	30.86	1.714	1.309	57.41	3.189	1.786	10.82	0.601	0.775
Risperidone	16	13.26	0.829	0.910	56.28	3.512	1.875	0.19	0.119	0.109
Conventional	17	26.39	1.552	1.246	27.10	1.594	1.263	2.36	0.139	0.373

		TCHOL			TGs		
	n	s^2	VM	SEM	s^2	VM	SEM
Clozapine	34	1.90	0.059	0.236	19.70	0.579	0.761
Olanzapine	18	1.58	0.088	0.296	12.97	0.721	0.849
Risperidone	16	1.02	0.064	0.252	7.01	0.438	0.662
Conventional	17	0.84	0.049	0.222	0.51	0.03	0.173

Table 7: Variances of the samples (s^2), variances of the means (VM), and standard errors of the mean (SEM) for BMI, fasting plasma glucose (FPG), fasting plasma insulin (FPI), total cholesterol (TCHOL), and triglycerides (TGs).

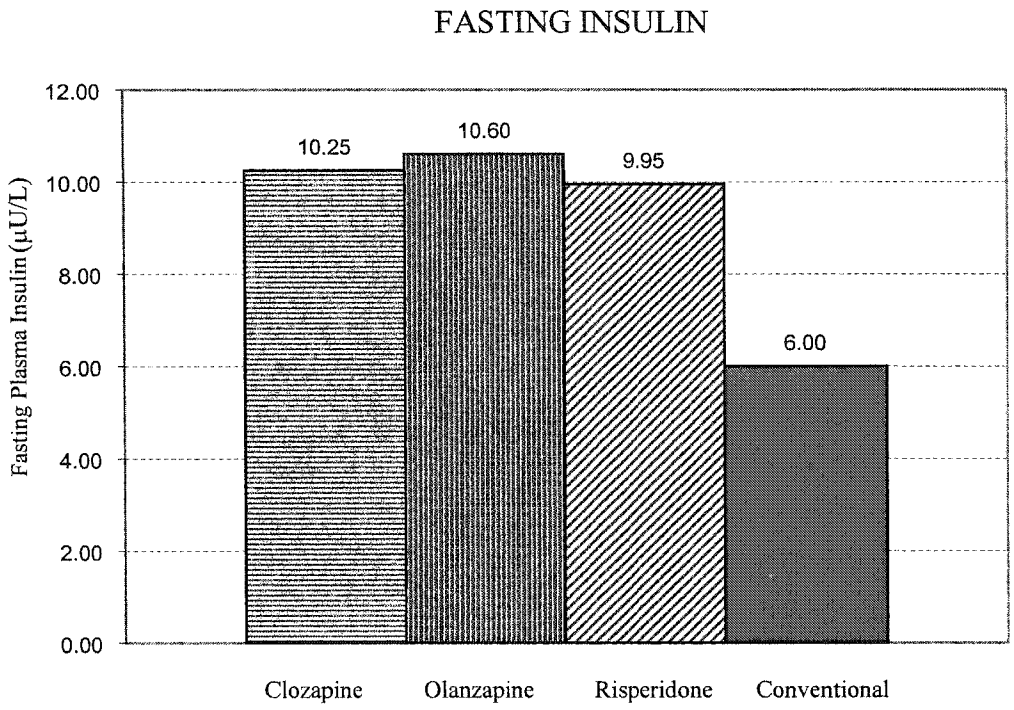
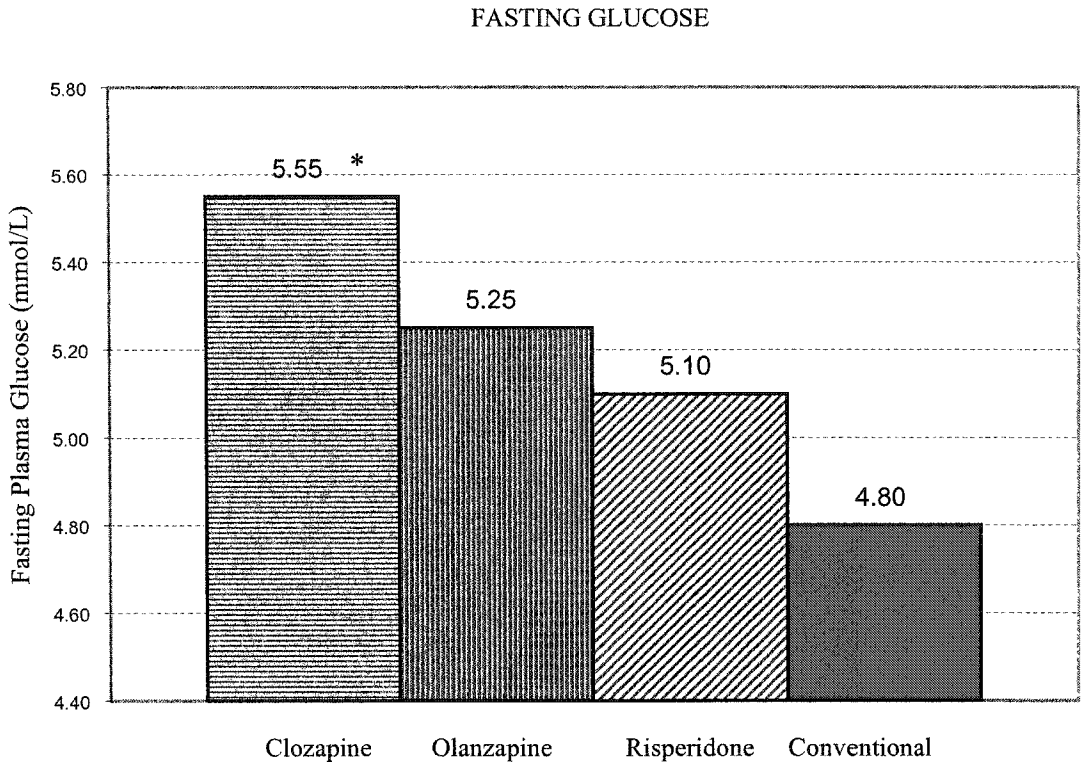


Figure 1: Fasting plasma insulin levels in patients treated with APs (median values).



* statistically significant compared to conventional, $P < 0.05$

Figure 2: Fasting plasma glucose in patients on APs (median values).

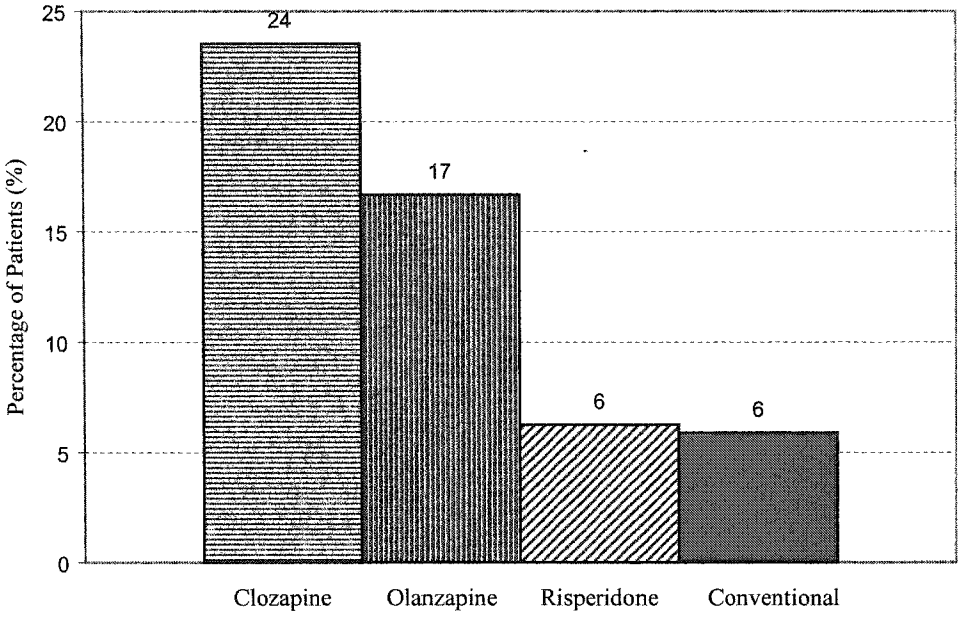


Figure 3: Percentage of patients on APs with hyperinsulinemia.

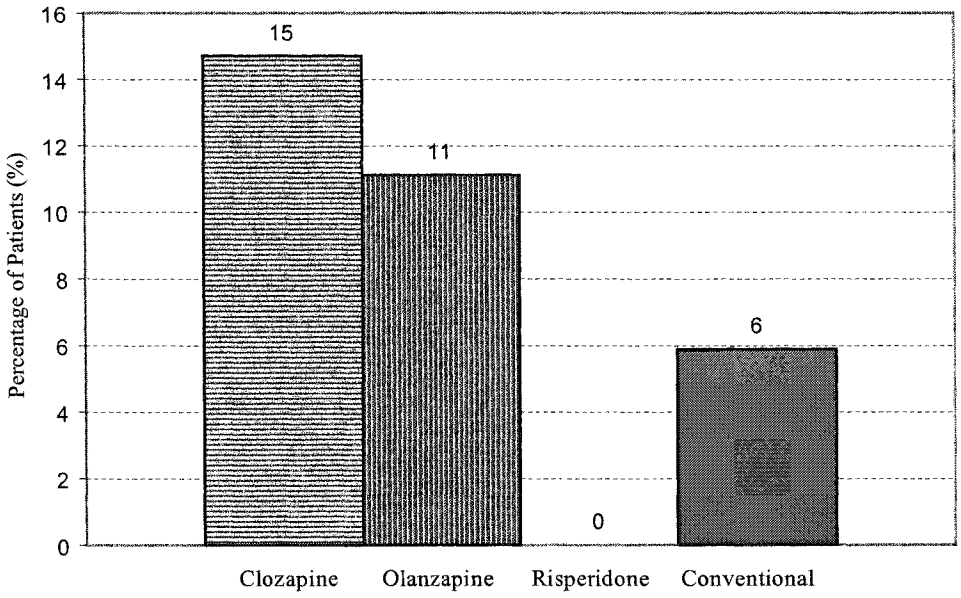


Figure 4: Percentage of patients on APs with diabetes.

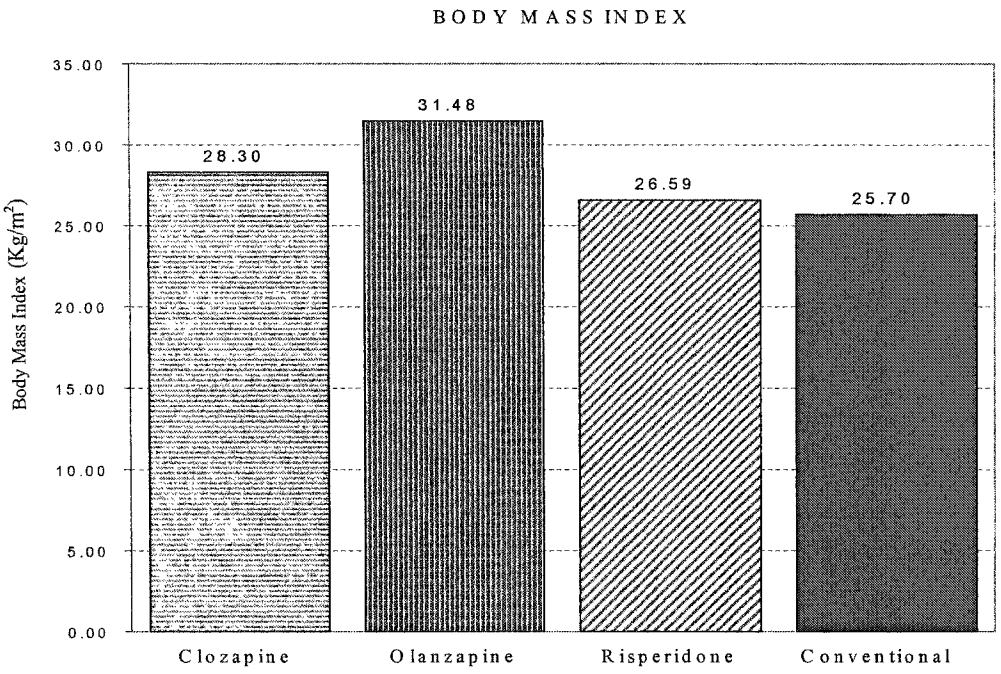


Figure 5: BMI of patients on APs (median values).

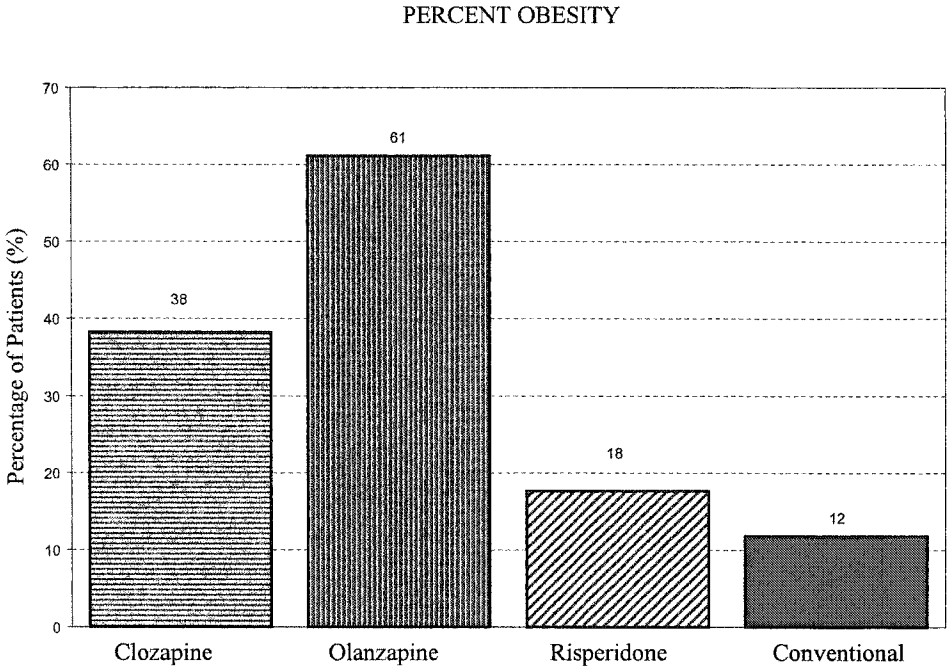


Figure 6: Percentage of patients on APs with obesity (BMI > 29.9).

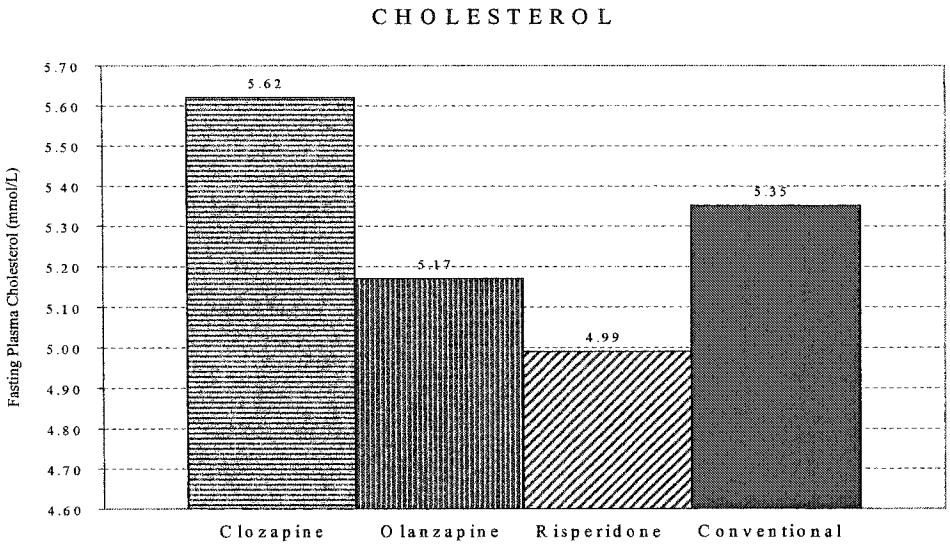
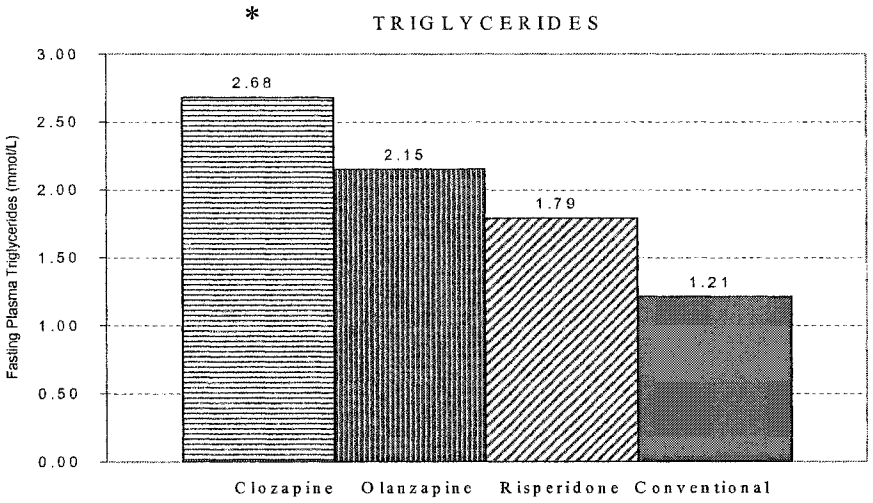


Figure 7: Cholesterol values of patients on APs (median values).



*statistically significant compared to CAPs, $P < 0.01$

Figure 8: Triglyceride values of patients on APs (median values).

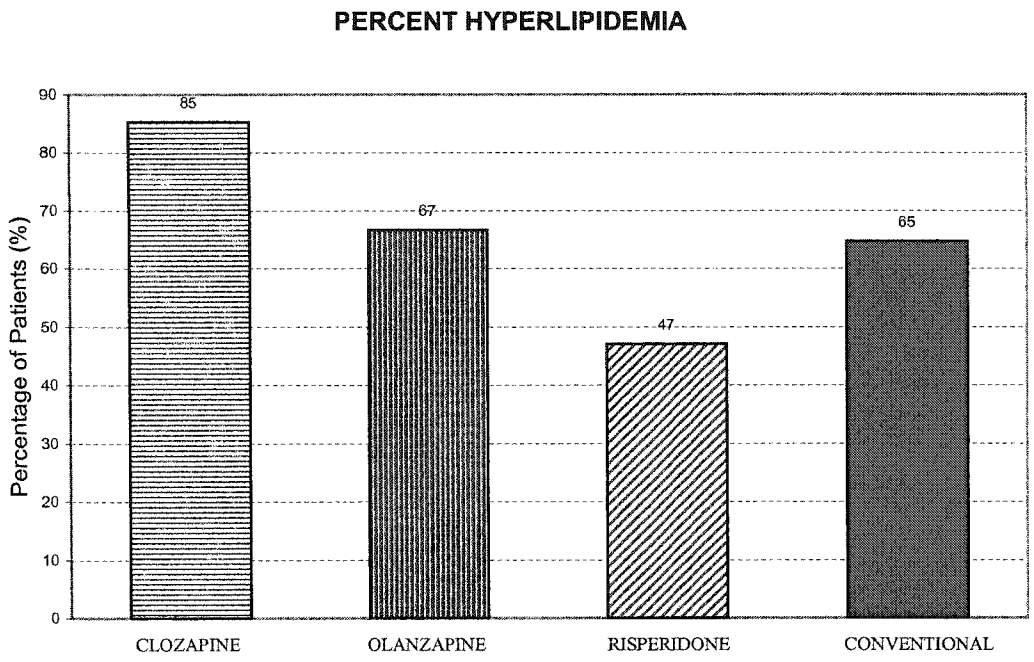


Figure 9: Percentage of patients on APs with hyperlipidemia.

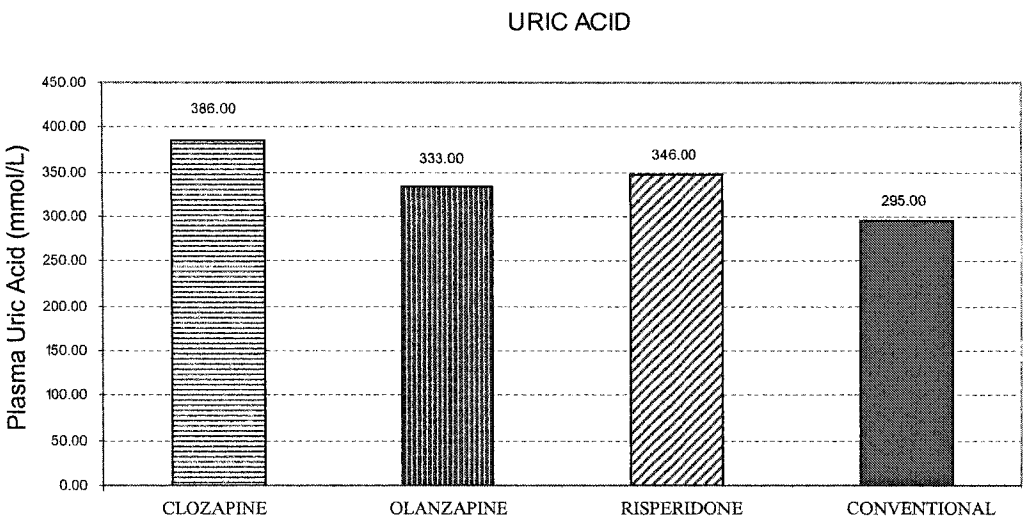


Figure 10: Uric acid values of patients on APs (median values).

Chapter 5

Discussion

5.1 Preface to discussion

Patients with schizophrenia are at greater risk of developing DM and cardiovascular morbidity and mortality than the normal population (Curkendall et al., 2001). Increasing experience with AAPs suggests that there is a hierarchy of diabetic association (Leibzeit et al., 2001; Mir & Taylor, 2001). The mechanisms are complex and multifactorial, but likely include the effects of the receptor profile antagonism of the different APs influencing IR - a metabolic syndrome characterized by hyperinsulinemia, IFG and IGT, central obesity, hyperuricemia, hypertension and hyperlipidemia.

In comparison to non-diabetics with lipid disorders, DM type 2 patients tend to have higher levels of TG and VLDL and lower levels of HDL-C, but TCHOL and LDL-C levels are similar in both groups (Amsterdam et al., 2001). Hyperlipidemia is generally defined by the following values; TCHOL >5.2 mmol/L, TG >2.3 mmol/L, LDL -C >3.4 mmol/L, HDL-C <0.9 mmol/L and TCHOL/HDL >9. However, overall cardiovascular risk is influenced by age, presence of DM, lipid values, systolic BP, and smoking status. Thus, target lipid values stratified by level of risk are shown in Table 7, and it is currently suggested that in the presence of DM, the recommended values are as follows; LDL -C <2.5 mmol/L, TG <2 mmol/L and TCHOL/HDL <4. Any patient over the age of 30 years with DM or clinical evidence of atheroclerosis, and any patient who has already suffered a cardiovascular event, is automatically in the very high-risk category. Improved glycemic control can ameliorate TG levels.

Level of Risk	Target Values		
	LDL-C Level (mmol/L)	Total Cholesterol HDL-C ratio	Triglyceride level, (mmol/L)
Very high (history of cardiovascular disease or diabetes)	< 2.5	< 4	< 2.0
High	< 3.0	< 5	< 2.0
Moderate	< 4.0	< 6	< 2.0
Low	< 5.0	< 7	< 3.0

Table 8: Target lipid values by level of risk

There is also a hierarchy of weight gain liability with AAPs (Allison et al., 2001; Wirshing et al., 1998). The mechanisms are again complex but leptin (which also mediates insulin sensitivity) likely plays a role. Studies have shown increases in serum leptin levels in 57% of olanzapine-treated patients occurring within 12 weeks (Kraus et al., 1999; Melkersson et al., 2000) as well as a doubling of leptin levels with clozapine within 2 weeks (Bromel et al., 1998). Previous studies in this area, including a pilot study by the author (Prior et al., 1998) have not always adequately controlled for duration of current therapy, reason for switch to current AP, age, or concomitant medications. If the previous AP was changed because of weight gain, this biases against the new drug.

Additional confounds include psychiatric diagnosis and acuity, smoking status, personal or family history of DM, obesity (BMI > 30.0), inactivity, ethnicity and gender. Not only is schizophrenia more likely to be associated with DM than other psychiatric disorders, but also acute schizophrenia is associated with greater impairment of GTT than chronic schizophrenia. Furthermore, the risk of AP-associated DM overlaps with predisposing factors for IR, including smoking, physical inactivity, older age, family history of DM and increased BMI. Accurate fasting blood work is very difficult to obtain in this population and random glucose data, particularly extrapolated from clinical trials, is of limited value (Beasley et al., 2001; Allison et al., 2001).

5.2 Effect of antipsychotics on diabetic indices

The higher levels of FPI and FPG with olanzapine and clozapine compared to risperidone or CAPs in this study are consistent with data from other studies suggesting that these 2 AAPs are associated with greater IR than other AAPs (Melkersson et al., 1999; Cohn et al., 2001; Henderson et al., 2000).

Fasting plasma insulin values were numerically greatest in the olanzapine cohort, but the percentage of patients with hyperinsulinemia was highest in the clozapine cohort. Although 60% of olanzapine-treated patients were obese in the study (mean BMI= 31.46), changes in IR have been shown to be independent of BMI (Newcomer et al., 1999; Melson et al., 1999), and to occur soon after treatment is initiated, i.e. often before there has been significant weight change. This has been shown to occur within 6 weeks of olanzapine treatment compared to ziprasidone (Fryburg et al., 2000; Glick et al., 2001), with the risk of DM being highest in the first 3 months of treatment for olanzapine compared to risperidone (Caro et al., 2000). HOMA-IR was statistically significantly different only for clozapine compared to the CAPs. The lack of any other significant differences probably reflects the effect of the compensatory hyperinsulinemia, which maintains a normal FPG until homeostasis can no longer be sustained. Thus, median FPG values were within the normal range (below 6.1 mmol/L for all cohorts). Although FPG determinations are used in the diagnosis of DM, recent studies have shown that FPG can be normal in 37% of diabetics and 85% of IGT individuals diagnosed by OGTT (Wolever, 2001). Olanzapine was also associated with more hypoinsulinemia than the other AAPs, but since hypoinsulinemia was also noted with the CAPs, the significance of this finding is unknown. It is unlikely to reflect the stage in the evolution of DM associated with pancreatic β-cell failure in end stage type 2 DM, which can precede the development of type 1 DM.

The prevalence of DM as determined by an OGTT response of > 11.1 mmol/L, ranged from 15% for patients on clozapine, 12% for patients on olanzapine, to 6% for patients on CAPs. Although there were no patients on risperidone with DM according to

OGTT values, there were numerically more risperidone patients with IGT as defined by OGTT responses of > 7.8 and < 11.1 mmol/L, than for the other treatment groups. This is more difficult to explain, and may be related to the fact that the risperidone cohort contained the largest percentage of non-Caucasians. Thus, it would be important to determine if this finding is still present with further study and larger sample size. Most studies based on prescription claims data (Moisan et al., 2001; Mahmoud et al., 2000; Caro et al., 2000), chart review data (Wilson et al., 1999; Sernyak et al., 2001; Hagg et al., 1998; Casey et al., 2001), or naturalistic data (Henderson et al., 2000) for patients with a diagnosis of schizophrenia, consistently report the highest prevalences and incidences of new onset type 2 DM in olanzapine- and clozapine-treated patients. In contrast, the prevalence and incidence data from the same studies with risperidone and high potency CAPs, are very close to the base rate for type 2 DM in populations of patients with schizophrenia.

If anything, the findings of the present study underestimate the incidence of IR and DM since patients that had been switched to their current AP because of significant weight gain or IR were excluded. Thus, patients who did not show these changes were more likely to have been maintained on a particular therapy. Clozapine-treated patients, however, were likely to have continued with clozapine even with evidence of metabolic dysregulation presumably because of their treatment refractory status (a trial of clozapine generally requires a history of failure of response to other APs). Similarly, many of the patients on CAPs were likely receiving depot neuroleptics because of a history of non-compliance with oral AP therapy, and would therefore be maintained on depot. Hence the longest duration of therapy (4.6 years) was seen in this group. Furthermore, this is one of

the few studies that applied a rigorous and current diagnostic criterion i.e., only patients with a stable DSM-IV diagnosis of schizophrenia were enrolled. The chronicity of the sample is also reflected in the duration of illness (mean = 14.8 years).

5.3 Effect of antipsychotics on lipids

Other markers of IR, including hypertriglyceridemia and hypercholesterolemia were found, and are consistent with other studies reporting greater hypertriglyceridemia with olanzapine and clozapine compared to risperidone or CAPs (Osser et al., 1999; Meyer, 2001; Bouchard et al., 2001; Gaulin et al., 1999; Ghaeli et al., 1996). Clozapine was associated with the greatest increases in TGs and TCHOL serum values, as well as the highest percentage of patients with hyperlipidemia.

5.4 Effect of antipsychotics on weight

Both the highest percentage of obese patients (defined as BMI = 30.0 – 34.9) and the greatest BMIs were seen in the olanzapine cohort, although patients in all treatment groups were overweight (defined as BMI = 25.0-29.9); the patients on CAPS had the lowest values of all with a median BMI of 25.7. This is consistent with the literature showing weight gain to be greatest with olanzapine and clozapine of the AAPs (Allison et al., 1999; Wirshing et al., 1999). Since patients whose treatment had been switched because of weight gain were excluded, the weight at the time of the study likely reflects weight directly attributable to their current AP, and duration of treatment with their current AP (overall mean for all cohorts= 3.3 years).

5.5 Effect of antipsychotics on uric acid

Uric acid levels were noted to be highest with clozapine, but levels with risperidone were greater than with olanzapine or CAPs. This may be explained by the

fact that although hyperuricemia is associated with IR, it is also significantly influenced by gender and heritability factors.

5.6 Mechanisms of antipsychotic-associated metabolic dysregulation

Olanzapine and clozapine share similarities of both structure and receptor antagonism thus, it is likely that these properties contribute to their similar effects on glucose, body mass and lipid regulation. Olanzapine [2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine] demonstrates the following receptor binding affinities *in vitro* (K_i) ; serotonin 5-HT_{2A} (1.5 nM), 5-HT_{2C} (4.1 nM), 5-HT_{1D} (150 nM), 5-HT_{1A} (610 nM), dopamine D_2 (20 nM), muscarinic $M_{1\text{-}5}$ (36 nM), histamine H_1 (0.1 nM), adrenergic-α_2 (280 nM) and adrenergic-α_1 (44 nM) (Richelson and Souder, 2000). Clozapine [8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine] demonstrates the following receptor binding affinities *in vitro* (K_i) ; 5-HT_{2A} (2.6 nM), 5-HT_{2C} (4.8 nM), 5-HT_{1D} (130 nM), 5-HT_{1A} (160 nM), dopamine D_2 (210 nM), muscarinic $M_{1\text{-}5}$ (36 nM), histamine H_1 (3.1 nM), adrenergic-α_2 (280 nM) and adrenergic-α_1 (44 nM) (Richelson and Souder, 2000). Clozapine shares a comparable receptor binding affinity with olanzapine for 5-HT_{2A} receptors, but it is also strongly anti-muscarinic, (except at the M_4 receptor, where it acts as a partial agonist), and it is less anti-histaminic than olanzapine. At dopamine receptors, clozapine demonstrates greater D_1/D_4 antagonism than D_2/D_3 antagonism.

The effects of APs on neurotransmitter receptors that in turn impact upon glucose and lipid metabolism, both directly and indirectly, are complex and often contradictory. Nonetheless, it is hypothesized that APs possessing primarily a profile of selective and strong antagonism at D_2/D_3, and secondarily antagonism at 5-HT_{2A}, 5-HT_{1A} and α_2

receptors, may be less likely to be associated with these metabolic effects (Uvnas-Moberg et al., 1994; Chaouloff et al., 1990a). Thus, APs such as haloperidol compared to chlorpromazine of the CAPs, and risperidone compared to clozapine of the AAPs, appear much less likely to be implicated in glucose and lipid metabolic dysregulation when confounding factors are adequately controlled for.

The effects of APs on glucose metabolism may be mediated at a cellular level through the expression of specific glucose transport (GLUT) proteins (Dwyer et al., 1999). Clozapine has been shown to increase GLUT1 and GLUT3 protein expression while haloperidol decreased the expression of both. Histamine H_1 antagonism is associated with weight gain, and histamine influences prolactin and oxytocin through noradrenergic mechanisms (Willems et al, 2000; Bealer & Crowley, 1999); olanzapine and clozapine are amongst the most anti-histaminic of the AAPs. Furthermore, given leptin's role in mediating insulin sensitivity and the relationship of IR to the aetiology of AP-associated weight gain and DM, it is possible that olanzapine and clozapine may also adversely influence glucose and body mass metabolism via leptin and cytokines, including tumour necrosis factor-α, although much work needs to be done in this area. Although other hormones such as prolactin have been postulated to impact upon IR, under physiological conditions prolactin does not appear to play an important role in glucose regulation. Thus, high potency CAPs such as haloperidol, and AAPs such as risperidone that cause hyperprolactinemia (being strong and selective dopamine D_2 antagonists), are less frequently associated with DM than prolactin sparing (lower potency) APs.

Chapter 6

Summary and Conclusion

6.1 Summary

The major findings of this study are summarized as follows (in order of decreasing values).

1. Prevalence of diabetes mellitus: clozapine > olanzapine > conventional antipsychotics > risperidone.
2. Higher fasting plasma glucose: clozapine > olanzapine > risperidone > conventional antipsychotics.
3. Higher fasting serum insulin: olanzapine > clozapine > risperidone > conventional antipsychotics.
4. Higher total cholesterol: clozapine > conventional antipsychotics > olanzapine > risperidone.
5. Higher triglycerides: clozapine > olanzapine > risperidone > conventional antipsychotics.
6. Greater BMI: olanzapine > clozapine > risperidone > conventional antipsychotics.
7. Higher uric acid: clozapine > risperidone > olanzapine > conventional antipsychotics.

Although most of the above findings were suggestive of trends, statistical significances were shown between clozapine and CAPs, for FPG, TGs and HOMA-IR.

6.2 Conclusions

Schizophrenics are at greater risk of cardiovascular morbidity and mortality, as well as for DM, than the general population and these risks are compounded by the use of certain APs. In this study, after attempting to control for confounding factors, clozapine

and olanzapine were associated with the highest prevalence of DM, the highest values of the indices of IR such as FPG and FPI, as well as the highest values of hyperlipidemia such as TGs. Olanzapine-treated patients were also the most obese and had the highest BMIs. However, further evaluable subjects are needed to increase the statistical power since the differences demonstrated between the APs thus far are small. At this point, the data are suggestive of trends, but statistically significant differences were not shown, except for clozapine compared to CAPs for FPI, TGs and HOMA-IR. Clozapine-treated patients also showed the highest plasma uric acid levels versus CAPs. Although hyperuricemia is associated with IR, a correlation has not been previously shown with AAPs.

Psychiatrists must be more proactive in the management of AP side effects, particularly DM, weight gain and dyslipidemia. This requires careful drug selection and use particularly in patients with potential risk factors. This differential liability may be particularly significant in the presence of pre-existing risk factors for IR. Because IR is associated with a cluster of significant cardiovascular risk factors consisting of obesity, hypertension, type 2 DM and particularly dyslipidemia, it is recommended that all patients receiving APs (specifically those with identified risk factors and treated with the more diabetogenic drugs) should have weight, BP, FPG and lipids monitored at baseline and regularly. Consideration should also be given to performing a GTT since a FPG may not be sufficiently sensitive to detect early IGT. Appropriate management strategies should be initiated early if metabolic dysregulation occurs, given the serious long-term health implications. In view of the complexity of the management of the medical

consequences of AP side effects, regular health screens and shared care with primary care and specialist physicians should be encouraged. Psychiatrists should discuss serious potential health risk side effects with patients prior to initiating treatment where possible and provide adequate psychoeducation concerning management of side effects, smoking, etc.

Finally, almost every compound used as a psychotropic appears to have some action either positive or negative on glycemic thresholds. Given that many patients with schizophrenia are receiving multiple medications, it becomes ever more important to be aware of the potential interactions that may contribute to an increased risk of DM as well as weight gain and dyslipidemia.

Chapter 7

Areas of Future Study

7.1 Areas of future study

The conclusions of this study were limited by sample size, particularly with respect to the quetiapine cohort; it would be valuable to continue to expand the sample in order to allow appropriate statistical analysis to validate the conclusions and to explore other areas such as the effect of gender.

A dose-dependent effect has been suggested in a number of studies, and it would be interesting to investigate this further with serum level monitoring of the different APs. The CAPs cohort included both high and low potency APs; with a larger sample it would be possible to investigate the effect of chemical class and possibly potency on metabolic parameters.

Leptin levels could not be measured by local laboratory services, but this investigation together with cortisol, IGF-1, and IGFBP-1 would represent a more complete analysis of potential metabolic disturbances, ultimately with a view to clearly demonstrating the diabetic risk of each AP. Whilst the OGTT is the most sensitive method of assessing glucose metabolism in practical clinical terms, IVGTT and FSIVGTT with Minimal Model analysis are even more sensitive measures of insulin secretion and action, but much more difficult to practicably utilize in the population studied. Similarly, hyperglycemic and euglycemic clamps are the gold standard in elucidating insulin metabolism, but are only available in specialized centers. Although BMI was calculated for each patient, waist circumference is a more sensitive, but difficult to obtain, measure of IR. Nonetheless, waist circumference and BP have not been systematically tracked in this population.

Finally, studies looking at the effects of pharmacological interventions such as early treatment with anti-diabetic drugs of different classes and modes of action, including metformin, rosiglitazone and acarbose, may hold clinical promise in delaying or preventing progression towards DM, particularly where patients have to continue with a psychotropic drug that is suspected of exacerbating or causing DM.

References

Agbayewa MO. Effects of lithium carbonate therapy on fasting blood sugar. Psychiatr J Univ Ottawa 1982;7:147-148.

Agbayewa MO. Glycosylated hemoglobin (risk of diabetes mellitus) in lithium therapy. Psychiatr J Univ Ottawa 1986;11:153-155.

Ai D, Roper T, Riley JA. Diabetic ketoacidosis and clozapine. Postgrad Med J 1998;74:493-494.

Albareda M, Udina C, Escartin A, Corcoy R. Seizures in a diabetic patient on monoamine oxidase inhibitors. Am J Emerg Med 1999;17:107-108.

Aldrich CK. Glucose tolerance in disturbed schizophrenic patients. AMA Arch Neurol & Psychiat 1948;60:569-576.

Aleyassine H, Gardiner RJ. Dual action of antidepressant drugs (MAO inhibitors) on insulin release. Endocrinology 1975;96:702-710.

Aleyassine H, Lee SH. Inhibition of insulin release by substrates and inhibitors of monoamine oxidase. Am J Physiol 1972;222:565-569.

Allison DB, Cavazzoni P, Beasley CM, et al. Random blood glucose levels in patients with schizophrenia treated with typical and atypical antipsychotic agents: an analysis of data from double-blind, randomized, controlled clinical trials. Presented at the International Congress on Schizophrenia Research, Apr 28th - May 2nd, 2001, Whistler, British Columbia.

Allison DB, Mentore J, Moonseong H, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686-1696.

Amdisen A. Diabetes mellitus as a side effect of treatment with tricyclic neuroleptics. Acta Psychiatrica Scand. 1964;40:411-414.

Ammon HPT, Orci L, Steinke J. Effect of chlorpromazine (CPZ) on insulin release in vivo and in vitro in the rat, J Pharmacol Exp Ther 1973;187:423-429.

Ammon HPT, Steinke J. Apparent biphasic effect of chlorpromazine (CPZ) on insulin release from isolated rat pancreatic islets. Diabetes 1971;15:345.

Amsterdam EA, Gianakos DG, Wayne Weart C. Lipid abnormalities in a patient with diabetes. Patient Care 2001;15:14-15.

Andersson DEH, Rojdmark H. Effect of verapamil on blood glucose and serum insulin in patients with hyper- and hypothyroidism. Acta Medica Scandinavica 1980;208:375-379.

Arnesson GA. Phenothiazine derivatives and glucose metabolism. J Neuropsychiatry 1964;5:181-198.

Aronson SM, Aronson BE. Intracranial vascular lesions in patients with diabetes mellitus. J Neuropathol Exp Neurol 1973;32:183-196.

Aruna, Paulose AP. Chlorpromazine induced diabetes mellitus. J Assoc Physicians India 1995;43:146.

Averbuch-Heller L. Ben-Hur T. Reches A. Valproate encephalopathy and hypocarnitinaemia in diabetic patients. J Neurol1994;1:567-9.

Azam H, Newton RW, Morris AD, Thompson CJ. Hyperosmolar nonketotic coma precipitated by lithium-induced nephrogenic diabetes insipidus. Postgrad Med J 1998;74:34-46.

Bagdy G, Kadogeras T. Stimulation of 5-HT_{1A} and 5-HT_2/5-HT_{1C} receptors induce oxytocin release in the male rat. Brain Res 1993;611:330-332.

Balter AM. Glucose tolerance curves in neuropsychiatric patients. Diabetes 1961;10:100-104.

Balzan M, Cacciotiolo JM. Neuroleptic malignant syndrome presenting as hyperosmolar non-ketotic diabetic coma. Br J Psychiatry 1992;161:257-258.

Baptista T, Teneud L, Contreras Q, et al. Lithium and body weight gain. Pharmacopsychiat 1995;28:35-44.

Baudrie V, Chaouloff F. Repeated treatment with the 5-HT1A receptor agonist, ipsaperone, does not affect 8-OH-DPAT- and stress-induced increases in plasma adrenaline levels in the rat. Eur J Pharmacol 1991;198:1129-135.

Bealer SL, Crowley WR. Neurotransmitter interaction in release of intranuclear oxytocin in magnocellular nuclei of the hypothalamus. Ann N Y Acad Sci 1999;897:182-191.

Beasley C, Berg P, Danaberg K, et al. Treatment-emergent potential impaired glucose tolerance and potential diabetes with olanzapine compared to other antipsychotic agents and placebo. Presented at the 56th Annual Convention of the Society of Biological Psychiatry, May 3rd- 5th, 2001, New Orleans, LA.

Bech P, Raabaek Olsen L, Jarlov N, et al. A case of sequential anti-stress medication in a patient with major depression resistant to amine-reuptake inhibitors. Acta Psychiatr Scand 1999;100:76-78.

Berent I, Carabeth J, Cordero M, et al. Pancreatitis associated with risperidone treatment. Am J Psychiatry 1997;154:130-131.

Berken GH, Weinstein DO, Stern WC. Weight gain: a side effect of tricyclic antidepressants. J Affect Disord 1984;7:133.

Bettinger TL, Mendelson SC, Dorson PG, Crismon ML. Olanzapine-induced glucose dysregulation. Ann Pharmacother 2000;34:865-7.

Bhide M, Tiwari N, Balwani J. Effect of chlorpromazine on peripheral utilization of glucose. Arch Int Pharmacodyn 1965;156:166-171.

Bieder J, Choisel G, Choisel-Hodicq D, Tournon JM. Diabetes in a psychiatric environment. Ann Med Psychol 1972;2:409-419.

Bina KG, Cincotta AH. Dopaminergic agonists normalize elevated hypothalamic neuropeptide Y and corticotrophin-releasing hormone, body weight gain, and hyperglycemia in ob/ob mice. Neuroendocrinology 2000;71:68-71.

Bonaccorsi A, Garatlini S, Jori A. Studies on hyperglycemia induced by chlorpromazine in rats. Br J Pharmacol 1964;23:93-100.

Bonanno DG, Davydov L, Botts S. Olanzapine-induced diabetes mellitus. Ann Pharmacotherap 2001;35:563-565.

Bonora E, Kiechl S, Willeit J et al. Prevalence of insulin resistance in metabolic disorders. The Bruneck Study. Diabetes 1998;47:1643-1649.

Bonora E, Targher G, Alberiche M, et al. Effect of chronic treatment with lacidipine or lisinopril on intracellular partitioning of glucose metabolism in type 2 diabetes mellitus. J Clin Endocrinol Metab1999 ;84:1544-1550.

Bouchard RH, Demers M-F, Simoneau I, et al. Atypical antipsychotics and cardiovascular risk in schizophrenic patients. J Clin Psychopharmacol 2001; 21;110-111.

Braceland FJ, Meduna LJ, Vaichulis JA. Delayed action of insulin in schizophrenia. Am J Psychiatry 1945;102:108-110.

Brambilla F, Guastalla A, Guerrini A, et al. Glucose-insulin metabolism in chronic schizophrenia. Dis Nerv Syst 1976;37(2):98-103.

Brambilla F, Guastalla A, Guerrini A, Riggi F, Rovere C, Zanoboni A, Zanoboni-Muciacci W. Glucose-independent metabolism in chronic schizophrenia. Progr Brain Res1975;42:373-374.

Brescan DW, Ramirez LF. Risperidone and glucose tolerance. Presented at the 150th Annual Meeting of the American Psychiaric Association, May 17th-22nd , 2001, San Diego, California, USA.

Bressler R, Johson D. New pharmacological approaches to therapy of NIDDM. Diabetes Care 1992;15:792-805.

Bressler R, Vargas-Cordon M, Lebovitz HE. Tranylcypromine: a potent insulin secretagogue and hypoglycemic agent. Diabetes 1968;17:617-624.

Breum L, Bjerre U, Bak JF, et al. Long-term effects of fluoxetine on glycemic control in obese patients with non insulin dependent diabetes mellitus or glucose intolerance: influence on muscle glycemic insulin receptor kinase activity. Metabolism 1995;44:1570-1576.

Breum L, Bjerre U, Bak JF, et al. Long-term effects of fluoxetine on glycemic control in obese patients with non-insulin-dependent diabetes mellitus or glucose intolerance: influence on muscle glycogen synthase and insulin receptor kinase activity. Metab Clin Exp1995;44(12):1570-1576.

Bromel T, Blum WF, Ziegler A, et al. Serum leptin levels increase rapidly after initiation of clozapine therapy. Mol Psychiatry 1998;3:76-80.

Brugman NJ, Cohen D, de Vries RH. Diabetes mellitus after treatment with clozapine. Ned Tijdschr Geneeskd 2000;144:437-9.

Bruno G, Barbero G, Vuolo A, et al. A population-based prevalence survey of known diabetes mellitus in Northern Italy based upon multiple independent sources of ascertainment. Diabetologica 1992;35:851-856.

Buijus RM. Vasopressin and oxytocin: their role in neuro-transmission. Pharmacol Ther 1983;22:127-141.

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

Buschiazzo HO, Mordujovich de Buschiazzo, Hernandez RE, Rodriguez RR. Preventive action of tranylcypromine on alloxan diabetes in rats. Diabetes 1967;16:810-2.

Cabezas-Cerrato J, Garcia-Estevez DA, Araujo D, Iglesias M. Insulin sensitivity, glucose effectiveness, and beta-cell function in obese males with essential hypertension: investigation of the effects of treatment with a calcium channel blocker (diltiazem) or an angiotensin-converting enzyme inhibitor (quinapril). Metab Clin Exp1997;46(2):173-178.

Canadian Phamacists Association. Compendium of Pharmaceuticals and Specialities 2002. 37th edition. Published by Canadian Pharmacists' Association. Ottawa, Ontario, Canada.

Canestro de Vasini E, Mordujovich de Buschiazzp, Buschiazzo HO. Chemical interaction between monoamine oxidase inhibitors and alloxan. Acta Physiol Lat Am 1971;21:137-140.

Carlson A, Hillarp M. Uptake of phenyl and indole alkylamines by the storage granules of the adrenal medulla in vitro. Med Exp 1961;5:122-124.

Carlsson S, Persson P, Alvarsson M et al. Weight history, glucose intolerance and insulin levels in middle-aged Swedish men. Am J Epidemiol 1998;148:539-545.

Carney RM, Freedland KE, Lustman PJ, Griffith LS. Depression and coronary disease in diabetic patients: a 10-year follow up. Psychosom Med 1994;56:149.

Caro J, Ward A, Levington C, et al. The risk of developing diabetes in users of atypical antipsychotics. Presented at 3rd Ann Eur Congr Int Soc Pharmacoeconomic Outcomes Res, Nov 5th-7th , 2000, Antwerp, Belgium.

Carroll BJ. Neuroendocrine Function in Manic Illness. Edited by Shopsin B. New York, Raven Press, 1979, pp 163-176.

Casey DE et al. Prevalence of diabetes in schizophrenia patients treated with antipsychotics. Presented at the 152nd Ann Meet Am Psychiatric Assocn, May 5th -10th, 2001, New Orleans, LA.

Casey DE. Haloperidol and clozapine effects on glucose, insulin and extrapyramidal syndrome in nonhuman primates. Neuropsychopharmacology 1994;10:P58-186.

Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. Schizophr Res 1999;35:S61-S66.

Casey DE. Weight gain and glucose metabolism with atypical antipsychotics. Presented at the 38th Ann Meet Am College Neuropsychopharmacology, Dec 12th - 16th, 1999, Acapulco, Mexico.

Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 1999;156:1417-1420.

Cavazzoni P, Baker RW, Kwong K, et al. A pharmacoepidemiological study of diabetes mellitus and antipsychotic treatment in the United States. Presented at the 41st Meet New Clinical Drug Evaluation Unit, May 28th -31st, 2001, Phoenix, AZ.

Champeyroux J, Moinade S, Marcheix J-C, et al. Diabete sucre et lithium. Nouv Presse Med 1978;7:2969.

Chan JC. Cockram CS. Critchley JA. Drug-induced disorders of glucose metabolism. Mechanisms and management. Drug Safety 1996;15:135-57.

Chan JCN, Cockram CS. Drug-induced disturbances of carbohydrate metabolism. Adverse Drug React Toxicol Rev 1991;10:1-29.

Chaouloff F, Baudrie V, Laude D. Evidence that 5-HT_{1A} receptors are involved in the adrenline-releasing effects of 8-OH-DPAT in the conscious rat. Arch Pharmacol 1990b;341:381-384.

Chaouloff F, Baudrie V, Laude D. Evidence that the 5-HT_{1A} receptor agonists buspirone and ipsapirone activate adrenaline release in the conscious rat. Eur J Pharmacol 1990c;77:107-110.

Chaouloff F, Baudrie V, Laude D. Ganglionic transmission is a prerequisite for the adrenaline-releasing and hyperglycemic effects of 8-OH-DPAT. Eur J Pharmacol 1990d;185:11-18.

Chaouloff F, Baudrie V. Effects of the 5-HT_{1C} / 5-HT_2 receptor agonists DOI and alpha-methyl-5-HT on plasma glucose and insulin levels in the rat. Eur J Pharmacol 1990a;187s:435-443.

Chaouloff F, Jeanrenaud B. 5-HT_{1A} and α_2-adrenergic receptors mediate the hyperglycemic and hypoinsulinemic effects of 8-hydroxy-2-(di-n-propylamino)tetralin in the conscious rat. J Pharmacol Exp Ther 1987;243:1159-1166.

Charactan FB, Bartlett NG. The effect of chlorpromazine (Largactil) on glucose tolerance. J Ment Sci 1955;101:351-353.

Christy NP, Longson D, Horwitz WA, et al. Inhibitory effect of chlorpromazine upon the adrenal cortical response to insulin hypoglycemia in man. J Clin Invest 1957;36:543-549.

Clissiounis N. Effect of adrenergic drugs on morphone-induced hyperglycemia. Life Sci 1979;25:391-394.

Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic antidepressants. Am J Med 2000;108(1):2-8.

Cohn TA, Remington G, Lieter L, Kameh H. Antipsychotic medication and insulin resistance. Presented at the 151st Ann Meet Am Psychiatric Assocn, May 5th-10th , 2001, New Orleans, LA.

Colditz GA, Willett WC, Rotnitzky A et al. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481-486.

Colli A, Cocciolo M, Francobandiera F, Rogantin F, Cattalini N. Diabetic ketoacidosis associated with clozapine treatment. Diabetes Care 1999;22:176-177.

Connolly VM. Gallagher A. Kesson CM. A study of fluoxetine in obese elderly patients with type 2 diabetes. Diabet Med 1995; 12:416-8.

Cookson JC, Silverstone T, Williams S, Besser GM. Plasma cortisol levels in mania: associated clinical ratings and changes during treatment with haloperidol. Br J Psychiatry 1985;146:498-502.

Cooper AJ, Ashcroft G. Potentiation of insulin hypoglycemia by MAOI antidepressant drugs. Lancet 1966;1:407-409.

Cooper AJ, Keddie KMG. Hypotensive collapse and hypoglycemia after mebanazine, a monoamine oxidase inhibitor. Lancet 1964;1:1133-1135.

Cooperberg AA, Eidhow S. Hemolytic anemia, jaundice and diabetes mellitus following chlorpromazine therapy. Can Med Assoc J 1956;75:746-749.

Corry DB. Tuck ML. Glucose and insulin metabolism in hypertension. Am J Nephrol 1996;16:223-36.

Coudore F, Besson A, Shrivastava R, et al. Comparison of amitriptyline metabolism in hepatocytes from streptozocin-induced diabetic rats and from non-diabetic rats. Cell Biol Toxicol 1997;13:131-7.

Cowie CC, Eberhart MS. Diabetes 1996 vital statistics. American Diabetes Association 1996: 13-20.

Craig J, Abu-Saleh M, Smith B, et al. Diabetes mellitus in patients on lithium. Lancet 1977;2:1028.

Croarkin PE, Jacobs KM, Bain BK. Diabetic ketoacidosis associated with risperidone treatment. Psychosomatics 2000;41:369-370.

Curkendall S, Mo J, Jones J, Glasser D. Increased cardiovascular disease in patients with schizophrenia. Presented at the 151st Ann Meet Am Psychiatric Association, May 5th-10th, 2001, New Orleans, LA.

Dagli AJ. Severe hyperglycemia following ingestion of chlorpromazine. J Assoc Physicians India 1984;32:762-763.

Daubresse JC, Kolanowski, Krzentowski G, et al. Usefulness of fluoxetine in obese non-insulin-dependent diabetics: a multicenter study. Obesity Res 1996;4:391-6.

De Boer C, Gaete HP. Neuroleptic malignant syndrome and diabetic keto-acidosis. Br J Psychiatr 1992;161:856-8.

Deeg MA, Lipkin EW. Hypoglycemia associated with the use of fluoxetine. West J Med 1996;164:262.

DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173-194.

Derot M, Roux E, Herauld G. Lithium et troubles de la glycoregulation. J Annu Diabetol Hotel Dieu 1078;27:295-306.

Dickson RA, Hogg L. Pregnancy of a treatment treated with clozapine. Psychiatr Services 1998;49:1081-1083.

Dupont RM, Jernigan TL, Butters N, et al. Subcortical abnormalities detected in bipolar affective disorder using magnetic resonance imaging. Arch Gen Psychiatry 1990;47:55-59.

Dwyer DS, Pinkofsky HB, Liu Y, Bradley RJ. Antipsychotic drugs affect glucose uptake and the expression of glucose transporters in PC12 cells. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:69-80.

Dynes JB. Diabetes in schizophrenia and diabetes in nonpsychotic medical patients. Dis Nerv Syst 1969:341-344.

Efron HY, Balter AM. Relationship of phenothiazine intake and psychiatric diagnosis to glucose level and tolerance. J Nerv Ment Dis 1966;142:555-561.

Erle G, Basso M, Federspil G, et al. Effect of chlorpromazine on blood glucose and plasma insulin in man. Eur J Clin Pharmacol 1977; 11:15-18.

Faas S, Trucco M. The genes influencing the susceptibility to IDDM in humans. J Endocrinol Invest 1994;17:477-495.

Fava M. Weight gain and antidepressants. J Clin Psychiatry 2000;23:90-97.

Federspil G, Casara D, Stauffacher W. Chlorpromazine in the treatment of endogenous organic hyperinsulinism. Diabetologica 1974;10:189-191.

Feldman JM. Inhibition of pancreatic islet monoamine oxidase by adrenergic antagonists and ethanol. Endocrine Research Communications 1975;2;503-520.

Fernandez Lopez MI, Sanchez Esteban J, Jiminez Bello, Meseguer Zaragoza A. Suggestive episodes of hypoglycemia related to fluoxetine. Aten Primaria 1996;18:581.

Ferner RE. Drug-induced diabetes. Bailliere's Clin Endocrinol Metab 1992;6:849-865.

Fernstrom MH, Krowinskui RL, Kupfer DJ. Appetite and food preferences in depression: effects of imipramine treatment. Biol Psychiatry 1987;22:529-539.

Ferrero E, Marioni G. Influenza della nialamide sul metabolismo glucidio del vecchio. Giornale de Gerontologia 1964;12:1047-1055.

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

Finney GOH. Juvenile onset diabetes and schizophrenia? Lancet 1989;2:1214-1215.

Foss MC, Paula FJ, Paccola GM, Piccinato CE. Peripheral glucose metabolism in human hyperprolactinemia. Clin Endocrinol 1995;43:721-726.

Frank GR, Navon RE. Growth failure associated with the use of high dose prozac (fluoxetine hydrochloride) in a patient with type 1 diabetes mellitus. J Pediatr Endocrinol Metab 1999;12:467-9.

Frankenburg FR, Kando J. Eosinophilia, clozapine and pancreatitis. Lancet 1992;340:251.

Freeman H, Almadjan F. Carbohydrate and lymphoid studies in schizophrenia. Am J Psychiatry 1950;106:660-667.

Freeman H, Zabarenko RN. Relation of changes in carbohydrate metabolism to psychotic states. AMA Arch Neurol & Psychiat 1949;61:569-576.

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

Fryburg DA, O'Sullivan RL, Siu C, et al. Insulin resistance in olanzapine and ziprasidone –treated subjects; interim results of a double-blind controlled six-week trial. Presented at 37th Ann Meet Am College Neuropsychopharmacol, Dec 10th-14th, 2000, San Juan, Puerto Rico.

Furman BL, Wilson GA. Further studies on the effects of 5-hydroxytrytophan on plasma glucose and insulin in the mouse. Diabetologica. 1980;19:386-390.

Furman BL. The hypoglycemic effect of 5-hydroxytrytophan. Br J Pharmacol 1974;50:575-580.

Gade GN, Hofeldt FD, Treece GL. Diabetic neuropathic cachexia. Beneficial response to combination therapy with amitriptyline and fluphenazine. JAMA 1980;243:1160-1161.

Ganguli R. Weight gain associated with antipsychotic drugs. J Clin Psychiatry 1999;60:20-24.

Ganzini L, Casey DE, Hoffman WF, Heintz R. Tardive dyskinesia and diabetes mellitus. Psychopharmacol Bull 1992;28:281-6.

Ganzini L, Heintz R, Hoffman WF, Casey DE. The prevalence of tardive dyskinesia in neuroleptic-treated diabetes controlled study. Arch Gen Psychiatr 1991;48:259-63.

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

Gatti G, Crema F, Attardo-Parrinello G, et al. Serum protein binding of phenytoin and valproic acid in insulin-dependent diabetes mellitus. Ther Drug Monitor 1987; 9:389-91.

Gaulin BD, Markowitz JS, Caley CF et al. Clozapine-associated elevation in serum triglycerides. Am J Psychiatry 1999;156:1270-2.

Gelenberg AJ. Weight gain, diabetes, and related adverse effects of antipsychotics. Biological Therapies in Psychiatry 1999;22:41-44.

Gerich JE, Martin MM, Recant M. Clinical and metabolic characteristics of hyperosmolar nonketotic coma. Diabetes 1971;20:228-238.

Ghaeli P, Dufresne RL. Serum triglyceride levels in patients treated with clozapine. Am J Health Syst Pharm 1996;53;2079-2081.

Gill D, Hatcher S. Antidepressants for depression in people with physical illness. Cochrane Database Syst Rev 2000;4:CD001312.

Gilmore J, Kinon B, Basson BR, Tollefson GD. Effect of long-term olanzapine treatment on weight change in schizophrenia. Presented at Ann Meet Coll Int Neuropsychologicuum, July 9th-13th, 2000, Belgium, Brussels.

Ginsberg HN. A symposium: implications beyond insulin resistance: concerns beyond glucose. Am J Cardiology 1999;84:1-2.

Giugliano D, Torella R, Cacciapuoti et al. Impairment of insulin secretion in man by nifedipine. Eur J Clin Pharmacol 1980;18;395-398.

Glick ID, Fryburg D, O'Sullivan R, et al. Ziprasidone's benefits versus olanzapine on weight and insulin resistance. Presented at 151st Ann Meet Am Psychiatric Assocn, May 5th-10th, 2001, New Orleans, LA.

Goldman S. Medical illness in patients with schizophrenia. J Clin Psychiatry 1999;60:10-5.

Goldstein LE, Sporn J, Brown S, et al. New onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics 1999;40:438-443.

Goncalves N, Gruneberg F. Oral glucose tolerance test in schizophrenics under long-term neuroleptic treatment. Pharmakopsychiatr Neuropsychopharmakol 1975;8:289-295.

Goodnick PJ, Henandez M. Treatment of depression in comorbid medical illness. Expert Opin Pharmacother 2000;1:1367-1384.

Goodnick PJ, Henry JH, Buki VM. Treatment of depression in patients with diabetes mellitus. J Clin Psychiatry 1995; 56:128-36.

Goodnick PJ, Kumar A, Henry JH, et al. Sertraline in coexisting major depression and diabetes mellitus. Psychopharmacol Bull1997;33:261-4.

Grabowska MJ. Effects of niamide administration on brittle diabetes. Pol Tyg Lek 1971;26:1272-1274.

Granberry MC, Fonseca VA. Insulin resistance syndrome: options for treatment. Southern Med J 1999;92 :2-14.

Gray DS. Fujioka K. Devine W. Bray GA. A randomized double-blind clinical trial of fluoxetine in obese diabetics. Int J Obes Relat Metab Disord 1992;16(4):S67-72.

Green AI, Patel JK, Goisman RM, Allison DB, Blackburn G. Weight gain from novel antipsychotic drugs :need for action. Gen Hosp Psychiatry 2000;22:224-35.

Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Arch Intern Med 2000;160(2):174-180.

Groop LC. Insulin resistance: the fundamental trigger of type 2 diabetes. Diabetes Obes Metab 1999;1:S1-7.

Haeckel R, Oellerich M. Hydrazonopropionic acids, a class of hypoglycemic substances.1. Hypoglycemic effect of 2-(phenylhydrazono)- and 2-(2-cyclohexyl-ethylhydrazono)-propionic acid. Horm Metab Res 1979;11:606-611.

Hagg S, Joelsson L, Mjorndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998;59:294-299.

Hagg S, Soderberg S, Ahren B, et al. Leptin concentrations are increased in subjects treated with clozapine or conventional antipsychotics. J Clin Psychiatry 2001;62:843-848.

Hardy H, Esch LD, Morse GD. Glucose disorders associated with HIV and its drug therapy. Ann Pharmacotherapy 2001;35:343-351.

Harris B, Young J, Hughes B. Changes occurring in appetite and weight during short-time antidepressant treatment. Br J Psychiatry 1984;145:645-648.

Harris MI, Flegal KM, Cowie CC, et al. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996;37:68-73.

Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults. The Third National Health and Nutrition Examination Survey, 1988-1994. Diabetes Care 1998;21:518-524.

Harris MI, Hadden WC, Knowler WC, Bennett PH. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20-74 yr. Diabetes 1987;36:523-534.

Hasselblatt A, Schuster R. Wirkung von megaphen und veronal auf die rastinonhypoglykamie. Klin Wochensch 1958;36:814-819.

Hauptmann B, Kupsch A, Arnold G. Hyperglycemia associated with low-dose clozapine treatment. J Neural Transm 1999;106:XII.

Hayek Dv, Hutti V, Reiss J, et al. Hyperglycemia and ketoacidosis associated with olanzapine. Nervenarzt 1999;70:836-837.

Henderson D, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities:a five year naturalistic study. Am J Psychiatry 2000;157:975-981.

Henderson DC, Cagliero E, Borba CP. Atypical antipsychotic agents and glucose metabolism: Bergman's minmod analysis. Presented at 31st Ann Meet Am Soc Consultant Pharmacists, Nov 1st-4th, 2000, Boston, MA.

Heninger GR, Mueller PS. Carbohydrate metabolism in mania. Arch Gen Psychiatry 1970;23:310-319.

Hiles BW. Hyperglycemia and glycosuria following chlorpromazine therapy. JAMA 1956;162:1651.

Hinze-Selch D, Schuld A, Kraus T et al. Effects of antidepressants on weight and on the plasma levels of leptin, THF-alpha and soluble THF receptors: a longitudinal study in patients treated with amitriptyline or paroxetine. Neuropsychopharmacology 2000;23:13-19.

Holbrook TL, Barret-Connor E, Wingard DL. The association of weight and weight control patterns with diabetes among men and women in an adult community. Int J Obes 1989;13:723-729.

Horrobin DF and Bennett CN. Depression and bipolar disorder: relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities, cancer, aging and osteoporosis. Prostaglandins, Leukotrienes Essent Fatty Acids 1999;60:217-234.

Houston MC. Adverse effects of antihypertensive therapy on glucose intolerance. Cardiology Clinics 1986;4:117-135.

Hoyer S, Oesterreich K. Blood flow and oxidative metabolism of the brain in patients with schizophrenia. Psychiatrica Clinica 1975;8:304-313.

Hu M, Wu H, Chao C. Assisting effects of lithium on hypoglycemic treatment in patients with diabetes. Bio Trace Element Res 1997a;60:131-137.

Hu M, Wu Y-S, Wu H-W. Effects of lithium deficiency in some inulin-sensitive tissues of diabetic Chinese hamsters. Bio Trace Element Res 1997b;58:91-102.

Hunt NJ. Hypoglycemic effect of lithium. Biol Psychiatry 1987;22:798-799.

Huntsinger NJ. Hypoglycemic effect of lithium. Biol Psychiatry 1987;22:798-799.

Iawata A, Koike F, Arasaki K, Tamaki M. Blood brain barrier destruction in hyperglycemic chorea in a patient with poorly controlled diabetes. J Neurol Sci 1999;163:90-3.

Ismahan G, Parvez H, Paevez S, et al. The effect of selective monoamine oxidase inhibitors, clorgyline and deprenyl, upon tissue glycogen stores and blood glucose levels. J Neural Transm Suppl 1978;14:143-152.

Isojarvi IT, Rattya J, Myllyla V, et al., Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. Ann Neurol 1998;43:446-451.

Isotani H, Kameoka K. Hypoglycemia associated with maprotiline in a patient with type 1 diabetes. Diabetes Care 1999;22:862-3.

Jacobsen LK, Hamburger SD, Van Horn JD, et al. Cerebral glucose metabolism in childhood onset schizophrenia. Psychiatry Research 1997;75:131-144.

Jeste DV, Caliguiri MP. Tardive dyskinesia. Schizophr Bull 1993;19:303-15.

Jetton TL, Liang Y, Cincotta AH. Systemic treatment with sympatholytic dopamine agonists improves aberrant beta-cell hyperplasia and GLUT2, glucokinase, and insulin immunoreactive levels in ob/ob mice. Metabolism 2001;50:1377-1384.

Johnston BB. Diabetes mellitus in patients on lithium. Lancet 1977 29;2:935-936.

Johnston DG, Alberti KGMM, Natrass M, et al. Hyperinsulinemia in hyperprolactinemic women. Clin Endocrinol 1980;13:361-368.

Jon A, Carrara MC. On the mechanism of hyperglycemic effect of chlorpromazine. J Pharm Pharmacol 1966;18;623-624.

Jones GR, Lazarus JH, Davies CJ, Greenwood RH. The effect of short term lithium carbonate in type II diabetes mellitus. Horm Metab Res 1983;15:422-4.

Jori A, Bernardi D, Garatlini S. Chlorpromazine and glucose metabolism. Int J Neuropharmacol 1964;3:553-558.

Jori A, Carrara MC. On the mechanism of hyperglycemic effect of chlorpromazine. J Pharm Pharmacol 1966;18:623-624.

Joshi PM, Joshi U. Risperidone in treatment resistant geriatric patients with chronic psychoses and concurrent medical illnesses. Presented 149th Ann Meet Am Psychiatric Assocn, May 4th -9th, 1996, New York, USA.

Joss JD. Tricyclic antidepressant use in diabetic neuropathy. Ann Pharmacother 1999;33:996-1000.

Jubert P, Fernandez R, Ruiz A. Clozapine-related pancreatitis. Intern Med 1995;122:397.

Kalmijn S, Feskens EJ, Launer LJ, et al. Glucose intolerance, hyperinsulinemia and cognitive function in a general population of elderly men. Diabetologica 1995;38:1096-1102.

Kamei J, Saitoh A, Iwamoto Y, et al. Effects of diabetes on spontaneous locomotor activity of mice. Neurosc Lett 1994;178(1);69-72.

Kamei K, Mizutani H, Nakai H, et al. Side effects of long term treatment with lithium. Folia Psychiat Neurol Jap 1984;38:407-408.

Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine. Am J Psychiatry 1994 ;151:1395.

Kaplan SM, Maas JW, Pixley JM, et al. Use of imipramine in diabetics. JAMA 1960;174:511-517.

Kasanin J. The blood sugar curve in mental disease. The schizophrenic (dementia praecox) groups. Arch Neurol and Psychiatry 1926;16:414-419.

Katz LM, Fochtmann LF, Pato MT. Clomipramine, fluoxetine and glucose control. Ann Clinical Psychiatry 1991;3:271-274.

Kawachi I. Physical and psychological consequences of weight gain. J Clin Psychiatry 1999;60:5-9.

Kellner A, Wiedermann K, Krieg JC, et al. Toxic hepatitis by clozapine treatment. Am J Psychiatry 1993;150:985-6.

Kenny SJ, Aubert RE, Geiss LS. Prevalence and incidence of non-insulin dependent diabetes, in Diabetes in America, 2nd edition, NIH Publication 95-1468. Betheseda, Md, Nat Inst Diabetes Digestive Kidney Diseases, 1995,47-68.

Keskiner A, El Toumi A, Bousquet T. Psychotropic drugs, diabetes, and chronic mental patients. Dis Nerv Syst 1973;14:176-181.

Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42-8.

Kondziela JR, Kaufmann MW, Klein MJ. Diabetic ketoacidosis associated with lithium: case report. J Clin Psychiatry 1985;46:492-493.

Kooy FH. Hyperglycemia in mental disorders. Brain 1919;42:214-218.

Kopin IJ, Fischer JE, Mussachio JM et al. False neurochemical transmitters and the mechanism of sympathetic blockade by monoamine-oxidase inhibitors. J Pharmacol Exp Ther 1965;147:186.

Koren W, Kreis Y, Duchowiczny K, et al. Lactic acidosis and fatal myocardial failure due to clozapine. Ann Pharmacother 1997;31:168-170.

Korenyi C. Lowenstein B. Chlorpromazine induced diabetes. Dis Nerv Syst 1968;29:827-828.

Kostakoglu AE, Yazici KM, Erbas T, Guvener ET. Ketoacidosis as a side-effect of clozapine:a case report. Acta Psychiatrica Scand 1996;93:217-218.

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

Kraus T, Haack M, Schuld A, et al. Body weight and plasma leptin levels during treatment with antipsychotic drugs. Am J Psychiatry 1999;156:312-314.

Lambert AE. Henquin JC, Orci LO. Use of chlorpromazine in the prevention of hypoglycemia in malignant insulinoma. Br Med J 1972;3:701.

Landgraf R, Landgraf-Leurs MMC, Weisman A, et al. Prolactin: a diabetogenic hormone. Diabetologica 1977;13:99-104.

Langfeldt G. The insulin tolerance test in mental disorders. Acta Psychiatrica Scand 1952;80:189-200.

Launer LJ, Masaki K, Petrovich H et al. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA 1995;274:1846-1851.

Leak D, Dormandy TL. Possible relations of hypoglycemia induced by monoamine oxidase inhibition and angina pectoris. Proc Soc Exp Biol Med 1961;108:597-600.

Lear J, Burden AC. Fluoxetine side-effects mimicking hypoglycemia. Lancet 1992;339:1296.

Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. Eur Neuropsychopharmacol 2001;11:25-32.

Lilliker SL. Prevalence of diabetes in a manic-depressive population. Comp Psychiatry 1980;21:270-275.

Lind L. Berne C. Pollare T. Lithell H. Metabolic effects of anti-hypertensive treatment with nifedipine or furosemide: a double-blind, cross-over study. J Human Hypertension. 1995;9:137-41.

Lindenmayer JP, Patel R. Olanzapine-induced ketoacidosis with diabetes mellitus. Am J Psychiatry 1999;156:1471.

Lindenmayer JP, Smith RC, Singh A. Hyperglycemia in patients with schizophrenia who are treated with olanzapine. J Clin Psychopharmacol 2001;3:351-353.

Lingjaerde O. Failure in the utilization of carbohydrates in mental disease. Acta Psychiat Scand 1956;106:302-310.

Lithell HO. Insulin resistance and diabetes in the context of treatment of hypertension. Blood Pressure 1998; 3:28-31.

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

Lu HM, Yu HX. Reassessment of the side effect profile of clozapine. Chinese J Clin Psychol Med 1997;7:298-300.

Lund BC, Perry PJ, Brooks JM, Arndt S. Clozapine and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Arch Gen Psychiatry 2001;58:1171-6.

Lundquist I, Ekholm R, Ericson LE. Monoamine in the pancreatic islets of the mouse. Monoamines in the pancreatic islets of the mouse. 5-hydroxytryptamine as an intracellular modifer of insulin secretion, and the hypoglycemic action of monoamine oxidase inhibitors. Diabetologica 1971;7:414-22.

Lustman PJ, Griffith LS, Clouse RE, et al. Psychiatric illness in diabetes mellitus. Relationship to symptoms and glucose control. J Nerv Ment Dis 1986;174:736-742.

Lustman PJ, Griffith LS, Clouse RE. Depression in adults with diabetes. Diabetes Care 1988;11:605-612.

Ma Z, Gingerich RL, Santiago JV, et al. Radioimmunoassay of leptin in human plasma. Clin Chem 1996;42:942-946.

Madhusoodanan S, Brenner R, Araujo L, Abazza A. Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder or senile dementia in 11 geriatric patients: a case series. J Clin Psychiatry 1995;56:514-518.

Maheux P. Ducros F. Bourque J. Garon J. Chiasson JL. Fluoxetine improves insulin sensitivity in obese patients with non-insulin-dependent diabetes mellitus independently of weight loss. Int J of Obesity & Related Metab Disord 1997;21:97-102.

Mahmoud R, Gianfrancesco F, Grogg A, Nasrallah H. Differential effects of antipsychotics on type II diabetes: findings from a large health plan database. Presented at 37th Ann Meet Am College Neuropsychopharmacol, Dec 10th-14th, 2000, San Juan, Puerto Rico.

Mammarella A, Paoletti V, Bucci O, et al. Drug-induced hyperglycemia as a possible cardiovascular risk factor. Clin Ter 1988;124:425-33.

Mannisto P, Kovisito V. Antidiabetic effects of lithium 1972;2:1031.

Marcus MD, Wing RR, Guare J, et al. Lifetime prevalence of major depression and its effect on treatment outcome in obese type II diabetic patients. Diabetes Care 1992;15:253-255.

Mardon K, Kassiou M, Donald A. Effects of streptozotocin-induced diabetes on neuronal sigma receptors in the rat brain. Life Sci 1999; 65:281-6.

Martin A. Acute pancreatitis associated with clozapine use. Am J Psychiatry 1992;149:714.

Martin P, Massol J, Pichat P, Puech AJ. Decreased central GABA B receptor binding sites in diabetic rats. Neuropsychology 1988;19:148-8.

Marvin G, Sharma A, Aston W, et al. The effects of buspirone on perceived exertion and time to fatigue in man. Exp Physiol 1997;82:1057-1060.

Masand PS. Weight gain associated with psychotropic drugs. Expert Opin Pharmacother 2000;1:377-89.

Massol J, Martin P, Belon JP, Puech AJ, Soubrie P. Helpless behaviour (escape deficits) in streptozotocin-diabetic rats: resistance to antidepressant drugs. Psychoneuroendocrinology 1989;14:142-53.

Massol J, Martin P, Puech AJ. Antidepressant effect of tricyclic antidepressants and selective serotonin-uptake blockers in diabetic rats. Diabetes 1989;38:1161-4.

Maule S, Giannella R, Lanzio M, et al. Diabetic ketoacidosis with clozapine treatment. Diabetes Nutr Metab 1999;12(2):187-188.

Mayer GA. Chlorpropamide or chlorpromazine? CMAJ 1991;144:119.

Mayer-Gross W. The diagnostic significance of certain tests of carbohydrate metabolism in psychiatric patients and the question of oneirophrenia. Br J Psychiatry 1951;58:683-686.

McKee HA, D'Arcy PF, Wilson P. Diabetes and schizophrenia: a preliminary study. J Clin Hosp Pharm 1986;11:297-299.

McMillan R. Management of acute severe verapamil intoxication. J Emerg Med 1988;6:193-196.

Meduna LJ. Oneirophrenia. 1950. Urbana: University of Illinois Press.

Meatherall R, Younes J. Fatality from olanzapine induced hyperglycemia. Presented at Ann Meet Soc Forensic Tox, Sep 29th-Oct 5th, 2001, New Orleans, LA.

Melamed Y, Mazeh D, Elizur A. Risperidone treatment for a patient suffering from schizophrenia and IDDM. Can J Psychiatry 1998;43:956.

Melga P, Mansi C, Ciuchi E, et al. Chronic administration of levosulpiride and glycemic control in IDDM patients with gastroparesis. Diabetes Care 1997; 20:55-58.

Melkersson KI, Hulting AL, Brismer KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. J Clin Psychiatry 1999;60:783-91.

Melkersson KI, Hulting AL, Brismer KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000;61:742-9.

Melkersson KI, Hulting AL. Insulin and leptin levels in patients with schizophrenia or related psychoses – a comparison between different antipsychotic agents. Presented at Ann Meet Coll Int Neuropsychopharmacol, Jun 9th- Jun 13th 2000, Brussels, Belgium.

Mellerup ET, Plenge PK, Rafaelsen OJ. Lithium and insulin effects on carbohydrate metabolism. Dan Med Bull 1974;21:88-92.

Mellerup ET, Thomsen HG, Plenge P, et al. Lithium effect on plasma glucagon. Psychiatr Res 1970;8:37-42.

Melson AK, Selke G, Fucetola R, et al. Clozapine can change glucose regulation in schizophrenia independent of body mass index (BMI). Neuroscience 1999;25:2074

Meltzer S, Leiter L, Daneman D, et al. 1998 Clinical practice guidelines for the management of diabetes in Canada. CMAJ 1998;159:S1-S29.

Mennear JH. Miya TS. Chlorpromazine-induced glucose intolerance in the mouse. Proc Soc for Exp Biol Med 1970;133:770-773.

Messier C, Gagnon M. Glucose regulation and cognitive functions: relation to Alzheimer's disease and diabetes. Behav Brain Res 1996;75:1-11.

Meyer JM. Novel antipsychotics and severe hyperglycemia. J Clin Psychopharmacol 2001;21:369-374.

Mir S, Taylor D. Atypical antipsychotics and hyperglycemia. Int Clin Psychopharmacol 20001;16:63-73.

Mirouze J, Mary P, Schmouker Y. Neuropsychiatric agents and diabetes mellitus. Diabetes 1971;19:171-8.

Mohan D, Gordon H, Hindley N, Barker A. Schizophrenia and diabetes mellitus. Br J Psychiatry 1999;174:180-181.

Moisan J, Gregoire J, Gaudet M. Risk of diabetes among risperidone and olanzapine users. Presented at 4th Ann Eur Congress Int Soc Pharmacoeconomic Outcomes Research, Nov 11th-13th , 2001, Cannes, France.

Mordujovich de Buschiazzo, Buschiazzo HO, Bosch R, Rodriguez RR. Preventive action of the monoaminooxidase inhibitor, nialamide, on experimental diabetes in rats. Diabetes 1966;15:686-90.

Mueller-Oerlinghausen VB, Passoth PM, Poser W, et al. The influence of long-term treatment with major tranquilizers or lithium salts on the carbohydrate metabolism. Arzneim Forsch Drug Res 1978;28;1522-1524.

Mukherjee S, Bilder RM, Sackheim HA. Tardive dyskinesia and glucose metabolism. Arch Gen Psychiatry 1986;43:193.

Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996;37:68-73.

Mukherjee S, Mahadik SP. Diabetes Mellitus and tardive dyskinesia. In: Yassa R, Jeste DV, Nair NVP (eds): Neuroleptic-Induced Movement Disorders: A Comprehensive Survey. Cambridge, UK, Cambridge University Press.

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

Mukherjee S, Schnur DB, Reddy R. Family history of type 2 diabetes in schizophrenic patients. Lancet 1989;1:495.

Mukherjee S, Winsiewski A, Bilder RM, Sackheim HA. Possible association between tardive dsykinesia and altered carbohydrate metabolism. Arch Gen Psychiatry 1985;42:42-205.

Mukherjee S. High prevalence of type II schizophrenic patients (Abstract). Schizophr Res 1995;15:195.

Muller-Oerlinghausen B, Passoth P-M, Poser W, Pudel V. Impaired glucose tolerance in long-term lithium-treated patients. Int Pharmacopsychiat 1979;14:350-362.

Nakra BRS, Rutland P, Verma S, et al. Amitriptyline and weight gain: a biochemical and endocrinological study. Curr Med Res Opin 1977;4:602-606.

National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039-1057.

Newcomer JW, Craft S, Fucetola R et al. Glucose-induced increase in memory performance in patients with schizophrenia, Schizophrenia Bull 1999;25:321-335.

Newcomer JW, Fucetola R, Haupt DW, et al. Abnormalities in glucose regulation during antipsychotic treatment. Presented at the 38th Annual Meeting of the American College of Neuropsychopharmacology, Dec 12th-16th, 1999, Acapulco, Mexico.

Newcomer JW, Fucetola R, Haupt DW, et al. Presented at 39th Ann Meet Am Coll of Neuropsychopharmacol, Dec 12th-16th, 2000, San Juan, Puerto Rico.

Newcomer JW, Melson AK, Selke G, et al. atypical antipsychotic-associated changes in glucose regulation in schizophrenia may occur independent of changes in adiposity. Presented at 38th Ann Meet Am Coll Neuropsychopharmacology, Dec 12th-16th, 1999, Acapulco, Mexico.

Nicolletti F, Felito S, Grasso Am, et al. Current knowledge of the relations between the nervous system and carbohydrate metabolism. Acta Neurol Napoli 1996;2:798-830.

Norman D, Hiestand WA. Glycemic effects of chlorpromazine in the mouse, hamster and rat. Proc Soc Exp Biol 1955;90:89-91.

Obembe A. Carbamazepine-induced diabetes mellitus. Cent Afr J Med 1991;37:96-98.

Ober SK, Hudak R, Rusterholz A. Hyperglycemia and olanzapine. Am J Psychiatry 1999;156:970.

Ohwovoriole AE, Obembe AO, Adeosun SA, Olorondu JO. Glucose tolerance in psychiatric patients. West Afr J Med 1992 Oct-Dec;11(4):278-83.

Okada S, Ichiki, Tanokuchi S, et al. Improvement of stress reduces glycosylated haemoglobin levels in patients with type 2 diabetes. J Int Med Res 1995;23:119-122.

Okamura F, Tashiro A, Utsumi A, et al. Insulin resistance in patients with depression and its changes in the clinical course of depression: a report on three cases using the minimal model analysis. Intern Med 1999;38:257-60.

O'Kane M. Wiles PG. Wales JK. Fluoxetine in the treatment of obese type 2 diabetic patients. Diabetic Medicine 1994;11:105-1.

Opara JU, Levine JH. The deadly quartet-the insulin resistance syndrome. Southern Med J 1997;90:1162-8.

Orci L, Amnon H, Steinke J. The effect of chlorpromazine on insulin release from isolated pancreatic rat islets:A correlated morphological and biochemical study, Diabetologica 1972;8:61.

Osser DN, Najarian DM, Dufresne RL. Olanzapine increase weight and serum triglycerides. J Clin Psychiatry 1999;60:767-770.

Ostenson CG, Hjemdahl P, Efendic S. Release of catecholamines is increased but does not contribute to impaired insulin secretion in the perfused pancreata of diabetic rats. Pancreas 1993;8:34-8.

Paizis M, Cavaleri S, Schwarz M, et al. Acute-onset diabetic ketoacidosis during olanzapine treatment in a patient without pretreatment obesity or treatment-associated weight gain. Primary Psychiatry 1999;6:37-38.

Parodi F. On the antidiabetic effect of phenelzine. Clin Ther 1967;42(5):443-8.

Paykel ES, Mueller PS, De La Vergne PM. Amitriptyline, weight gain and carbohydrate cravings:a side effect. Br J Psychiatry 1973;123:501-507.

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

Pierides M. Clozapine monotherapy and ketoacidosis. Br J of Psychiatry 1997;171:90-91.

Pinkofsky HB, Dwyer DS, Bradley RJ. The inhibition of GLUT1 glucose transport and cytochalasin B binding activity by tricyclic antidepressants. Life Sci. 2000;66:271-8.

Pijl H, Ohashi S, Matsuda M, et al. Bromocriptine: a novel approach to the treatment of type 2 diabetes. Diabetes Care 2000;23:1154-1161.

Podolsky S, Pattavina CG. Hyperosmolar nonketotic diabetic coma: a complication of propanolol therapy. Metabolism 1973;22:685-693.

Poersch M, Hufnagel A, Smolenski C. Drug-induced asterixis amplified by relative hypoglycemia. Nervenarzt 1996;67:323-326.

Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997;58:108-11.

Porte D. Beta adrenergic stimulation of insulin release in man. Diabetes 1967;16:150.

Potter van Loon BJ, Radder JK, Frolich M, et al. Fluoxetine increases insulin action in obese nondiabetic and in obese non-insulin-dependent diabetic individuals. Int J Obesity Related Metab Disorders.1992;16:79-85.

Potter WZ, Zaharko DS, Beck LV. Possible role of hydrazine group in hypoglycemia associated with the use of certain monoamine-oxidase inhibitors (MAOIs). Diabetes 1969;18:538-541.

Prior T, Chue P, Tibbo P. GTT and atypical antipsychotics. Presented at 9th Biennial Winter Workshop on Schizophrenia, Feb 24th-Mar 1st, 1998, Davos, Switzerland.

Proakis AG, Mennear JH, Miya TS et al. Phenothiazine-induced hyperglycemia: relation to CNS and adrenal effects. Proc Soc Exp Biol Med 1971;137:1385-1388.

Procyshyn RC, Kennedy NB, Marriage S, Wasan KM. Plasma protein and lipoprotein distribution of clozapine. Am J Psychiatry 2001;158;949-951.

Procyshyn RC, Pande S, Tse G. New-onset diabetes mellitus associated with quetiapine. Can J of Psychiatry 2000;45:668-669.

Rabkin J, Quitkin F, Harrison W, ey al. Adverse reactions to monoamine oxidase inhibitors, I: a comparative study. J Clin Psycholpharmacol 1984;4:270-278.

Ramaekers GM, Rambharos R, Matroos G. Diabetes mellitus after treatment with clozapine. Ned Tijdschr Geneeskd 2000;14430:1463-4.

Ramirez LC, Rosenstock J, Strowig S, et al. Effective teatment of bulimia with fluoxetine, a serotonin reuptake inhibitor, in a patient with type 1 diabetes mellitus. Am J Med 1990;88:540-1.

Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595-1607.

Reinstein M, Sirotovskaya L, Jones L, et al. Effect of clozapine-quetiapine combination therapy on weight and glycemic control: preliminary findings. Clin Drug Invest 1999;18:99-104.

Reiter PJ. Uber storungen des zuckerstoffwechsels bei geisteskranken, insbesondere bei syntonen. Z Ges Nerurol Psychiat 1927;107:65-145.

Richardson JTE. Cognitive function in diabetes mellitus. Neurosci Biobehav Rev 1990;14:385-388.

Rigalleau V, Gatta B, Bonnaud S, et al. Diabetes as a result of atypical antipsychotic drugs-a case report of three cases. Diabet Med 2000;7:484-6.

Rivera-Calimlim L, Kerzner B, Karch FE. Effect of lithium on plasma chlorpromazine levels. Clin Pharm Ther 1978;23:451-455.

Roefaro J, Mukherjee S. Olanzapine-induced hyperglycemic nonketonic coma. Ann Pharmacother 2001;35:300-302.

Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. Eur Heart J 1999;20:246-7.

Roth A, Miller HI, Belhassen B, et al. Slow-release verapamil and hyperglycemic metabolic acidosis. Ann Int Med 1989;110:171-172.

Rouer E, Lemoine A, Cresteil T, et al. Effects of genetic or chemically induced diabetes on imipramire metabolism. Respective involvement of flavin monooxygenase and cytochrome p-450-dependent monooxygenases. Drug Metab Dispos 1987;15:524-528.

Rowland DL, Myers L, Culver A, Davidson JM. Bupropion and sexual function:a placebo-controlled prospective study on diabetic men with erectile dysfunction. J Clin Psychopharmacol 1997;17:350-357.

Rubinow DR. Nelson JC. Tricyclic exacerbation of undiagnosed diabetic uropathy. J Clin Psychiatry 1982;43:210-212.

Rutishauser M. Beeinflussung des kohlenhydrats-stoffwechsels des rattenhirns durch psychopharmaka mit sedativer wirkung. Nauny Schmiedeberg Arch Exp Path 1963;245:396-413.

Ryall RW. Some actions of chlorpromazine. Br J Pharmacol 1956;11:339-345.

Sachs GS, Guille C. Weight gain associated with use of psychotropic medications. J Clin Psychiatry 1999;60:16-19.

Saitoh A, Morita K, Sodeyama M, Kamei J. Effects of the experimental diabetes on dopamine D1 receptor locomotor-enhancing activity in mice. Pharmacol Biochem Behav 1998;60:161-6.

Sajatovic M, Ramirez LF, Vernon L, et al. Outcome of risperidone therapy in elderly patients with chronic psychosis. Int J Psychiatry Med 1996;26(3):309-317.

Salkovic M, Laekovic Z. Brain D1 dopamine receptors in alloxan-induced diabetes. Diabetes 1992;(199):1119-21.

Saller CF, Kreamer LD. Glucose concentrations in the brain and blood:regulation by dopamine receptor subtypes. Brain Res 1991;546:235-240.

Sandyk R, Kay SR, Awebuch GI, Iacono R. Risk factors for neuroleptic-induced movement disorders. Int J Neurosci 1991;61:149-88.

Sandyk R. Increased incidence of neuroleptic-induced perioral movements by hyperglycemia. Int J Neuroscience 1990;50:227-232.

Saran AS. Antidiabetic effects of lithium. J Clin Psychiatry 1982;43:383-384.

Sawicki PT. Berger M. Effects of antihypertensive treatment with beta-blockers on glucose metabolism. J Cardiovasc Pharmacol.1992;11:S45-S48.

Sawka AM, Burgart V, Zimmerman D. Loss of hypoglycemia in an adolescent with type 1 diabetes mellitus during treatment with fluoxetine hydrochoride. J Pediatr 2000;136:394-6.

Scandellari C, Zaccaria M, Sicolo N, et al. Medical treatment of endogenous organic hyperinsulinism. Horm Metab Res 1976;6:46-54.

Schmidt AM, Stern D. A radical approach to the pathogenesis of diabetic complications. Trends Pharmaceutical Science 2000;21:367-9.

Schultz SK, Arndt S, Ho BC, et al. Impaired glucose tolerance and abnormal movements in patients with schizophrenia. Am J Psychiatry 1999;156:640-642.

Schwartz L. Munoz R. Blood sugar levels in patients treated with chlorpromazine. Am J Psychiatry.1968; 125:253-255.

Scislowski PW, Tozzo E, Zhang Y, et al. Biochemical mechanisms responsible for the attenuation of diabetic and obese conditions in ob/ob mice reated with dopaminergic agonists. Int J Obes Relat Metab Disord 1999;23:425-431.

Sernyak M, Rosenheck RA, Leslie D. Association of diabetes mellitus with atypical neuroleptics. Presented at 151st Ann Meet Am Psychiatric Assocn, May 5th-10th , 2001, New Orleans, LA.

Shader RI, Belfer ML, DiMascio A. Endocrine effects of psychotropic drugs: III.Glucose metabolism. Conneticut Med 1968;32:389-394.

Sherman KE, Bornemann M. Amitrityline and asymptomatic hypoglycemia. Ann Intern Med 1988;109:683-4.

Shopsin B, Stern S, Gershon S. Altered carbohydrate metabolism during treatment with lithium carbonate (absence of diagnostic specificity in hospitalized psychiatric patients). Arch Gen Psychiatr 1972;26:577-571.

Shrivastava RK, Edwards D. Hypoglycemia associated with imipramine. Biol Psychiatry 1983;18:1509-1510.

Siaud P, Puech R, Assenmacher L, Alonso G. Microinjection of oxytocin into the dorsal vagal complex decreases pancreatic insulin secretion. Brain Res 1991;546:190-194.

Skouby SO, Kuhl C, Hornnes PJ, Andersen AN. Prolactin and glucose tolerance in normal and gestational diabetic pregnancy. Obst Gynaecology 1986;67:17-20.

Smith H, Kenney-Herbert J, Knowles L. Clozapine-induced diabetic ketoacidosis. Aust N Z J Psychiatry 1999;33:120-121.

Smith L. Hyperglycemia in patients treated with olanzapine. Presented at Am Psychiatric Assocn Institute on Psychiatric Services, Oct 30th – Nov 2nd 1999, New Orleans, LA.

Sobel M, Jaggers ED, Franz MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment. J Clin Psychiatry 1999;60:556-57.

Sorenson RL, Brelje TC. Adaption of islets of Langerhans to pregnancy: Beta cell growth, enhanced insulin secretion and the role of lactogenic hormones. Horm Metab Res 1997;29:301-307.

Steele V, Vokras CS, Jaskiw E, et al. Clozapine effects on bvody weight, glucose and cholesoerol levels. Schizophrenia Res1997;24:267.

Stein EM, Stein S, Linn MW. Geriatric sweet tooth. Am J Geriatr Soc 1985;33:687-692.

Stern M. Natural history of macrovascular disease in type 2 diabetes: The role of insulin resistance. Diabetes Care 1999;22:C2.

Sternbach LH, Randall LO, Gustafson SR. 1,4- benzodiazepines (chordiazepoxide and related compounds). In: Psychopharmacological Agents. Gordon M (Ed). Vol 1. New York, Academic Press 1964, pp 198-200.

Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment and dementia. Diabet Med 1999;6:93-112.

Su T-P, Elman I, Malhotra AK, Adler CM, et al. Comparison of weight gain during risperidone and clozapine treatment in chronic schizophrenia. Presented at 149th Ann Meet Am Psychiatric Assocn, May 4th –9th 1996, New York, USA.

Sugimoto Y, Yamada J, Kimura I, Horisaka K. The effects of the serotonin 1A receptor agonist buspirone on tolbutamine-induced hypoglycemia in rats. Biol Pharm Bull 1995;18:1296-1298.

Sumiyoshi T, Ichikawa J, Meltzer HY. Increased S(-)-apomorphine-induced vacuous chewing and attention of chronic haloperidol treatment in streptozocin-induced diabetes. Pharmacol Biochem Behav 1997;57:19-22.

Sumiyoshi T, Ichikawa J, Meltzer HY. The effect of streptozocin-induced diabetes on dopamine 2, serotonin 1A and serotonin 2A receptors in the rat brain. Neuropsychopharmacology 1997;16:183-90.

Surridge DH, Williams Erdahl DL, Lawson JS, et al. Psychiatric aspects of diabetes mellitus. Br J Psychiatry 1984; 145:269-276.

Sussman KE, Vaughan GD. Insulin release after ACTH, glucagons and 3'5' cyclic AMP in the perfused isolated rat pancreas. Diabetes 1967;16:449.

Sussman N, Ginsberg D. Atypical neuroleptics and glucose regulation. Primary Psychiatry 1999:38-40.

Suzuki H, Ishikawa M, Kamma N, et al. The effect of sulpiride on the endocrine pancreas. Nippon Naibunpi Gakkai Zasshi 1981;57(12):1710-15.

Tabata H, Kikuoka M, Kikuoka L,Bessho H, Hirayama J, Hanabusa T, et al. Characteristics of diabetes mellitus in schizophrenic patients. J Med Assoc Thai 1987;70(2):90-93.

Takhar J. Williamson P. Hypoglycemia associated with high doses of sertraline and sulphonylurea compound in a noninsulin-dependent diabetes mellitus patient. Can J Clin Pharmacol 1999; 6:12-4.

Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT2C receptors. Nature 1995;374:542-6.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2001;23:S4-S19.

Thompson J, Chengappa KNR, Good CB, et al. Hepatitis, hyperglycemia, pleural effusion, eosinophilia, hematuria and proteinuria occurring early in clozapine treatment. Int Clin Psycopharmacol 1998;13:95-98.

Thonnard-Neumann E. Phenothiazines and diabetes in hospitalized women. Am J Psychiatry 1968 ;124:978-982.

Todd RD, O'Malley KL. Population frequencies of tyrosine hydroxylase restriction fragment length polymorphisms in bipolar affective disorder. Biol Psychiatry 1989;25:626-630.

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

Tourniare J, Pallo D, Pousset G, et al. Diminution de la tolerance glucidique et hyperinsulinisme dans l'adenome a prolactine. Nouvelle Presse Med 1974;3:1705-1707.

True BL, Perry PJ, Burns EA. Profound hypoglycemia with the addition of a tricyclic antidepressant to maintenance sulfonylurea therapy. Am J Psychiatry 1987;144:1220-1.

Turkington RW. Depression masquerading as diabetic neuropathy. JAMA 1980;243:1147-50.

Turnbull DM, Bone AJ, Tames FJ, et al. The effect of valproate on blood metabolite concentrations in spontaneously diabetic, ketoacidotic, BB/E Wistar rats. Diabetes Research. 1985 ;2:45-8, 1985.

Turtle JR, Kipnis DM. An adrenergic receptor mechanism for the control of cyclic 3'5' adenosine monophosphate synthesis in tissues. Biochem Biophys Res Commun 1967;28:797.

Turtle JR, Littleton GK, Kipnis DM. Stimulation of insulin secretion by theophylline. Nature 1967;213:727.

U.S. Department of Health, Education, and Welfare: Glucose Tolerance for Adults, National Center for Health Statistics, Series 11, No. 2, May 1964, p. 5.

Uvnas-Moberg K, Ahlenius S, Alster P, Hillegaart V. Effects of selective serotonin and dopamine agonists on plasma levels of glucose, insulin and glucagons in the rat. Peripheral Neuroendocrinol1996;63:269-274.

Van der Velde CD, Gordon MW. Manic-depressive illness, diabetes mellitus and lithium carbonate. Arch Gen Psychiatry 1969;21:478-485.

Van Praag HM, Leijnst B. Depression, glucose tolerance, peripheral glucose uptake and their alterations under the influence of antidepressive drugs of the hydrazine type. Psychopharmacology 1965b;8:67-78.

Van Praag HM, Leijnst B. The influence of some antidepressants of the hydrazine type on glucose metabolism in depressed patients. Clin Chim Acta 1963;8:466-475.

Van Praag HM, Leijnst B. The xylose metabolism in depressed patients and its alterations under the influence of antidepressive hydrazines. Clin Chim Acta 1965a;11:13-23.

Van Praag HM, Leijnst B. Monoamine-oxidase inhibiting hydrazines and carbohydrate metabolism. Lancet 1964;2;103.

Velde CD van der and Gordon MW. Manic-depressive illness, diabetes mellitus, and lithium carbonate. Arch Gen Psychiatr 1969;21:322-329.

Vendsborg PB and Prytz S. Glucose tolerance and serum lipids in man after long-term lithium administration. Acta Psychiatr Scand 1976;53:64-69.

Vendsborg PB, Rafaelsen OJ. Lithium in man: effects on glucose tolerance and serum electrolytes. Acta Psychiatrica Scand 1973;49:601-610.

Vendsborg PB. Lithium treatment and glucose tolerance in manio-melancholic patients. Acta Psychiatrica Scand 1979;59:306-316.

Vestergaard P and Schou M. Does long-term lithium treatment induce diabetes mellitus? Neuropsychobiol 1987;17:130-132.

Vigas M, Klimes I, Jurcovicova, Jesova D. Acute elevation of endogenous prolactin does not influence glucose homeostasis in healthy men. Physiol Res 1993;42:341-345.

Von Hayek DV, Huttl V, Reiss J, Schweiger HD, Fuessl HS. Hyperglycemia and ketoacidosis associated with olanzapine. Nervenarzt 1999;70:836-837.

Von Opitz K. Wirkungen psychotroper substanzen auf den stoffwechsel.3.Mitteilung. Arzneimittel-Forsch 1962;12:618-626.

Waitzkin LA. A survey for unknown diabetics in a mental hospital: I Men under age fifty. Diabetes 1966;15:97-104.

Waitzkin LA. A survey for unknown diabetics in a mental hospital: II Men from age fifty. Diabetes 1966;15:164-172.

Waitzkin LA. Glucose tolerance in man during chlorpromazine therapy. Diabetes 1970;19:186-188.

Waldman MD, Safferman A. Pregnancy and clozapine. Am J Psychiatry 1993;150:168-9.

Wannarka GI, Fletcher HP, Maickel RP. Centrally mediated drug-induced hyperglycemia in mice. Neuropharmacology 1993;22:341-346.

Ward JL. Glucose tolerance in schizophrenia. Orthomol Psychiatry 1972;44:137-140.

Waring EM, Weisz G, Heilbrunn D, Lefcoe D, Green RN. A pilot evaluation of liaison psychiatry in a diabetic outpatient clinic. Psychiatric J Univ of Ottawa 1978;V:53-57.

Warnock JK, Biggs F. Nefazodone-induced hypoglycemia in a diabetic patient with major depression. Am J Psychiatry 1997;154(2):288-289.

Warnock JK. Mutzig EM. Diabetes mellitus and major depression: considerations for treatment of Native Americans. J Oklahoma State Med Assoc1998; 9:488-93.

Wehring H, Alexander B, Perry PJ. Diabetes mellitus associated with clozapine therapy. Pharmacotherapy 2000;20(7):844-847.

Welch R, Chue P. Antipsychotic agents and QT changes. J Psychiatry Neurosci 2000; 25:154-160.

Weiss H. Ueber eine neue behandlungs methode des diabetes mellitus und verwandter stoffwechselstorungen. Wien Klin Wochenschr 1924;37;1142-1143.

Wickstrom L, Petterson K. Treatment of diabetics with monoamine oxidase inhibitors. Lancet 1964;2:995-997.

Willems E, Knigge U, Jorgensen H, et al. Effect of blockade of postsynaptic H1 or H2 receptors or activation of presynaptic H3 receptors on catecholamine-induced stimulation of ACTH and prolactin secretion. Eur J Endocrinol 2000;141:637-641.

Wilson DR, D'Souza L, Sarkar N, et al. Diabetogenesis and ketoacidosis with atypical antipsychotics. Presented at 38th Ann Meet Am Coll Neuropsychopharmacol, Dec 12th-16th, 1999, Acapulco, Mexico.

Wilson DR, D'Souza L, Sarkar N. New-onset diabetes and ketoacidosis with atypical antipsychotics. Presented at US Psychiatric Mental Health Congr, Nov 11th -14th 1999, Atlanta, Georgia.

Wilson GA, Furman BL. Effects of inhibitors to 5-hydroxytryptamine uptake on plasma glucose and their interaction with 5-hydroxytrytophan in producing hypoglycemia in mice. Eur J Pharmacol 1982;78:263-270.

Winkelmayer R. Diabetes mellitus in chronic mental patients. Psychiatr Quarterly 1966;36:530-536.

Winokur A, Maislin G, Phillips JL, et al. Insulin resistance after glucose tolerance in patients with major depression. Am J Psychiatry 1988;145:325-330.

Wirshing DA, Erhart SM, Pierre JM, Boyd JA. Nonextrapyramidal side effects of novel antipsychotics. Curr Opin Psychiatry 2000;13:45-50.

Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778-783.

Wirshing DA, Wirsching WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999;60:358-363.

Wirshing DA. Adverse effects of atypical antipsychotics. J Clin Psychiatry 2001;62(21):7-10.

Wizniewski K. Buczko W. The central pharmacological effect of chlorpromazine in rats with alloxan-diabetes. Biochem Pharmacol 1967;16:2227-30.

Woermer MG, Saltz BL, Kane JM, Lieberman JA, Alvir JM. Diabetes and development of tardive dyskinesia. Am J Psychiatry 1993;150:966-968.

Wolever TMS. Dietary carbohydrates in the insulin resistance syndrome. Can J CME 2001;11:121-132Wolter-Henseler D. Blood glucose dysregulation with mianserin. Psychiatr Prax 1996;23:200.

Wozniak KM, Linnoila M. Hyperglycemic properties of serotonin receptor antagonists. Life Sci 1991;49:101-109.

Wu G, Dias P, Chun W, et al. Hyperglycemia, hyperlipemia, and periodic paralysis: a case report of new side effects of clozapine. Prog Neuropsychopharmacol Biol Psychiatry 2000;24:1395-400.

Yamada J, Sugimoto Y, Yoshikawa T, Kimura I, Horisaka K. The involvement of the peripheral 5-HT2A receptor in peripherally administered serotonin-induced hyperglycemia in rats. Life Sci 1995;57:819-825.

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

Zhu BH, Sakai Y. Alteration of contractile properties to serotonin in gastric fundus smooth muscle isolated from streptozocin (STZ)-induced rats. J Smooth Muscle Res 1996;32(4):165-173.

Zogno MG, Tolfo L, Draghi E. Hypoglycemia caused by maprotiline in a patient taking oral antidiabetics. Ann Pharmacother 1994;28:406.

Zoler ML. Antipsychotics linked to weight gain, diabetes. Clin Psychiatry News 1999;27:20-21.

Zumoff B, Hellman L. Aggravation of diabetic hyperglycemia by chlordiazepoxide. JAMA 1977;237:1960-1.

Zumoff B. The effects of psychotropic drugs and diuretics on blood glucose levels in diabetes mellitus. Comprehensive Therap 1979;4:72-74.

Zung A, Blumenson R, Kupchik M et al. Are the atypical antipsychotic drugs diabetogenic? Presented at 38th Ann Meet Eur Soc Pediatric Endocrinol, Aug 29th-Sep 1st 1999, Warsaw, Poland.