CNS Drugs • 2005, Vol. 19, Suppl. 1, pp. 1-93 Second-Generation (Atypical) Antipsychotics and Metabolic Effects Adis

CNS Drugs™ Supplement

DRUG THERAPY IN NEUROLOGY AND PSYCHIATRY

2005, Vol. 19, Supplement 1 (pp. 1-93)
ISSN: 1172-7047

Second-Generation (Atypical) Antipsychotics and Metabolic Effects

A Comprehensive Literature Review

GUEST EDITOR
W. W. Fleischhacker

Available Online

Adis INTERNATIONAL

adis INTERNATIONAL

CNS Drugs™

Aim and Scope: *CNS Drugs* promotes rational pharmacotherapy and effective patient management within the disciplines of clinical psychiatry and neurology by providing a regular programme of review articles covering important issues in the drug treatment of psychiatric and neurological disorders.
The Journal includes:

- Leading/current opinion articles providing an overview of contentious or emerging issues.
- Definitive reviews on approaches to the management of neurological and psychiatric illnesses.
- Therapy in Practice reviews providing practical recommendations for specific clinical situations.
- Adis Drug Evaluations reviewing the properties and place in therapy of both newer and established drugs in neurology and psychiatry.
- Adis Drug Profiles reviewing innovations in therapy with expert commentaries.
- Original research articles will also be considered for publication.

All manuscripts are subject to peer review by international experts.
Letters to the Editor are welcomed and will be considered for publication.

Senior Managing Editor, Supplements: Wendi Anderson
wanderso@lww.com

Editorial Office and Inquiries: Adis International Ltd, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand. Information on the preparation of manuscripts will be provided to authors.

E-mail: cnsdrugs@adis.co.nz http://www.adisonline.info/cns

CNS Drugs (ISSN 1172-7047) is published as 1 volume with 12 issues by Adis International Limited. The annual 2005 institutional subscription price for print and online is $US2405 and for online only is $US2145. The personal subscription price for print and online is $US240 and for online only is $US235. All online subscriptions include access to online archived articles. Further subscription information is given at the back of each issue.

CNS Drugs™
Supplement

Second-Generation (Atypical) Antipsychotics and Metabolic Effects

A Comprehensive Literature Review

Guest Editor
W. Wolfgang Fleischhacker

Peer Review Panel
Henry A. Nasrallah

This publication has been made possible by an educational grant from Bristol-Myers Squibb.

CNS Drugs is indexed in *Index Medicus, Medline, EMBASE/Excerpta Medica, Current Contents/Clinical Medicine, Current Contents/Life Sciences, International Pharmaceutical Abstracts, Science Citation Index, SciSearch, Research Alert, PASCAL,* the *Medical Documentation Service™, Sociedad Iberoamericana de Información Científica (SIIC)* and *Chemical Abstracts*. Individual articles are available through the ADONIS document delivery service and online via the World Wide Web through Ingenta. Further details are available from the publisher.

Vol. 19, Supplement 1, 2005 CNS Drugs™ Supplement

Contents

CONTRIBUTORS

GUEST EDITOR

W. Wolfgang Fleischhacker
Professor of Psychiatry, Department of Biological Psychiatry, Innsbruck University Clinics, Innsbruck, Austria

PEER REVIEW PANEL

Henry Nasrallah
Associate Dean, Professor of Psychiatry, Neurology & Neuroscience, University of Cincinnati Medical Center, Cincinnati, Ohio, USA

CONTRIBUTORS

John W. Newcomer
Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA

REVIEW ARTICLE

CNS Drugs 2005; 19 Suppl. 1: 1-93
1172-7047/05/0001-0001/$34.95/0

Second-Generation (Atypical) Antipsychotics and Metabolic Effects

A Comprehensive Literature Review

John W. Newcomer

Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA

Abstract

Increasing numbers of reports concerning diabetes, ketoacidosis, hyperglycaemia and lipid dysregulation in patients treated with second-generation (or atypical) antipsychotics have raised concerns about a possible association between these metabolic effects and treatment with these medications. This comprehensive literature review considers the evidence for and against an association between glucose or lipid dysregulation and eight separate second-generation antipsychotics currently available in the US and/or Europe, specifically clozapine, olanzapine, risperidone, quetiapine, zotepine, amisulpride, ziprasidone and aripiprazole. This review also includes an assessment of the potential contributory role of treatment-induced weight gain in conferring risk for hyperglycaemia and dyslipidaemia during treatment with different antipsychotic medications.

Substantial evidence from a variety of human populations, including some recent confirmatory evidence in treated psychiatric patients, indicates that increased adiposity is associated with a variety of adverse physiological effects, including decreases in insulin sensitivity and changes in plasma glucose and lipid levels. Comparison of mean weight changes and relative percentages of patients experiencing specific levels of weight increase from controlled, randomised clinical trials indicates that weight gain liability varies significantly across the different second-generation antipsychotic agents. Clozapine and olanzapine treatment are associated with the greatest risk of clinically significant weight gain, with other agents producing relatively lower levels of risk. Risperidone, quetiapine, amisulpride and zotepine generally show low to moderate levels of mean weight gain and a modest risk of clinically significant increases in weight. Ziprasidone and aripiprazole treatment are generally associated with minimal mean weight gain and the lowest risk of more significant increases.

Published studies including uncontrolled observations, large retrospective database analyses and controlled experimental studies, including randomised clinical trials, indicate that the different second-generation antipsychotics are associated with differing effects on glucose and lipid metabolism. These studies offer generally consistent evidence that clozapine and olanzapine treatment are associated with an

increased risk of diabetes mellitus and dyslipidaemia. Inconsistent results, and a generally smaller effect in studies where an effect is reported, suggest limited if any increased risk for treatment-induced diabetes mellitus and dyslipidaemia during risperidone treatment, despite a comparable volume of published data. A similarly smaller and inconsistent signal suggests limited if any increased risk of diabetes or dyslipidaemia during quetiapine treatment, but this is based on less published data than is available for risperidone. The absence of retrospective database studies, and little or no relevant published data from clinical trials, makes it difficult to draw conclusions concerning risk for zotepine or amisulpride, although amisulpride appears to have less risk of treatment-emergent dyslipidaemia in comparison to olanzapine. With increasing data from clinical trials but little or no currently published data from large retrospective database analyses, there is no evidence at this time to suggest that ziprasidone and aripiprazole treatment are associated with an increase in risk for diabetes, dyslipidaemia or other adverse effects on glucose or lipid metabolism.

In general, the rank order of risk observed for the second-generation antipsychotic medications suggests that the differing weight gain liability of atypical agents contributes to the differing relative risk of insulin resistance, dyslipidaemia and hyperglycaemia. This would be consistent with effects observed in nonpsychiatric samples, where risk for adverse metabolic changes tends to increase with increasing adiposity. From this perspective, a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity. However, case reports tentatively suggest that substantial weight gain or obesity may not be a factor in up to one-quarter of cases of new-onset diabetes that occur during treatment. Pending further testing from preclinical and clinical studies, limited controlled studies support the hypothesis that clozapine and olanzapine may have a direct effect on glucose regulation independent of adiposity. The results of studies in this area are relevant to primary and secondary prevention efforts that aim to address the multiple factors that contribute to increased prevalence of type 2 diabetes mellitus and cardiovascular disease in populations that are often treated with second-generation antipsychotic medications.

Reports of treatment-emergent adverse events such as diabetes mellitus, diabetic ketoacidosis, hyperglycaemia and dyslipidaemias in patients receiving atypical or second-generation antipsychotics have increased in recent years. This has led to growing concern about a possible link between these metabolic effects and therapy with second-generation antipsychotics, and a number of issues have been raised:

- Is there an increased risk of diabetes associated with second-generation antipsychotic therapy, or do these reports simply reflect an increased risk of diabetes in patients with schizophrenia?
- If there is an increased risk of diabetes with second-generation antipsychotics, does this risk differ between the different agents?
- If there is an increased risk of diabetes with second-generation antipsychotics, is it related to their effects on bodyweight or adiposity, or action through other mechanisms?
- Is there an increased risk of dyslipidaemia associated with second-generation antipsychotics? If so, does this risk vary between the different agents? Is this also related to adiposity?

This comprehensive literature review considers the evidence for an association between glucose

and/or lipid dysregulation and the second-generation antipsychotics currently available in the US and/or Europe: clozapine, olanzapine, risperidone, quetiapine, zotepine, amisulpride, ziprasidone and aripiprazole. It includes published reports of database analyses, chart reviews, clinical trials and case studies examining glucose and lipid regulation in patients treated with any of the eight atypical agents. Detailed below in the search methodology section, references extending into 2004 were identified by Medline search, as well as review of selected meeting abstracts. Searches were performed for each of the individual antipsychotic agents, plus 'atypical antipsychotics', combined with the following terms: diabetes, glucose, ketoacidosis, hyperglycaemia, triglycerides, hypertriglyceridaemia, hyperlipidaemia, lipidaemia, dyslipidaemia and cholesterol. Data are presented and discussed for each of the eight antipsychotics individually, with the overall findings reviewed in a final discussion section.

1. Background: Obesity, Insulin Resistance, Diabetes and Dyslipidaemias

1.1 Overweight and Obesity

Overweight and obesity are increasing problems in the US and throughout the Western world and have significant health implications. In the US, data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988–1994 showed that 58% of people aged 20 years and above were either overweight (body mass index [BMI] 25.0–29.9 kg/m^2) or obese (BMI ≥30 kg/m^2). The prevalence of overweight was higher for men than for women (39.9% vs 25.7%), whereas obesity prevalence was higher among women than men (25.5% vs 19.9%). In the most recent NHANES data for 1999–2000, the prevalence of overweight and obesity combined had risen to 64%. Trends in obesity prevalence over the last 40 years showed little change from 1960 to 1980, then a marked increase to the present day (men 1980, 13%; 1991, 21%; 1999–2000, 28%; women 1980, 17%; 1991, 26%; 1999–2000, 34%). The increasing prevalence of overweight has also been observed in children and adolescents. In children (6–11 years), the proportion overweight (BMI >95th percentile) increased from 4% in 1965 to 13% in 1999, while for adolescents (12–19 years), the percentage rose from 5% in 1970 to 14% in 1999.

Findings are similar in European countries. Data from the International Obesity Task Force (IOTF) and the European Association for the Study of Obesity (EASO) published in 2002 showed that 40–50% of men and 25–40% of women were overweight, and that 10–20% of men and 10–25% of women were obese.[1] In each country, overweight was more prevalent among men than women, while obesity rates were almost always higher for women than men. The prevalence of obesity has also shown a marked increase in recent years, with the majority of European countries showing a 10–50% increase in rates over the last 10 years. Prevalence of overweight in children and adolescents has also increased. Surveys conducted over the last 10 years typically show that 10–20% children aged around 10 years are overweight, although in some countries prevalence rates were over 30%.[1]

Overweight and obesity are associated with increased rates of mortality and morbidity. Mortality rates increase for both men and women throughout the range of moderate and severe overweight.[2] Among obese individuals, the risk of death from all causes is 50–100% greater than for those of normal weight (BMI 20–25 kg/m^2); most of the increased risk is due to cardiovascular causes.[3] Estimates put the number of deaths attributable to obesity in the US at 300 000 per year.[4]

Overweight and obesity are known to increase the risk for a number of diseases, including diabetes, cardiovascular disease (e.g. coronary heart disease [CHD] and cerebrovascular disease), hypertension and certain cancers.[3] In addition, they are associated with abnormal metabolic changes such as insulin resistance and dyslipidaemia, which are themselves risk factors for cardiovascular disease (CVD) and diabetes. The considerable overall impact of overweight and obesity

on health is therefore not surprising, with CVD representing the major cause of mortality in the developed world: in 2000, heart disease accounted for almost 30% of all deaths in the US.[3]

Increasing adiposity is directly associated with increases in morbidity and mortality from CVD, in addition to indirect effects through adiposity-related increases in known CVD risk factors, such as hyperglycaemia, dyslipidaemia and hypertension. Recent studies have suggested, for example, that even modest increases in BMI increase the risk of CHD. In the Nurses' Health Study, for example, the relative risk of CHD at BMI levels of 25–28.9 kg/m^2 and ≥29 kg/m^2 was 2-fold and 3-fold greater, respectively, than at BMI below 21 kg/m^2. Weight gain of 5–8kg increased the risk of CHD by 25% compared with individuals with stable weight.[6] A study in British men showed a 10% increase in the risk of coronary events with each 1-point increase in BMI at BMI levels above 22 kg/m^2.[7]

Overweight and obesity are linked to an increased risk of other cardiovascular events. Several studies, including the Framingham Heart Study, have shown that overweight and obesity are independent risk factors for congestive heart failure (CHF). CHF is a frequent complication and a major cause of death in severe obesity.[8] The Framingham Heart Study also suggests that overweight increases the risk for stroke independent of the effects of hypertension and diabetes. More recent studies have shown an association between overweight and ischaemic, but not haemorrhagic, stroke, with risk increasing with increasing BMI.[9,10]

In addition to the direct association between increasing adiposity and increases in morbidity and mortality from CVD-related events, increasing adiposity is associated with increases in other known risk factors for CVD, such as hyperglycaemia, dyslipidaemia and hypertension. Overweight and obesity are well established risk factors for diabetes, with increased rates of diabetes associated with increasing adiposity in both men and women. Recent studies have reported increases in the risk of diabetes beginning at BMI values as low as 22 kg/m^2.[11,12] In one study, each unit (1 kg/m^2) increase in BMI over 22 kg/m^2 increased the risk of diabetes by about 25%.[12] Numerous studies have similarly demonstrated the association between blood pressure and BMI or weight. NHANES III data showed increasing rates of high blood pressure with increasing BMI in both men and women.[13] Obesity and weight gain are also associated with dyslipidaemia, another established risk factor for CVD.[3,14] Obesity, overweight and excess abdominal fat are predictive of increased levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides and reduced levels of high-density lipoprotein (HDL) cholesterol.[3] In a recent US population survey, both overweight and obese individuals showed an increased risk of elevated cholesterol levels compared with normal individuals.[15] The changes in cholesterol levels seen in overweight and obese individuals result in a high LDL to HDL cholesterol ratio, increasing the risk of atherogenesis.

1.2 Adiposity and the Effect of Fat Distribution

The distribution of fat (adipose tissue) within the body is recognised as a key factor influencing the effect of increasing weight on health. Several studies have demonstrated a link between abdominal adiposity and overall mortality, with visceral adiposity particularly related to an increased risk of disease. Visceral adiposity is associated with an increased risk for dyslipidaemia and glucose intolerance.[16] The changes in lipid parameters observed with visceral adiposity increase the risk for CVD. The association between visceral adiposity and increased insulin resistance is a key factor contributing to increased risk for glucose intolerance and dyslipidaemia. Differences in visceral adiposity accounted for much of the variation in insulin resistance seen between individuals in a study of African Americans with type 2 diabetes.[17] Reductions in visceral adiposity in non-diabetic obese individuals were the best predictor of improved insulin sensitivity in a weight loss intervention study.[18] Other aspects of regional adiposity may also have an effect on insulin resistance. In the lower extremities, intramuscular adipose tissue

is strongly correlated with insulin resistance, whereas subcutaneous adiposity is only weakly associated.[19]

Recent research has begun to address the pathophysiological mechanisms that link adiposity to insulin resistance (reviewed by Goldstein[20]). Adipose tissue secretes a number of factors, including free fatty acids (FFA), peptides and cytokines, which can adversely affect insulin action and may have a detrimental effect on beta cell function. Secretion of these factors is influenced by overall adiposity and by fat distribution, with visceral adiposity appearing more pathogenic. Increased visceral adiposity is associated with increased release of FFA from adipose tissue. Prolonged exposure to elevated FFA levels can directly reduce the response of skeletal muscle and liver to insulin action through activity on insulin receptor signalling pathways. Elevated FFA levels also appear to compromise pancreatic beta cell function, reducing insulin secretion.

1.3 Diabetes Mellitus – a Growing Health Problem

Diabetes is a growing health problem, both in the US and worldwide. According to latest American Diabetes Association (ADA) estimates (based on 2002 census data), there are 13 million individuals with diagnosed diabetes in the US – 4.5% of the population.[21] Other estimates put the prevalence of diagnosed diabetes in the US at more than 7%.[15]

WHO data indicate that diabetes prevalence ranges from about 2% to over 6% in western European countries.[22] Population studies have also revealed large numbers of individuals with undiagnosed diabetes. In NHANES III, 2.7% of the surveyed population had undiagnosed diabetes, based on blood glucose analysis (i.e. fasting plasma glucose ≥126 mg/dL).[23] This compares with 5.1% with diagnosed diabetes. Undiagnosed diabetes is also widespread in Europe. Data from 13 studies performed in nine European countries showed that more than half of diabetes was undiagnosed in individuals younger than 50 years.[24] The ADA estimates that up to one-third of individuals with diabetes are undiagnosed. This represents an additional 5.2 million people in the US with the disease, giving an overall total of 18.2 million individuals with diabetes – 6.3% of the US population.[21] In addition, large numbers of individuals in the US have 'pre-diabetes'. That is, they have blood glucose levels that are above normal, but do not meet the diagnostic criteria for diabetes (see below). According to the ADA, an estimated 41 million people in the US have 'pre-diabetes'.[21]

Diabetes is associated with increased mortality compared with the general population. Analysis of NHANES I data showed that overall age-adjusted mortality in individuals with diabetes was approximately twice that in the non-diabetic population.[25] Mortality rates were observed to increase with age, although the relative risk of death in diabetic individuals compared with non-diabetic individuals decreased from 3.6 in those aged 25–44 years to 1.5 in those aged 65–74 years. Median life expectancy for individuals with diabetes was 8 years lower for those aged 55–64 years and 4 years lower for those aged 65–74 years compared with non-diabetic adults. The relative risk of death was higher in diabetic individuals than non-diabetic individuals for all major causes of death, except malignant neoplasms.[25]

Diabetes is also associated with increased morbidity. Individuals with the disease are at increased risk of morbidity due to CVD, hypertension and stroke. In general, diabetes and pre-diabetes (see below) increase the risk of macrovascular disease (i.e. atherosclerosis), including CVD-related events (e.g. myocardial infarction and stroke) and peripheral vascular disease-related events (e.g. amputations). Diabetes is also associated with microvascular disease, including nephropathy (kidney or renal disease), retinopathy and neuropathy. It is the leading cause of treated, end-stage renal disease and new cases of blindness among adults aged 20–74 years. The healthcare burden associated with diabetes is apparent from the high economic costs associated with treatment. Estimated direct costs exceeded $US91 billion in 2002, and medical expenditure was approximately

2.4 times higher for individuals with diabetes than those without the disease in the US.[26] In Europe, a study estimated the total direct medical costs for type 2 diabetes for eight European countries to be €29 billion per year, with an estimated average yearly cost per patient of €2834.[27]

1.3.1 Diagnosis of Diabetes Mellitus

The current diagnostic criteria for diabetes were developed in 1997 by an Expert Consensus Committee established by the ADA. The three different criteria (table I) all require blood glucose measurements and all except the third require confirmation on a subsequent day by any one of the three blood sampling criteria. The diagnostic guidelines were developed on the basis of epidemiological studies examining the risks of diabetic complications at increasing blood glucose levels. The values used represent approximate threshold levels, above which individuals have an increased risk of adverse outcomes, such as microvascular complications.[30] In addition, the committee identified a further category of individuals, those with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) where relevant glucose measures are above normal but not high enough to meet the criteria for diabetes, but still associated with increased risk of adverse medical outcomes. The guidelines for identifying these individuals were revised in 2004,[29] with the threshold level IFG reduced from 110 mg/dL to 100 mg/dL (table I). Individuals with IFG and/or IGT are referred to as having 'pre-diabetes' and are at increased risk of developing diabetes, as well as microvascular and macrovascular complications.

Diabetes mellitus is divided into two main types: type 1 and type 2.[30] In addition, diabetes that develops during pregnancy – gestational diabetes – is recognised as a separate category of diabetes. There are also a number of other less common forms of diabetes, characterised by specific genetic abnormalities (e.g. defects of beta-cell function or insulin action) or aetiological agents (e.g. drugs or chemicals, or infections).

Table I. Criteria for diabetes and impaired glucose tolerance and impaired fasting glucose

A. Diabetes – 1997 American Diabetic Association criteria[28]		
Fasting plasma glucose (FPG) ≥126 mg/dL (≥7.0 mmol/L)		
2-hour postload plasma glucose (2hPG)[a] ≥200 mg/dL (≥11.1 mmol/L)		
Symptoms of diabetes plus random plasma glucose ≥200 mg/dL (≥11.1 mmol/L)		
B. 'Pre-diabetes' – 2004 American Diabetic Association criteria[29]		
	FPG (mg/dL)	2hPG[a] (mg/dL)
Normal	<100	<140
Impaired glucose tolerance	–	140–199
Impaired fasting glucose	100–125	–
Diabetes	≥126	≥200

[a] After 75g oral glucose load.

1.3.2 Type 1 Diabetes

The defining characteristic of type 1 diabetes is the almost total loss of insulin secretory capacity by the beta cells of the pancreas. This is usually as a result of the selective cell-mediated autoimmune destruction of the beta cells, although for a minority of patients with type 1 diabetes there is no current evidence of autoimmunity.[30] The severe loss of beta-cell function means that patients with type 1 diabetes are dependent on exogenous insulin treatment. The rate of beta-cell destruction varies considerably between individuals, with some people not developing type 1 diabetes until adulthood. Typically, however, the disease develops during childhood or adolescence. In contrast, type 2 diabetes usually develops later in life, with most cases occurring in individuals aged 45 years and older. Thus type 1 diabetes accounts for the majority of cases in people younger than 20 years. Approximately 5–10% of individuals with diabetes have type 1 diabetes, although in non-Caucasian populations the proportion with type 1 disease may be lower, and could be as low as 2%. Overall, about 1 in every 400 children and adolescents in the US has type 1 diabetes.

1.3.3 Type 2 Diabetes

Type 2 diabetes is the most common form of diabetes, accounting for 90% or more of the cases of diabetes. Although increasingly detected in children in recent years, it typically occurs later in life,

with prevalence of the disease increasing with age. In the NHANES III survey,[31] the prevalence of physician-diagnosed diabetes (type 1 and type 2) was 1.1% in people aged 20–39 years, compared with 3.9% in those aged 40–49 years and 8.0% in those aged 50–59 years. In people aged 60–74 and ≥75 years, rates were 12.6% and 13.2%, respectively. In a more recent survey in the US, prevalence increased from 2.1% in the 18–29 age group to 15.5% in those aged 70 years and over.[15]

Two key pathological processes underlie the development of type 2 diabetes.[31] Deficient insulin secretion and impaired insulin action at the insulin receptor (insulin resistance) together lead to the development of hyperglycaemia and type 2 diabetes. The initial development of insulin resistance, resulting from a combination of genetic and environmental factors, leads to a compensatory increase in insulin secretion (hyperinsulinaemia), allowing normal glycaemic control to be maintained. However, after a period that averages 7–10 years in vulnerable individuals, beta-cell function can begin to deteriorate, so that plasma insulin levels are no longer sufficient to overcome insulin resistance. Worsening of relative hypoinsulinaemia as beta-cell function continues to decline leads to progressive loss of glycaemic control and the eventual development of type 2 diabetes. The resulting hyperglycaemia can potentially accelerate the process. High levels of glucose can have an inhibitory effect on beta cells, an effect known as glucose toxicity, further reducing insulin secretion. In addition, excess glucose can increase insulin resistance through reductions in glucose transporter levels and alterations in insulin signal transduction.

The gradual decline in plasma insulin levels is associated with gradual change in clinical presentation, as different insulin-dependent metabolic pathways become affected.[31] Glucose uptake by skeletal muscle requires relatively higher insulin concentrations, so insulin insufficiency is first apparent as postprandial hyperglycaemia, due to impaired postprandial glucose insulin-mediated glucose uptake into muscle cells. As insulin insufficiency increases, insulin-mediated inhibition of hepatic glucose production is affected, resulting in fasting hyperglycaemia. Further progression of insulin deficiency can lead to significant impairment in insulin-mediated inhibition of lipolysis in adipose tissue, resulting in excessive lipolysis and release of FFA, which contribute to the characteristic hypertriglyceridaemia associated with insulin resistance and diabetes. Under certain circumstances excess release of FFA can set the stage for exaggerated ketone body production and the development of diabetic ketoacidosis.

1.3.4 Diabetic Ketoacidosis

Diabetic ketoacidosis is a particular form of serious metabolic decompensation that, like nonketotic hyperosmolar hyperglycaemic states, can lead to diabetic coma and death. Diabetic ketoacidosis occurs in part as a result of severe insulin deficiency, so is most likely to occur in patients with type 1 diabetes, as they have very little or no endogenous insulin secretion. In contrast, ketoacidosis is relatively less common in patients with type 2 diabetes, as most patients retain some insulin secretory activity. Diabetic ketoacidosis has been observed increasingly in type 2 diabetes in various clinical settings, ranging from later stages of the disease where insulin secretion is markedly impaired to acute presentations in never-previously diagnosed individuals where glucose toxicity may contribute to acute suppression of beta-cell function. In diabetic ketoacidosis, the excessive flux of fatty acids from adipose tissue to the liver leads to the overproduction of ketone bodies, resulting in hyperketonaemia. Excess ketones appear in the urine, affecting ion regulation and leading to the loss of cations from the body, such as potassium. Ketoacidosis is also accompanied by hyperglycaemia, due to the lack of insulin activity.

1.3.5 Peripheral versus Central Actions of Insulin

Insulin acts at receptors both peripherally and in the CNS in the regulation of blood glucose levels and body adiposity.[32] In peripheral tissues, insulin lowers blood glucose levels by stimulating

the uptake of glucose into skeletal muscle and adipose tissue and suppressing the production of glucose by the liver. In addition, insulin acts to promote fat storage through the inhibition of lipolysis from adipocytes. Centrally, insulin acts at receptors in the CNS to reduce food intake, reducing the absorption of glucose and other nutrients into the body. In general, insulin plays an important role in energy regulation. For example, Brüning and coworkers[33] reported that mice with a neuron-specific deficit in insulin receptors had increased levels of body fat compared with normal controls. These insulin receptor-deficient mice also showed increased levels of obesity when given a high-fat diet compared with control mice, changes that were not simply the result of increased food intake. The development of insulin resistance therefore can have a significant effect on overall metabolic regulation. Central insulin resistance would be expected to lead to increased food intake and an increased propensity for developing obesity, which may aggravate the effects of peripheral insulin resistance.

1.4 Dyslipidaemia

Increases in circulating levels of certain lipid species are established risk factors for CVD, and represent important treatment targets for the reduction of CVD risk, through either lifestyle changes or drug therapy.[34] Numerous clinical and population studies measuring LDL-cholesterol or total cholesterol (the majority of which is LDL) have shown that elevated LDL-cholesterol levels are a strong risk factor for CHD. Current guidelines from the National Cholesterol Education Program (NCEP) Expert Panel recommend that LDL-cholesterol is the primary target of cholesterol-lowering therapy.[34] Treatment goals for LDL-cholesterol are based on the risk of CHD during the next 10 years. Thus, they vary depending on the presence of other risk factors (age, hypertension, smoking, low HDL-cholesterol and family history of CHD), existing CHD or other specific diseases associated with a similar increased risk of cardiovascular events (including peripheral artery disease and diabetes) [table II]. In addition to LDL-cholesterol, other lipids are involved in the development of CHD. Elevated triglycerides and low HDL-cholesterol levels are both independent risk factors for CHD (table II) and so represent important secondary targets for therapy.

In addition to NCEP guidelines, findings from a number of important clinical trials, including the Heart Protection Study (HPS), have been published.[35,36] The HPS showed that the reduction in the rate of major vascular events with simvastatin therapy appeared to be independent of baseline lipid levels. Thus, patients with baseline LDL-cholesterol levels ≥135 mg/dL and those with LDL-cholesterol <115 mg/dL showed similar significant reductions in vascular event rate. Significantly, patients with baseline LDL-cholesterol levels below 100 mg/dL (the NCEP target for patients with CHD or CHD risk equivalent) also experienced significant reductions in major vascular events with simvastatin. Lowering LDL-cholesterol to levels below the 2002 NCEP targets could

Table II. Criteria for abnormal lipid levels

A. Dyslipidaemia – NCEP criteria[34]		
LDL-cholesterol	<100 mg/dL	optimal
	100–129 mg/dL	near optimal / above optimal
	130–159 mg/dL	borderline high
	160–189 mg/dL	high
	≥190 mg/dL	very high
Total cholesterol	<200 mg/dL	desirable
	200–239 mg/dL	borderline high
	≥240 mg/dL	high
HDL-cholesterol	<40 mg/dL	low
	>60 mg/dL	high (beneficial – reduced risk of CHD)
Triglycerides	<150 mg/dL	normal
	150–199 mg/dL	borderline high
	200–499 mg/dL	high
	≥500 mg/dL	very high

B. Treatment goals for LDL-cholesterol – NCEP Adult Treatment Panel III	
Risk level	LDL-cholesterol goal
CHD[a]	<100 mg/dL (optional goal: <70 mg/dL)[b]
Multiple (2+) risk factors	<130 mg/dL
0–1 risk factor	<160 mg/dL

[a] CHD (coronary heart disease) or other diseases associated with a similar increased risk of cardiovascular events (CHD risk equivalent).
[b] For individuals with very high risk.

therefore provide additional benefit for individuals. In response to the findings from five major clinical trials including HPS, an update to the NCEP guidelines published in 2004[37] recommends an LDL-cholesterol level below 70 mg/dL as an optional therapeutic target for individuals at very high risk of CHD (table II). This includes individuals with established CVD plus either multiple major risk factors (especially diabetes), severe and poorly controlled risk factors, multiple criteria for the metabolic syndrome, or acute coronary syndromes. As further clinical trial data become available, future treatment guidelines may recommend tighter control of lipid levels to reduce the risk of CHD. Results from ongoing studies, such as HPS-2, the Treat-To-New-Targets (TNT) and Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trials, should help to determine these new targets.

1.4.1 Insulin Resistance and Dyslipidaemia

Insulin resistance is a key factor in the pathophysiology of dyslipidaemia and is associated with a characteristic pattern of lipid abnormalities. These include elevated triglyceride levels, low HDL-cholesterol levels, and only slight if any elevation in LDL-cholesterol.[38] Insulin resistance also leads to changes in the composition and functional characteristics of lipoproteins, increasing the levels of small, dense oxidised LDL and HDL particles. This altered plasma lipid profile is more atherogenic and is associated with changes in coagulation, oxidative stress, inflammation and endothelial function, adversely affecting cardiovascular health.

Insulin resistance leads to a decrease in the ability of adipocytes to inhibit lipolysis.[38] Increases in lipid breakdown result in elevated levels of FFA in the circulation and may also be accompanied by defects in the uptake and incorporation of FFA into triglycerides in adipocytes. The increase in the flux of FFA increases triglyceride production, leading to increased production and secretion of triglyceride-enriched very low-density lipoprotein (VLDL) by the liver into the circulation. The changes in plasma lipid composition and insulin resistance are also associated with changes in the composition of LDL and HDL particles. Smaller and more dense LDL and HDL particles are preferentially synthesised over larger particles. Increased concentrations of small, dense LDL particles in the circulation are associated with a 3- to 5-fold increased risk of coronary artery disease, due to a number of factors including increased potential for endothelial injury. Small, dense HDL particles have reduced antioxidant and endothelial protective properties and show increased clearance in the kidneys, reducing HDL-cholesterol concentrations.

1.5 The Metabolic Syndrome

It has been known for several decades that intra-abdominal fat or visceral fat is a risk factor for CVD and diabetes.[39] The terms 'syndrome X', the insulin resistance syndrome and the metabolic syndrome have been used to describe a set of commonly co-occurring conditions that include obesity (particularly abdominal obesity), insulin resistance, impaired glucose tolerance, disturbances in uric acid and lipid metabolism, hypertension, and prothrombotic and proinflammatory states, which can increase the risk of CVD.[40] The core features of the metabolic syndrome, focusing on five key risk factors, are presented in table III.[41] The US Public Health Service has aimed to increase awareness of the metabolic syndrome, with the NCEP Expert Panel[34] defining this to include obesity, dyslipidaemia, elevated blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. The current NCEP clinical guidelines for its identification are also shown in table III.

Obesity and overweight, physical inactivity and genetic factors can all contribute to the metabolic syndrome. The metabolic syndrome is closely associated with insulin resistance, although specific pathophysiological mechanisms regulating the emergence of the metabolic syndrome remain complex and incompletely understood.

Approximately 23% of the overall US population meet the NCEP definition for the metabolic

Table III. The metabolic syndrome

A. Five major features of the metabolic syndrome[41]	
Obesity	
Excess total body fat	
Central fat distribution/upper body obesity	
Increased visceral fat	
Insulin resistance/hyperinsulinaemia	
Dyslipidaemia	
Hypertriglyceridaemia	
Decreased HDL-cholesterol	
Increased LDL-cholesterol	
Impaired glucose tolerance/type 2 diabetes	
Hypertension	
B. Clinical identification of the metabolic syndrome[99]	
Risk factor	Defining level
Abdominal obesity	Waist circumference
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL-cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥135/85mmHg
Fasting glucose	>110 mg/dL

syndrome, and approximately 47 million Americans are affected. Approximately 60% of BMI-calculated obese (≥30 kg/m^2) US men and 50% of obese US women are affected, underscoring the public health impact of this condition. Among those with the syndrome, prevalent features are central obesity in 38% of individuals, low HDL-cholesterol in 36% and hypertension in 34%. Hypertriglyceridaemia occurs in about 30% of these patients, and insulin resistance in 12%.[42] The metabolic syndrome increases the risk for CHD at any given level of LDL-cholesterol, making it a target for therapeutic intervention. In a study conducted in Sweden and Finland, individuals with metabolic syndrome had a 3-fold increased risk of CHD and stroke.[43] NCEP guidelines recommend that root mediators of the syndrome (i.e. overweight and lack of physical activity) should be addressed in addition to the reduction of cholesterol levels. Weight reduction and increased activity are also effective at reducing insulin resistance, while additional medication should be used to treat high blood pressure and the prothrombic state.

Despite the widespread occurrence of metabolic syndrome throughout the Western world and recent campaigns to raise awareness of this health problem, and the potential relationship between antipsychotic-induced weight gain and the development of this problem, a recent survey revealed a low awareness among US psychiatrists of the risk of metabolic syndrome with second-generation antipsychotic therapy.[44] Although relatively higher percentages of psychiatrists associated second-generation antipsychotic treatments with a risk of weight gain/obesity (59%) and diabetes (51%), both of which are major features of metabolic syndrome, only 3% mentioned metabolic syndrome.

1.6 Cardiovascular Disease Risk Factors in Patients with Schizophrenia

There is increasing public health concern regarding the increased prevalence of known CVD risk factors in patients with schizophrenia and other mental disorders, as well as concern that treatment effects may contribute to this problem. As discussed above, weight gain and obesity, hyperglycaemia, smoking and dyslipidaemia are well known modifiable risk factors for CVD and are the targets of extensive health campaigns in industrialised countries. Weight gain and obesity have an adverse effect on glucose and lipid metabolism and are associated with an increased risk of hypertension, suggesting that potential adverse treatment effects on weight alone may contribute to increases in four key modifiable risk factors for CVD.

Brown et al.[45] reported that individuals with schizophrenia were more likely to have an unhealthy lifestyle than the general population, and Baxter[46] estimated that adjusting for social class accounted for 20% of excess mortality in a population with mixed mental illness. Lack of exercise and poor diet (i.e. high in fat and low in fibre) tend to be more prevalent in those with schizophrenia, increasing their risk for weight gain, diabetes and CVD. An estimated 75% of the schizophrenia population are smokers, 40–80% have a BMI ≥20% above normal, and the symptoms of the disease lead to an inactive lifestyle, all increasing CVD risk.[47-49] The increased level of CVD mortality in patients with schizophrenia (two to three times that of the general population), discussed below, sug-

gests that efforts should be made to lower risk factors for CVD in psychiatric populations and that one goal of therapy would be to use medications to manage these disorders, which do not themselves further increase adiposity or other risk factors for CVD.

2. Mental Illness and Excess Mortality

2.1 Mortality in Mental Illness

Numerous studies in the literature have demonstrated that mental illnesses, including schizophrenia, bipolar disorder and depression, are associated with excess medical mortality. This increased mortality has been observed consistently across various populations, with similar findings reported from studies in North America and western Europe, although further study is needed from different ethnic groups and in developing and non-Westernised countries. In schizophrenia, a meta-analysis of 18 studies,[50] which used record-linkage or patient follow-up studies or hospital record analysis, showed a statistically significant increase in mortality in all except one study involving the smallest patient cohort. Standardised mortality rate (SMR) was calculated for each study, which is the number of observed deaths in the study population divided by the number of expected deaths for an age- and sex-matched cohort from the general population, with the resulting value multiplied by 100 in some studies. Aggregate analysis for the 18 studies revealed an overall SMR of 1.51, a crude mortality rate of 189 deaths per 10 000 population per year and a 10-year survival of 81%.

Overall, the analysis showed that 80% of individuals with schizophrenia die from natural causes (i.e. related to medical illness as opposed to accidents, suicide, etc.) compared with approximately 97% of the general population.[50] Both natural and unnatural deaths increased statistically significantly in schizophrenia. Natural deaths accounted for 59% of excess mortality (overall SMR 1.34), while unnatural deaths made up 41% of excess mortality (overall SMR 4.26). Suicide was the single largest cause of excess mortality, accounting for about 28% of the excess deaths and 12% of all deaths in the meta-analysis. Aggregate SMR for suicide was 8.38, and was statistically significantly higher in male patients than female patients (9.56 vs 6.73). In a more recent study of schizophrenic patients conducted in Sweden,[51] suicide was also the major cause of excess mortality in male patients, whereas CVD was the main cause of excess deaths among females.

Overall, CVD was the most common cause of mortality among patients with schizophrenia in the meta-analysis, accounting for 34% of deaths among male patients and 31% in female patients.[50] Neoplastic disease (male 13%; female 16%) and respiratory disease (male 8%; female 9%) were the next most common causes of mortality, although in male patients, both were less frequent than suicide (male 17%; female 6%). Mortality from cardiovascular and respiratory disease, but not neoplastic disease, was significantly elevated in schizophrenia compared with the general population. In the Swedish study,[51] CVD was the largest single cause of death in both male and female patients, and mortality rates were elevated compared with the normal population (SMR: male 2.30; female 2.10).

Increased mortality rates have also been observed in patients with affective disorders. Twelve studies involving either large populations (>5000 individuals) or long observation periods (>5 years), summarised by Angst et al.,[52] all showed elevated mortality for affective disorder patients compared with the general population, with overall SMR ranging from 1.23 to 2.50.

A long-term follow-up over 34–38 years of more than 400 patients with affective disorders (unipolar depression or bipolar disorder) showed elevated mortality compared with the general population (SMR 1.61).[52] While suicide showed the greatest increase compared with the general population (SMR 18.04), patients with affective disorders also showed increased mortality for cardiovascular/coronary heart disease (SMR 1.61). This increase was particularly apparent among female patients (SMR 170), while male patients showed increased deaths from cerebrovascular and other vascular disorders (SMR 2.21). Overall, both male and female patients with affective disorders showed an increase in mortality from vascular dis-

ease (SMR: male 1.63; female 1.47). A comparison of patients with unipolar depression and those with bipolar disorder showed that both had elevated overall mortality (SMR: unipolar 1.63; bipolar 1.58) and that the difference between the groups was small but statistically significant. As in the overall population, SMR for suicide was statistically significantly higher in both groups than for the general population, but was statistically significantly greater in patients with unipolar depression than those with bipolar disorder (26.72 vs 12.28). Death from all vascular diseases was also elevated for both unipolar (SMR 1.34) and bipolar (SMR 1.69) groups, while patients with bipolar disorder also showed a statistically significant increase in cardiovascular/coronary heart disease mortality compared with the general population (SMR 1.84).

A meta-analysis of 25 community studies showed elevated mortality in patients with depression.[53] The overall relative risk (RR) of dying was 1.81 (95% CI 1.58, 2.07) in depressed compared with non-depressed individuals. The RR was higher for men (2.25) than for women (1.75), although the confidence intervals overlapped. Further analysis of three studies showed that the RR in severe depression was not statistically significantly different from that in subclinical depression.

The increased mortality from vascular disease among patients with schizophrenia, bipolar disorder and depression underscores the importance of attending to well established risk factors such as increased weight, insulin resistance, and elevated glucose and lipid levels in patients with major mental disorders. Obesity and weight gain are important risk factors for insulin resistance, hyperglycaemia and dyslipidaemia, suggesting the importance of lifestyle factors as well as potential drug effects on patient health.

2.2 Increased Rates of Metabolic Disturbance among Patients with Psychiatric Disorders

Reports of abnormal glucose regulation among individuals with schizophrenia pre-date the introduction of antipsychotic therapy (reviewed by Haupt and Newcomer[54]), underscoring the importance of effects such as lifestyle, nutrition and activity level and raising the possibility of potential pathophysiological relationships between schizophrenia and glucose regulation. These early reports suggest that patients with psychotic disorders may have an elevated baseline risk for disturbances in glucose regulation, independent of any adverse medication effects. These findings should, however, be viewed with caution, as the definitions of diabetes and schizophrenia used differ from current ones, and the studies are limited by their lack of assessment of or controls for age, weight, adiposity, activity, diet, family history or ethnicity.

More recent population studies have examined the prevalence rates for diabetes in patients with schizophrenia. Three chart reviews of patients with schizophrenia have reported increased rates of diabetes compared with the general population. A Japanese study[55] reported an increased incidence of diabetes in 420 patients with schizophrenia compared with 312 control individuals (8.8% vs 5.0%). A smaller study, involving 95 schizophrenic patients (aged 45–74 years) admitted to a long-term care facility in Italy, reported an overall prevalence of diabetes of 15.8%.[56] This was higher than prevalence rates reported in population surveys conducted in Italy. The largest of these studies[57] reported diabetes prevalence in patients with schizophrenia based on analyses of Medicare and Medicaid data from 1991 and a survey of more than 700 inpatients. Prevalence rates, based on diabetes claims data, were 11.1% for the Medicaid sample (n = 6066) and 12.5% for the Medicare sample (n = 14 182), while the lifetime diabetes prevalence from the patient survey was 14.9%. In all three groups, increasing age, female sex and African American or 'other' ethnicity were all associated with increased likelihood of diabetes. Prevalence rates from Medicaid and Medicare data for patients aged 45–64 years were 18.8% and 14.9%, respectively, and for those ≥65 years were 18.8% and 20.8%. No control group was included in the study. Reported rates were greater than estimated rates for the overall age-adjusted US population (2000 values: ADA 6.2%; Behavioral Risk

Factor Surveillance System [BRESS] 7.1%[58]), and similar to rates seen in older nonpsychiatric populations (ADA: ≥65 years 20.1%; BRFSS: 60–69 years 14.5%; ≥70 years 14.9%) or some non-Caucasian populations, suggesting that major psychiatric illness may be a risk factor analogous to age or ethnicity that can adversely affect prevalence.

Although all three studies suggest an increased prevalence of diabetes in patients with schizophrenia, a number of confounding factors could have had an effect on these findings. For example, the studies do not take into account the use of antipsychotic medication independent of the diagnosis of schizophrenia, which may affect the risk of diabetes either directly or through the increases in bodyweight seen with some antipsychotic agents, as discussed below.[59] In addition, weight and lifestyle factors, such as nutrition and activity levels, were not considered in these studies – important issues, as individuals with schizophrenia are also more likely to be obese and have an unhealthy lifestyle than the general population.[45]

A recent study examines the prevalence of diabetes in patients with psychiatric disorders compared with the rate expected for an age-, ethnicity- and sex-matched group of individuals from the general US population.[60] This relatively small retrospective chart review involved 243 inpatients, aged 50–74 years, diagnosed with schizophrenia (n = 71), schizoaffective disorder (n = 20), unipolar major depression (n = 65), bipolar I disorder (n = 53) or dementia (n = 34). Rates of type 2 diabetes differed significantly between the diagnostic groups ($p = 0.006$): schizoaffective disorder 50%; bipolar disorder 26%; major depression 18%; dementia 18%; and schizophrenia 13%. These rates were significantly greater than matched groups from the general US population for schizoaffective (10%; $p < 0.02$) and bipolar (13%; $p < 0.05$) disorders, but did not differ statistically significantly for schizophrenia (15%), depression (14%) or dementia (15%). Overall, the prevalence of type 2 diabetes in the psychiatric sample (25%) was significantly greater than the expected rate for a matched group in the general US population (14%; $p < 0.003$). Logistic regression analysis showed that BMI and psychiatric diagnosis were the only statistically significant and independent predictors of a diabetes diagnosis in this sample. In this study, use of potentially hyperglycaemic psychotropic medications (clozapine, olanzapine and phenothiazines) did not differ statistically significantly between diabetic and non-diabetic individuals.

To avoid the potential confounding effects of antipsychotic medication on glucose regulation, a recent study by Thakore and colleagues[61] examined the prevalence of impaired fasting glucose in 26 drug-naive, first-episode patients with schizophrenia in Ireland. The mean age of these patients was 33.6 years, and mean BMI was 24.5 kg/m^2. These schizophrenic patients were matched for age, sex, diet and exercise measures to 26 healthy controls. The frequency of impaired fasting glucose (fasting plasma glucose [FPG] >110 to <126 mg/dL) was significantly higher in patients with schizophrenia (15.4%; n = 4) compared with healthy controls (0%; $p < 0.02$). Mean fasting plasma levels of glucose (95.8 vs 88.2 mg/dL; $p < 0.03$), insulin (95.8 vs 88.2 μU/mL; $p < 0.05$) and cortisol (499.4 vs 303.2 nmol/L; $p < 0.0001$) were significantly higher in the schizophrenia group than the control group. A calculated insulin resistance, validated in population studies, was also significantly greater in schizophrenia patients than controls (mean HOMA insulin resistance: 2.3 vs 1.7; $p < 0.01$). This study, however, involved acutely ill, unmedicated patients, so the findings may not be comparable to those of the majority of studies involving patients with stable schizophrenia. In this study, it is likely that the acutely ill, acutely hospitalised patients were experiencing high levels of stress during the study period, as is reflected in the significantly increased plasma cortisol levels. Elevated cortisol is a known contributor to insulin resistance, potentially leading to increased blood glucose levels, and this study found a significant correlation between plasma cortisol and glucose regulation in these acutely ill, first-episode patients. In contrast, previous studies of glucose regulation involving patients with stable schizophrenia have detected no significant hypercortiso-

laemia or correlation between plasma cortisol and plasma glucose or insulin levels,[62] suggesting that this study may overestimate rates of impaired fasting glucose and insulin resistance by incorporating effects of acute illness and hospitalisation that exaggerate factors that increase insulin resistance and hyperglycaemia. In addition, the mean age of the drug-naive patients was significantly older than that in comparable samples of drug-naive first-episode subjects in the US, suggesting that prolonged periods of untreated psychotic illness may have contributed to worsening of adverse changes in lifestyle and economic conditions that might further exaggerate factors contributing to insulin resistance. In a more recent study, Ryan and coworkers[63] examined adiposity in an overlapping sample of 16 first-episode, drug-naive patients with schizophrenia. At the start of the study and prior to antipsychotic treatment, the schizophrenia patients had statistically significantly higher levels of intra-abdominal fat than healthy controls matched for age and BMI, suggesting that schizophrenia may be associated with changes in adiposity that could increase the risk for insulin resistance, hyperglycaemia and dyslipidaemia compared with the general population. As above, attributes of this particular sample may contribute to the degree to which adiposity and insulin resistance were increased, which might overestimate rates of adiposity and insulin resistance in drug-naive schizophrenia samples in other clinical settings.

Overall, these studies suggest that there may be an increased risk of type 2 diabetes in patients with schizophrenia. Evidence from a number of studies (e.g. Regenold et al.[60]) suggests that this is not limited to schizophrenia, but could also affect patients with other psychiatric disorders, such as bipolar disorder and depression. Decreased insulin sensitivity has been consistently reported for patients with depression compared with non-depressed individuals[64,65] (for review see Haupt and Newcomer[54]), suggesting abnormalities in glucose regulation associated with depression. However, as with the studies in schizophrenia patients, these reports have typically failed to characterise patient characteristics such as adiposity, diet and activity. Further large-scale studies in schizophrenia and other psychiatric disorders, controlling for factors such as BMI and medication, are therefore needed to address the question of glucoregulatory disturbances in these patients.

The occurrence of dyslipidaemia among patients with schizophrenia has been less well studied, with limited data available compared with that for diabetes. Lifestyle surveys typically show higher levels of obesity, reduced levels of exercise and less healthy diets among schizophrenic individuals than the general population – factors that point to an increased prevalence of dyslipidaemia among individuals with the disorder. In a recent literature review concerning the effects of antipsychotic medication on plasma lipid levels,[66] based largely on case series and uncontrolled observations, findings with typical agents suggest that chlorpromazine and other phenothiazines are associated with dyslipidaemia, while butyrophenone-derivatives (e.g. haloperidol) have little effect on lipid levels. Controlled studies concerning the effect of second-generation antipsychotics, discussed in detail in the following sections, suggest that treatment with some agents is associated with a risk of dyslipidaemia. However, as with the studies examining the prevalence of diabetes in schizophrenia, weight and lifestyle factors, such as diet and exercise, are likely to affect the occurrence of dyslipidaemia in these patients. Additional large-scale studies that control for factors such as BMI and medication are therefore needed to examine the prevalence of dyslipidaemia in patients with schizophrenia.

Although the evidence suggests an increased risk of diabetes mellitus associated with the presence of some psychiatric disorders, particularly depression, the reasons underlying such an increase are unclear and represent an important area for future research. Several studies in patients with depression have shown an approximately 2-fold increase in the relative risk of diabetes over the general population, while similar studies in schizophrenia suggest an increased risk that may be of similar magnitude to that seen in depression. Socioeconomic factors are thought to play at least some role in this increased risk. Individuals with

schizophrenia may experience less exercise and have a poorer, less healthy diet than the population as a whole.[45] Another possibility that has been the subject of some speculation is that patients with these disorders may share some underlying genetic or biological factor that predisposes them to an increased risk of metabolic disturbance. Clearly, further research is needed in this area.

3. Search Methodology and Overview of Findings

3.1 Search Methodology

This literature review examines the evidence for an association between dysregulation of either glucose or lipid metabolism and treatment with any of the eight second-generation antipsychotics currently available in the US and/or in Europe: clozapine, risperidone, olanzapine, quetiapine, zotepine, amisulpride, ziprasidone and aripiprazole.

Literature references were identified primarily via Medline searches. Searches were performed for the individual antipsychotic agents, plus 'atypical antipsychotics'. Each of these nine search terms was combined with each of the following terms to identify relevant references: diabetes, glucose, ketoacidosis, hyperglycaemia, triglycerides, hypertriglyceridaemia, lipidaemia, hyperlipidaemia, dyslipidaemia and cholesterol. Searches were performed on papers published before 1 January 2004, although more recent references were in some cases included as below.

In addition to the Medline searches, abstracts presented at selected scientific meetings (23rd Congress of the Collegium Internationale Neuropsychopharmacologicum [CINP 2002], 15th and 16th Congresses of the European College of Neuropsychopharmacology [ECNP 2002 and ECNP 2003] and the 12th Biennial Winter Workshop on Schizophrenia [WWS 2004]) were searched using the same terms, and any relevant abstracts are included in the report. Finally, published reports of key pivotal studies examining the safety and efficacy of the different second-generation antipsychotics in patients with schizophrenia were reviewed for glucose and lipid data.

This literature review is limited by its reliance largely on Medline to identify relevant studies reporting glucose and lipid regulation. Studies in publications not indexed by Medline are therefore missing, leading to the potential exclusion of some relevant data. In addition, Medline searches may miss glucose and lipid measurements that are generally not included in the abstract of reports concerning controlled trials of antipsychotic efficacy, although the review of key published pivotal trials of second-generation antipsychotic treatment in schizophrenia may mitigate this issue. Searches of abstracts presented at the CINP 2002, ECNP 2002 and 2003, and WWS 2004 congresses may also help to incorporate studies that have not yet been published in Medline journals. Review of these studies, however, may be restricted by the limited data and details available in such published abstracts.

3.2 Types of Reports

The number of reports identified in this literature review for each of the eight second-generation antipsychotics varies considerably between the different agents. This is to be expected, given the differences in their prescription rates and in the length of time that these treatments have been available and differences in the level of interest concerning metabolic adverse events with individual agents. Most information is available for clozapine, risperidone and olanzapine, which have been available for longer and, in the case of risperidone and olanzapine, have been the two most widely prescribed second-generation antipsychotics in the US. Fewer reports were identified for the more recently approved agents, quetiapine, ziprasidone and aripiprazole, and for the two agents not currently released in the US, zotepine and amisulpride.

The reports identified in this review can be broadly divided into three categories:

- case reports/chart reviews/FDA MedWatch-based reports/other uncontrolled observational studies

- large retrospective database analyses using prescription, administrative or, less commonly, population-based databases
- controlled experimental studies, including randomised clinical trials.

Not all categories of study are available for each antipsychotic agent.

3.3 Levels of Evidence

These three categories of reports provide different levels of evidence to assess the effect of each antipsychotic agent on the different metabolic parameters. Studies can be considered either 'hypothesis generating' or 'hypothesis testing', depending on their methodology. Case reports, chart reviews and open, observational studies all provide uncontrolled, largely anecdotal evidence and so are generally useful for hypothesis generation only. A critical factor to consider in all post-marketing adverse event reporting is that most reports happen in the first 2 years after the launch of a drug, with underreporting generally estimated to be in the range of 1/10 to 1/100 of the actual number of cases. In contrast, controlled experimental studies, including prospective, randomised, controlled clinical trials, are designed to address specific questions and can be useful for hypothesis testing.

Relevant retrospective database analyses, a few using population-based sample data, can provide higher or lower levels of evidence depending on the methodology and the study endpoints used. The studies identified in this literature review have a number of methodological limitations relating to the common use of pre-existing medical claims databases. These limitations include the lack of verification of psychiatric diagnosis and whether treatments were actually received, high rates of polypharmacy and limited, if any, knowledge of earlier treatment conditions that can contribute to current levels of adiposity and associated insulin resistance. Most importantly, these studies typically lack direct measures of metabolism, relying on surrogate markers for the presence of diabetes, such as the prescription of a hypoglycaemic agent or an ICD code for diabetes. Such surrogate markers require the successful and consistent diagnosis of diabetes in the relevant study sample, but underdiagnosis of diabetes is common and contributing factors are poorly understood. According to the ADA, approximately one-third of cases of diabetes are undiagnosed in the US.[23] Given that these database studies may involve samples that underestimate the prevalence of diabetes, missing perhaps 30% of actual cases, and that the hypothesised difference in prevalence rates across treatment or diagnostic groups is certainly less than 30%, this type of retrospective database analysis may suffer from signal-to-noise limitations. This may affect their ability to reliably detect differences between medications or across groups and may explain some of the variability in studies of this kind, suggesting that the results of such retrospective analyses using surrogate measures of diabetes should be interpreted with caution.

4. Second-Generation Antipsychotics and Weight Gain

4.1 Impact of Weight Gain

Overweight and obesity, along with increases in adiposity in general, are established risk factors for insulin resistance, hyperglycaemia and dyslipidaemia.[14] Increases in bodyweight are typically associated with increases in adiposity, with abdominal adiposity in particular a known risk factor for cardiovascular morbidity and mortality. In addition, abdominal adiposity is associated with insulin resistance, so that adiposity can secondarily contribute to hyperglycaemia and dyslipidaemia, which are, like obesity, independent risk factors for CVD.

The effects of antipsychotic medications on bodyweight therefore have significant implications for patient health. Weight gain is a well established side effect of antipsychotic therapy, reported in up to 50% of patients receiving long-term treatment for schizophrenia.[67] The causal effect of antipsychotic treatment to induce weight gain has been

established in randomised, double-blind, placebo-controlled clinical studies. However, marked differences in weight gain liability are seen between the different antipsychotic agents (figure 1).[59] The rank order of weight gain risk for the different agents closely matches the rank order of risk for hyperglycaemia and dyslipidaemia, discussed below, which has led to the hypothesis that the increased risk of diabetes, hyperglycaemia and dyslipidaemia seen with some second-generation antipsychotics could be largely related to their effect on body fat. Demonstrated in the following literature review, there is largely consistent evidence that the second-generation agents associated with more weight gain (i.e. clozapine and olanzapine) are associated with an increased risk of diabetes, hyperglycaemia and dyslipidaemia.[68] However, a considerable minority of reports of new-onset diabetes in the absence of obesity or substantial weight gain,[69-71] along with a limited amount of experimental evidence for changes in glucose regulation and insulin resistance independent of adiposity,[62,72,73] suggest that some second-generation antipsychotics may also have adverse effects on insulin secretion or sensitivity that are independent of adiposity.

A growing number of reports in the psychiatric literature have unfortunately subjected time-limited datasets to the simple question of whether weight gain within some specific (but always relatively short-term, with respect to the time frame for the onset of diabetes mellitus) time frame of sampling is statistically related to emergent diabetes or hyperglycaemia, without regard for the commonly

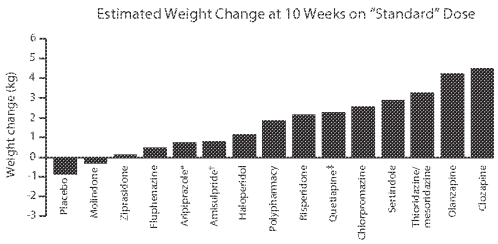

Fig. 1. Mean change in bodyweight with antipsychotic therapy. Adapted from Allison et al., Leucht et al. †(amisulpride), Jones et al. ‡(quetiapine) and Marder et al. *(aripiprazole).[59,74-76]

observed delay between the onset of insulin resistance and the emergence of hyperglycaemia (i.e. related to the delay in onset of pancreatic beta-cell failure). Detailed below, some of these analyses have detected a relationship between weight gain and hyperglycaemia and some have not. Given the strong evidence from nonpsychiatric samples and population studies linking weight gain with increased risk for diabetes, hyperglycaemia and dyslipidaemia, these recent *post hoc* analyses, dutifully listed below, do not provide compelling arguments against a role for weight gain in the development of metabolic changes seen with antipsychotic therapy. In addition, growing evidence indicates that treatment-induced increases in adiposity are associated with predictable increases in measures of insulin resistance and increases in fasting plasma triglyceride, changes that are known to predict long-term increases in plasma glucose in vulnerable individuals. Despite the absence of compelling evidence that the adverse effects of adiposity do not occur in psychiatric patient samples, some authors have taken a sceptical position, along the lines of recent US FDA comments, that the relationship of weight gain to hyperglycaemia has yet to be proven in patients taking antipsychotic medications.[77]

Given the important potential relevance of drug-induced increases in weight and adiposity on metabolic function, the effect of each second-generation antipsychotic on weight and adiposity is reviewed at the start of each section concerning individual medications. However, as this article is primarily a review of the effects of antipsychotic therapy on metabolic parameters, the sections covering the effect of this therapy on weight and adiposity provide an overview of most of the available data and are not intended as comprehensive reviews of the related literature.

4.2 Weight Gain in Children, Adolescents and the Elderly

The majority of studies and reports of the effects of antipsychotic therapy on bodyweight have been in adults. There is, however, a small but

increasing body of evidence that the findings in adults are not directly applicable to children and adolescents, or to the elderly, and that the weight increases observed with antipsychotic therapy are more severe in children and adolescent patients than in adults.

4.2.1 Children and Adolescents

Weight gain in children can be associated with normal growth-related increases in lean muscle mass or with increases in adiposity. The few studies in children that have attempted to address this distinction have compared treatment-induced weight gain with standardised growth curves rather than directly measuring changes in lean muscle versus fat mass. Child psychiatrists have clinically noted substantial weight gain in children during antipsychotic treatment, providing anecdotal reports and early observations that this effect in children is even more pronounced than that observed in adults. However, no controlled data are available to describe how treatment-induced changes in adiposity affect insulin sensitivity and other aspects of metabolism in children.

The few studies that have reported changes in bodyweight in children treated with antipsychotics raise concern that weight gain may be more significant in this treatment population than in adults. An open-label study of olanzapine (mean dose 10.7 mg/day) in 25 children with pervasive developmental disorder demonstrated an average weight gain of 4.7kg after 12 weeks of treatment,[78] corresponding to an increase in bodyweight of nearly 10%. Olanzapine treatment (mean dose 17.5 mg/day) of eight psychotic adolescents resulted in an average 14% increase in bodyweight over an average of 9 weeks of treatment.[79] A study of 8 weeks of randomised treatment with either risperidone (up to 3mg) or placebo in 26 children with Tourette's syndrome resulted in an average weight gain of 2.8kg compared with no weight change during placebo treatment.[80] A retrospective study with 50 patients younger than 18 years treated with olanzapine (mean dose 13.9mg) found an average weight gain of 3.8kg after an average duration of treatment of 39 days.[81] A multicentre, double-blind study of 118 children aged 5–12 years with mental retardation and disruptive behaviours found a mean weight increase of 2.2kg after only 6 weeks of treatment with risperidone (mean dose 1.16mg) compared with 0.9kg with placebo.[82] A recent study of 19 children aged 7–17 years with either Tourette's syndrome or chronic motor tic disorder reported an average weight gain of 1.9kg over the 4-week treatment period with risperidone (mean dose 2.5mg).[83] A similar open-label study of risperidone treatment (mean dose 1.26mg) in autistic children reported an average weight gain of 3.2kg after 4 weeks of treatment.[84] A multisite, randomised, double-blind trial of risperidone (mean dose 1.8mg) compared with placebo among 101 children aged 5–17 years with autism found an average weight gain of 2.7kg after 8 weeks of treatment compared with 0.8kg with placebo.[85] Sixty-three of these children treated openly for an additional 4 months had an average weight gain of 5.6kg after a total 6 months, suggesting that, as in adults, treatment effects on weight gain are not limited to the short term.[86] Sikich and co-workers[87] randomised 50 psychotic children and adolescents to 8 weeks of treatment with haloperidol, olanzapine or risperidone. While significant weight gain was seen in all groups, between-group differences in weight gain and BMI were statistically significant (olanzapine > risperidone > haloperidol). Risperidone-treated patients experienced an average weight gain of 4.9kg compared with an average weight gain of 7.1kg in those treated with olanzapine.

These reports suggest that weight increases associated with antipsychotic therapy are more prominent in children and adolescents than in adults. This is of particular concern, given the long-term effect of overweight and obesity on patient health and the increasing prevalence of overweight observed in children and adolescents in the general population.

4.2.2 Elderly Patients

Data regarding weight gain in elderly patients treated with second-generation antipsychotics are

modest. Furthermore, they are generally limited by the serious methodological issue of elderly patients having progressive loss of lean muscle mass, which has the potential to mask treatment-associated increases in bodyweight and adiposity.

Weight increases during antipsychotic treatment in younger patients are understood to be due to increases in fat mass, rather than changes in lean muscle mass. Using direct measures of fat mass and body composition in untreated elderly individuals, progressive decreases in lean muscle mass are routinely observed, with or without decreases in weight.[88] Progressive increases in fat mass in untreated weight-stable individuals can in fact mask decreasing lean muscle mass and sarcopenia.[89] Treatment with medications that can stimulate appetite, among other actions, is expected to increase fat rather than lean muscle mass in the sedentary elderly. Such changes are expected to have an adverse effect on health, as visceral adiposity is associated with an elevated risk for increased insulin resistance, dyslipidaemia and glucose intolerance, contributing to cardiovascular disease and diabetes.[16] Thus, elderly patients may be at increased risk of adverse metabolic changes, even if they do not experience marked increases in bodyweight.

Risperidone has been reported to cause minimal weight gain[90] or no significant gain[91,92] in the elderly. Madhusoodanan et al.[93] found insignificant mean weight gain of 0.84kg in a sample of elderly patients (mean age 71 years) treated with olanzapine. However, this study was retrospective and limited by a small sample size. In a relevant study of Alzheimer's dementia patients with psychosis, olanzapine treatment produced a modest mean weight gain of 0.8kg over 6 weeks, in contrast to a mean weight loss of 0.19kg in placebo-treated patients.[94] Although this study was limited by the use of weight measures rather than direct measures of body composition, it highlights the potential for progressive weight loss in untreated patients. Such weight loss can mask or minimise weight gain when patients are treated with antipsychotics. Unfortunately, many previous studies in the elderly included no untreated control group, so weight changes on treatment are not possible to interpret. Further studies are therefore needed to assess the effect of antipsychotic therapy on weight, adiposity and metabolic parameters in the elderly.

4.3 Possible Mechanisms of Antipsychotic-Induced Weight Gain and Metabolic Effects

4.3.1 Bodyweight

The mechanisms by which antipsychotic medications produce their effects on bodyweight and body composition are poorly understood, with many different receptor types (including 5-HT_{2A}, 5-HT_{2C}, H_1 histamine and α_1- and α_2-adrenergic receptors) hypothesised to be a relevant target of antipsychotic activity. Of these, H_1 receptors are currently the focus of much interest and more evidence, although the mechanisms by which H_1 receptor antagonism might induce weight gain are currently unclear.

A recent study suggests a strong association between the level of H_1 receptor affinity and antipsychotic-induced weight gain.[95] The receptor-binding affinities of 17 first- and second-generation antipsychotics (including all of the second-generation agents except zotepine and amisulpride included in this review) were examined for correlations with their short-term effects on bodyweight, as determined in a previous meta-analysis of the literature.[59] H_1 receptor-binding affinity showed a statistically significant correlation with weight gain, and 15 of the 17 drugs were correctly classified into two groups – those that induce weight gain and those that do not – based on their H_1 binding affinities using discriminant function analysis. Interestingly, affinity for the 5-HT_{2C} receptor did not correlate significantly with weight gain in this study, even though previous genetic studies have suggested a role for the 5-HT_{2C} receptor in weight regulation in rodents. Furthermore, an earlier study suggested a link between weight gain and polymorphisms in the 5-HT_{2C} receptor gene,[96] hypothesising that such genetic variation could predispose

individuals to more or less weight gain via as yet unknown mechanisms. Further studies examining this link between 5-HT_{2C} receptor gene polymorphisms and weight gain have, however, produced inconsistent results. In a study of patients with first-episode schizophrenia, those with one variant of the 5-HT_{2C} receptor gene showed significantly less weight gain after 6 weeks of clozapine therapy than patients who lacked this particular variation.[97] However, in another study of schizophrenic patients, no association was detected between the variant allele and weight gain after 12 weeks of clozapine therapy.[98]

Kroeze and colleagues[95] do not discount the role of other receptor types in the development of antipsychotic-induced weight gain. Sulpiride can induce significant long-term weight gain in some patients with schizophrenia, even though it is a selective dopamine D_2/D_3 receptor antagonist with virtually no affinity for H_1 receptors. Similarly, substantial weight gain has occasionally been reported with depot formulations of the typical antipsychotics haloperidol and fluphenazine,[99] although these agents also show relatively low H_1 receptor affinity.

4.3.2 Glucose Dysregulation

Mechanisms underlying the changes in glucose regulation associated with antipsychotic therapy are only beginning to be understood. A number of studies suggest that the effect of antipsychotic treatment on insulin resistance, rather than insulin secretion, may be more important for most patients. For most individuals, changes in insulin resistance occur secondary to increases in adiposity.[73,100] However, a significant minority of patients may experience glucose dysregulation independent of weight or adiposity differences,[62,69-71,73,78] suggesting the possibility of a direct effect of certain antipsychotic medications on insulin sensitivity or secretion. One possible mechanism for antipsychotic drug effects that could occur independent of changes in adiposity would involve drug effects on glucose transporter function. Dwyer and colleagues have shown that certain antipsychotic agents, including clozapine, olanzapine and chlorpromazine, can inhibit glucose uptake via interactions with glucose transporter proteins in *in vitro* studies using cloned cell lines, whereas other agents, such as haloperidol, had a marginal effect on glucose transport.[101,102] These drugs can also induce hyperglycaemia in mice in accordance with their effects on glucose transport.[103] Risperidone can also interact with these intracellular proteins, but the limited lipophilic nature of this agent results in reduced tissue-to-plasma concentration ratios, suggesting that intracellular protein interactions as well as intracellular drug concentrations may be critical to the prediction of drug effects in this area. These findings suggest that differing effects on glucose transport can be hypothesised to underlie the clinical observation of different adiposity-independent antipsychotic drug effects on insulin sensitivity, although additional laboratory and clinical studies are needed.

Serotonin receptor activity may also have a role in glucose regulation. Both 5-HT_{1A} and 5-HT_2 receptors have been implicated, although the exact role of these receptors appears complex, and the rank order of *in vitro* affinities of antipsychotic agents for serotonin receptors does not fit well with the rank order of their effects on glucose regulation.

Changes in noradrenaline and adrenaline turnover and plasma concentrations during clozapine treatment[104,105] may also be relevant to understanding drug effects on glucose metabolism that could occur independent of changes in adiposity. Increases in circulating noradrenaline and adrenaline could be predicted to reduce beta-cell function and increase glucose release from hepatocytes. It remains to be seen what role, if any, such changes in adrenergic function play in the development of abnormalities in glucose or lipid metabolism during antipsychotic treatment.

4.3.3 Lipid Dysregulation

The mechanisms underlying the changes in lipid parameters associated with antipsychotic therapy have been little studied, although a number of

possible mechanisms have been suggested.[66] Epidemiological studies in the general population provide a wealth of data showing that weight gain and obesity increase the risk of dyslipidaemia, with higher levels of obesity linked to increasing risk. Obesity and weight gain are associated with increased triglyceride and LDL-cholesterol levels and reduced HDL-cholesterol. Antipsychotic agents differ markedly in their weight gain potential, suggesting that the effects on lipid levels seen with antipsychotic agents may primarily be related to their effect on bodyweight and adiposity.

Other factors may also play a role in the development of treatment-associated dyslipidaemia. The development of glucose intolerance would be expected to affect lipid levels, as insulin resistance is a key factor in the pathophysiology of dyslipidaemia. However, as discussed above, most changes in insulin resistance are likely to be secondary to changes in adiposity, rather than through direct effects of antipsychotics on insulin action. Finally, a few reports of substantial elevations in triglyceride levels with only modest weight gain raise the possibility of a direct antipsychotic effect on lipid levels by some as yet unknown mechanism.

5. First-Generation Antipsychotics

Although this review concentrates on the potential effect of second-generation antipsychotics on metabolic parameters, reports of changes in glucose regulation, lipid levels and bodyweight are not confined to these agents, but have also been observed with some first-generation (typical) antipsychotics.

Reports of abnormal glucose regulation occurred following the introduction of chlorpromazine and other low potency phenothiazines. Cases of new-onset type 2 diabetes and exacerbation of existing diabetes were associated with phenothiazine treatment (for review, see Haupt and Newcomer[106]); in one report, the prevalence of diabetes increased from 4.2% to 17.2% following the introduction of chlorpromazine therapy.[107] In addition, phenothiazine treatment has been associated with adverse changes in plasma lipid levels and increases in bodyweight.[108,109]

However, not all first-generation antipsychotic agents appear to show the same propensity for adverse effects on glucose regulation as phenothiazines. Reports of diabetes associated with the use of high potency first-generation agents, such as haloperidol, have been limited, suggesting potential variability between medications in their effects on glucose metabolism. Koller et al.[71] identified 20 reports of hyperglycaemia with haloperidol treatment from the FDA MedWatch Drug Surveillance System and published reports from an estimated 6.5 million years of patient exposure. However, as with early studies of diabetes and hyperglycaemia in unmedicated schizophrenia patients, these studies are limited by their lack of controls and inadequate evaluation of other confounding factors, such as bodyweight and adiposity, so they should be interpreted with caution. In general, the widespread use of high potency first-generation antipsychotics, such as haloperidol, in the years before the introduction of the second-generation agents may have contributed to the relative lack of reports of antipsychotic-related hyperglycaemia and the subsequent relative lack of attention given to this issue during the clinical development of the newer, second-generation agents.

6. Clozapine

Clozapine was the first second-generation antipsychotic to be marketed, producing improvements in both positive and negative symptoms of schizophrenia, but without the significant risk of various movement disorders usually seen with first-generation antipsychotic agents. In addition, clozapine remains unique as an agent with established efficacy for individuals with treatment-resistant schizophrenia and for the prevention of suicide. It was introduced in the US in 1990, although it had been used in Europe since the 1980s. Clozapine treatment is associated with a risk of agranulocytosis, which means that it is now used most commonly in treatment-resistant individuals. Consequently, it accounts for a relatively

small proportion of prescriptions for second-generation antipsychotics.

To date, there is a large body of data examining the association between clozapine therapy and diabetes, hyperglycaemia, and abnormal glucose and lipid regulation. This includes case reports, FDA MedWatch Drug Surveillance information, database analyses and controlled experimental studies, including randomised clinical trials.

6.1 Bodyweight

Clozapine treatment is associated with marked increases in weight with both short- and long-term treatment, which has clinically significant implications for treatment adherence and long-term patient health. Allison et al.[59] reported an estimated weight gain of 4kg over 10 weeks of clozapine therapy in their meta-analysis of published studies, and Blin[110] reported a mean increase of 4.45kg with clozapine (and 4.15kg with olanzapine) in a 10-week comparison study. Longer-term treatment with clozapine is associated with additional weight gain, with increases of 6–12kg reported with 6–12 months of treatment. A study involving 21 patients reported a mean weight gain of 6.3kg over 16 weeks of clozapine therapy,[111] while in another study, 36 patients experienced a mean increase of 7.7kg over 6 months of clozapine treatment.[112] In a retrospective analysis of patient records,[113] clozapine-treated patients reported a mean weight increase of 6.8kg over a mean treatment duration of approximately 27 weeks. Maximum weight gain (7.5kg) was reached at a mean duration of 25 weeks, suggesting that weight gain occurs over a prolonged period with clozapine therapy. This is supported by findings from a 5-year naturalistic study of 82 clozapine-treated outpatients.[114] Although patients gained most weight during the first 12 months of treatment (0.5 kg/month), patients continued to show statistically significant weight gain out into the final observations of the study, at approximately month 46 of therapy.

The marked weight gain with clozapine therapy is also apparent when assessed as percentage increase from baseline. A review of clozapine trials reported that over 20% of clozapine-treated patients showed at least a 10% increase in weight from baseline with treatment lasting 12 weeks to 12 months.[115] In one study,[116] over 20% of patients gained more than 20% of their baseline bodyweight after 52 weeks of treatment. The substantial and prolonged increases in weight seen with clozapine treatment have clinically significant implications for long-term patient health.

6.2 Diabetes and Hyperglycaemia

6.2.1 FDA MedWatch Drug Surveillance System

Data from the FDA MedWatch Drug Surveillance System (January 1990 to February 2001), together with published reports and meetings abstracts, were used to identify reports of diabetes or hyperglycaemia associated with clozapine treatment.[69] A total of 384 cases were identified: 323 were 'new-onset' hyperglycaemia, 54 represented exacerbation of pre-existing diabetes, and for 7 patients this was unclear. Of the patients with new-onset hyperglycaemia, 171 (53%) met diagnostic criteria for diabetes based on blood glucose (fasting >126 mg/dL; nonfasting >200 mg/dL) or HbA_{1c} levels. For another 71 patients, diabetes was defined by initiation of antidiabetic medication or presence of metabolic acidosis or ketosis, while for the remaining 81 patients, hyperglycaemia was described as 'less well documented'.

Among patients with definitive new-onset diabetes (i.e. blood glucose or HbA_{1c} diagnosis), the mean age at onset was 39 ± 11 years, and more than 75% of these patients were aged 50 years or younger, suggesting that many patients were below the typical age of onset for type 2 diabetes. The time from initiation of clozapine therapy to onset of diabetes was generally short (figure 2). Diabetes occurred within 1 month of starting clozapine therapy for 27% of patients and within 3 months for 54%. Exacerbation of pre-existing diabetes also occurred rapidly after clozapine initiation: within 1 month for 38% of patients and within 3 months for 64%. For the majority of patients,

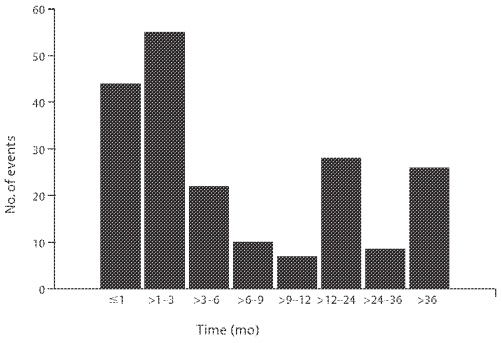

Fig. 2. Time to onset of newly diagnosed diabetes mellitus with clozapine.[58]

glycaemic control improved following withdrawal from clozapine treatment. Follow-up data, available for 54 of the 110 patients who withdrew from clozapine therapy, showed that 42 patients (78%) experienced improvement.

The severity of hyperglycaemia associated with clozapine therapy ranged from mild glucose intolerance to ketoacidosis and hyperosmolar coma. Fifty-one patients (45 with new-onset diabetes) experienced blood glucose levels of ≥700 mg/dL. Metabolic acidosis or ketosis accompanied hyperglycaemia in 80 cases, the majority of which (n = 73) were new-onset diabetes. There were 25 deaths during hyperglycaemic episodes; acidosis or ketosis was reported in 16 of these. Bodyweight data, available for 146 cases, showed obesity or substantial weight gain in the majority of cases, but no evidence of obesity or substantial weight gain in 38 individuals (26%).

6.2.2 Case Studies

Medline searches identified 26 published reports detailing associations between clozapine treatment and the occurrence of diabetes, diabetic ketoacidosis or hyperglycaemia (table IV).

These case reports, with the exception of those published after 2000, are analysed in a recent review.[143] A total of 30 individuals (25 male and 5 female) experienced diabetes, diabetic ketoacidosis or hyperglycaemia associated with clozapine treatment. The mean age of patients at detection of diabetes/ketoacidosis was 39.9 (range 25–54) years; 22 patients (73%) were aged 45 years or younger. The mean duration of clozapine treatment prior to detection was 17.7 (range 1–92) weeks, although for 19 (70%) of the 27 patients with available data, detection occurred within 12 weeks of treatment. In all, 12 individuals (40%) experienced diabetic ketoacidosis. Fifteen patients recovered completely after discontinuing clozapine therapy. Six patients experienced a rapid return to hyperglycaemia following rechallenge with clozapine.

One report of four cases[137] characterises some of the features of case reports with clozapine therapy. Two of the patients experienced new onset and two patients experienced severe exacerbation of type 2 diabetes, with the effects observed shortly after initiating clozapine therapy in all four cases. Weight gain did not appear to be a factor for these patients: two patients experienced no weight gain and two experienced minimal changes in bodyweight.

In other reports, Baymiller and co-workers[144] observed three cases of diabetes during long-term clozapine treatment of 50 patients with schizophrenia. For the two patients with bodyweight assessments, one showed an increase (12.7kg) and the other a decrease (7.3kg) in weight during the 12-month treatment period.

6.2.3 Chart Reviews and Observational Studies

The occurrence of diabetes in patients with psychotic disorders treated with clozapine has also been examined in observational clinical trials and reviews of patient records.

A 5-year naturalistic study[114] examined the incidence of treatment-emergent diabetes in patients with schizophrenia or schizoaffective disorder treated with clozapine. A total of 82 patients who had received clozapine therapy for at least 1 year were included in the study. Patients were treated at an outpatient clinic, and demographic and laboratory data (including fasting blood glucose [FBG] and lipid levels) were available at treatment initiation and at 6-monthly intervals thereafter.

Table IV. Case-based reports of diabetes, ketoacidosis or hyperglycaemia with clozapine

Reference	Case report details
Wehring et al.[117]	Three cases of lethal diabetic ketoacidosis in schizophrenia patients during long-term therapy (25.5, 14.5 and 59.5 months' treatment)
Beliard et al.[118]	Severe hyperglycaemia 3 months after starting clozapine in a 59-year-old male with existing type 2 diabetes
Lafayette et al.[119]	Diabetic ketoacidosis 10 weeks after starting clozapine in a 22-year-old female, which resolved after discontinuing therapy
Cohen & Gispen-de Wied[120]	Three cases of diabetes in male schizophrenia patients treated with clozapine therapy (original article in Dutch)
Kristensen & Porksen[121]	Diabetic ketoacidosis during clozapine treatment in a 54-year-old white female with type 2 diabetes and schizophrenia (original article in Danish)
Avram et al.[122]	Clozapine-induced diabetic ketoacidosis
Rigalleau et al.[123]	One case of new-onset diabetes with weight loss and ketosis with clozapine
Wu et al.[124]	Hyperglycaemia, hyperlipidaemia and periodic paralysis: a case report of new adverse effects of clozapine
Isakov et al.[125]	Insulin-resistant hyperglycaemia induced by clozapine
Wehring et al.[126]	Two patients developed diabetes mellitus associated with clozapine therapy
Brugman et al.[127]	A 40-year-old patient developed type 2 diabetes mellitus and hypertension when clozapine was added to his treatment regimen (original article in Dutch)
Maule et al.[128]	Diabetic ketoacidosis associated with clozapine treatment
Colli et al.[129]	Diabetic ketoacidosis associated with clozapine treatment
Mohan et al.[130]	Diabetic ketoacidosis associated with clozapine treatment
Smith et al.[131]	Clozapine-induced diabetic ketoacidosis
Ai et al.[132]	Diabetic ketoacidosis and clozapine treatment
Wirshing et al.[133]	Clozapine-associated new onset diabetes: 4 cases
Dickson & Hogg[134]	A pregnancy complicated by gestational diabetes, possibly exacerbated by clozapine
Thompson et al.[135]	A 48-year-old male developed hepatitis, hyperglycaemia, pleural effusion, eosinophilia, haematuria and proteinuria early in clozapine treatment
Pierides[136]	Clozapine monotherapy and ketoacidosis
Popli et al.[137]	Clozapine use associated with de novo onset (2 cases) or severe exacerbation of pre-existing diabetes mellitus
Koren et al.[138]	Extreme hyperglycaemia, severe lactic acidosis and fatal myocardial failure associated with clozapine in a 37-year-old Ashkenazic Jewish man
Peterson & Byrd[139]	Diabetic ketoacidosis from clozapine and lithium cotreatment
Kostakoglu et al.[140]	Ketoacidosis as an adverse effect of clozapine
Koval et al.[141]	Diabetic ketoacidosis associated with clozapine treatment
Kamran et al.[142]	Severe hyperglycaemia associated with high doses of clozapine

Patients had a mean age of 36.4 years, and only four were older than 50 years.

In all, 25 patients (30.5%) were diagnosed with type 2 diabetes by primary care physicians after initiation of clozapine therapy. Fourteen patients were treated using oral hypoglycaemic agents and four with insulin. One of the insulin-treated patients experienced two episodes of diabetic ketoacidosis within 6 months of starting treatment, although the authors report that this may be unrelated to clozapine and may represent a case of type 1 diabetes. A further five patients who experienced elevated FBG values during the 5-year study period were subsequently diagnosed and treated for diabetes. In total, 36.6% of the study sample were diagnosed with diabetes within 5 years of initiating clozapine therapy. Regression analysis showed a significant correlation between patient age and the development of diabetes. Although bodyweight increased significantly during the study, weight, change in weight, BMI and change in BMI were not significantly associated with an increased risk of diabetes in this sample. Furthermore, the authors report that some patients did not gain weight, but developed diabetes.

An earlier study conducted in Sweden[145] analysed blood glucose levels to determine the prevalence of diabetes among patients with psychotic disorders treated with clozapine. Sixty-three patients with psychosis, the majority (58) with schizophrenia, treated with clozapine were included in the study. A further 67 patients (53 with schizophrenia) receiving depot injections of typical antipsychotics formed the control group. The two

patient groups were similar in terms of sex, weight, height and BMI. However, patients in the clozapine group were significantly younger than those receiving depot treatment (mean age 41 ± 9 vs 48 ± 10 years) and had a significantly shorter duration of disease (15 vs 21 years) and of current antipsychotic treatment (3 vs 8 years) [all $p < 0.001$]. None of the patients had evidence of diabetes before the start of current antipsychotic therapy.

Blood glucose analysis (random samples) revealed that 21 patients (33%) in the clozapine group had hyperglycaemia (blood glucose >6.6 mmol/L) compared with 13 patients (19%) in the control group ($p = 0.07$). Based on oral glucose tolerance testing of these patients, 13 (22%) in the clozapine group were diagnosed with either type 2 diabetes (7 patients) or IGT (6) according to WHO criteria. This compared with 6 patients (10%) in the control group (diabetes 4; IGT 2). The difference between the groups showed a trend towards statistical significance ($p = 0.06$) for diagnosis of diabetes or IGT. Analysis of demographic data showed that 10 of the 13 patients in the clozapine group diagnosed with diabetes or IGT were aged 45 years or younger, compared with 1 of the 6 patients in the control group.

In a retrospective chart review of patients treated with first- or second-generation antipsychotic therapy (including clozapine, olanzapine, risperidone and quetiapine), Wirshing and colleagues[146] examined the changes in glucose levels that occurred following the initiation of antipsychotic treatment. In all, data were available from 215 patients, of whom 39 received clozapine treatment (mean duration 43.3 months). Analysis of clozapine-treated patients showed a significant increase from baseline in mean FBG level (+14%; $p = 0.05$) and maximum blood glucose level (+31%; $p = 0.03$). Significant increases in these measures were also seen with olanzapine therapy, but not with risperidone or quetiapine. In addition, five patients (13%) started treatment with a glucose-lowering agent following the initiation of clozapine therapy, while 44% of clozapine-treated patients with normal baseline glucose values experienced elevated FBG levels (≥126 mg/dL) during therapy. In a smaller naturalistic study of 75 patients with schizophrenia or related psychotic disorders receiving first- or second-generation therapy,[147] FBG levels also increased significantly from pretreatment levels after at least 2 months of clozapine treatment. In contrast, patients receiving typical therapy showed significant decreases in fasting glucose levels from baseline.

An open-label study by Chae and Kang[148] used weekly oral glucose tolerance tests (OGTTs) to assess blood glucose levels during 8 weeks of clozapine or haloperidol treatment in patients with psychotic disorders. Six of the 17 patients (35%) in the clozapine group developed IGT (WHO criteria) during treatment compared with none of 10 patients in the haloperidol group ($p = 0.056$). Seven patients (41%) in the clozapine group and one (10%) in the haloperidol group developed glycaemic peak delay. None of the patients in either group developed diabetes.

Other studies have measured plasma insulin levels in patients treated with clozapine. These studies can provide evidence of either decreased insulin secretion or increased secretion, suggesting decreased tissue insulin sensitivity. Melkersson and Hulting[149] reported elevated fasting insulin levels in 7 of the 14 patients receiving clozapine therapy, although median insulin levels remained within normal limits. Similarly, increases in mean insulin and glucose levels were observed during OGTTs in six patients with schizophrenia treated with clozapine.[150] Two studies have reported a positive correlation between insulin levels and clozapine serum concentration.[151,152] Analysis of data from 18 outpatients with schizophrenia or related psychoses who had received clozapine treatment for at least 6 months (mean duration, 8.2 years) showed that 11 patients (61%) had elevated fasting insulin levels and 13 (72%) had elevated fasting C-peptide levels.[151] Both insulin and C-peptide levels correlated significantly with clozapine serum concentration. Elevated FBG levels were reported for 2 of the 18 patients. In the earlier study, fasting insulin levels showed a positive correlation with clozapine serum concentration in 13 patients treated with clozapine ($p = 0.03$), whereas no correlation was observed

with typical antipsychotic therapy.[152] Insulin elevation was also more frequent in patients receiving clozapine than in patients receiving typical antipsychotic therapy. All except one patient in the study had normal fasting glucose levels. These findings suggest that clozapine could affect insulin secretion through induction of concentration-dependent insulin resistance. In a further study, metabolic parameters were examined in patients with schizophrenia treated continuously with antipsychotic therapy for at least 3 months.[153] Patients receiving clozapine therapy (n = 34) had significantly higher FPG levels ($p < 0.05$) and insulin resistance ($p < 0.05$) than those treated with typical antipsychotic therapy (n = 17). The proportions of patients with diabetes and hyperinsulinaemia were highest among patients treated with clozapine. In contrast, clozapine treatment had no significant effect on insulin resistance in a prospective study of 20 patients initiating clozapine treatment.[154] Mean insulin resistance and mean levels of other factors affecting glucose homeostasis did not differ significantly from baseline after an average of 2.5 months of clozapine therapy. However, baseline assessments indicated that patients already showed long-term insulin resistance at the start of clozapine therapy.

Two recent studies have used patient records to retrospectively assess the prevalence of hyperglycaemia among patients with schizophrenia or other psychotic illness treated with clozapine. One study identified 28 patients with hyperglycaemia (FPG ≥110 mg/dL), six of whom were diabetic using ADA criteria (FPG ≥126 mg/dL), among 121 patients diagnosed with schizophrenia between October 1999 and September 2000.[155] Patients identified with diabetes had a significantly greater BMI (33.1 kg/m^2) than those in the normal (<110 mg/dL) or impaired FPG (≥110 to <126 mg/dL) groups (28.8 and 27.3 kg/m^2, respectively; $p = 0.041$).

The second study was a retrospective chart review involving 208 patients with psychotic illness (including schizophrenia, schizoaffective disorder and bipolar disorder) treated with first- or second-generation antipsychotics in a range of clinical settings.[156] Overall, patients had a mean age of 46 years and a mean BMI of 30.8 kg/m^2. Of the 21 patients treated with clozapine, five (23.8%) had diabetes, but the prevalence of diabetes did not differ significantly between the different antipsychotics (clozapine, olanzapine, risperidone, quetiapine or typical agents). Similarly, mean fasting glucose values did not differ significantly between treatments (clozapine, 113.2 mg/dL).

6.2.4 Retrospective Database Analyses

The association between clozapine therapy and diabetes has been investigated in seven analyses of data from epidemiological and health service databases (table V).

In an analysis of healthcare data from the Veterans Health Administration, clozapine treatment was associated with an increased risk of diabetes compared with typical antipsychotic therapy. The study examined data from patients treated in the Veterans Health Administration of the Department of Veterans Affairs during a 4-month period in 1999.[157] The analysis included outpatients with schizophrenia treated with first- or second-generation antipsychotics. In all, 15 984 patients received first-generation antipsychotics and 22 648 received second-generation agents, of whom 1207 (5.3%) were prescribed clozapine.

Overall, the rate of diagnosis of diabetes (defined as an outpatient encounter or inpatient stay with a primary or secondary diagnosis of diabetes during the analysis period) was similar in patients treated with first- or second-generation antipsychotics, although significantly more younger patients (age groups: <40, 40–49 and 50–59 years) had a diagnosis of diabetes when treated with second- than with first-generation antipsychotics ($p < 0.001$). Logistic regression analysis, controlling for demographic, diagnostic and treatment factors, showed that the odds ratios (OR) of diagnosis with diabetes were significantly greater for patients receiving any second-generation agent compared with those receiving first-generation antipsychotic therapy (OR 1.09; 95% CI 1.03, 1.15; $p = 0.002$).

Table V. Summary of database analyses investigating association between clozapine therapy and diabetes

Reference	Risk of diabetes		
Sernyak et al.[157]	**Odds ratio vs typical antipsychotic**		
	All patients	1.25 (95% CI 1.07, 1.46)	$p < 0.005$
	<40y	2.13 (95% CI, 1.36, 3.35)	$p < 0.002$
	40–49y	1.43 (95% CI, 1.13, 1.81)	$p < 0.003$
	50–59y	1.17 (95% CI, 0.88, 1.54)	NS
	60–69y	0.50 (95% CI, 0.26, 0.96)	$p < 0.04$
	≥70y	1.61 (95% CI 0.59, 4.37)	NS
Lund et al.[158]	**Diabetes incidence vs typical antipsychotic**		
	All patients	4.0% vs 3.4%	
	20–34y	5.0% vs 2.0% [RR 2.5 (95% CI 1.2, 5.4)]	
Gianfrancesco et al.[159]	**Odds ratio vs no antipsychotic**		
	1mo	1.182 (95% CI 1.040, 1.344)	$p = 0.01$
	12mo	7.44 (95% CI 1.603, 34.751)	$p < 0.05$
	Odds ratio vs risperidone		
	12mo	8.45	$p < 0.05$
Lambert et al.[160]	**Odds ratio vs typical antipsychotic**		
		1.43 (95% CI 1.19, 1.69)	$p < 0.001$
Citrome et al.[161]	**Odds ratio vs typical antipsychotic**		
		7.61 (95% CI 2.36, 24.55)	
Wang et al.[162]	**Odds ratio vs no clozapine**		
		0.98 (95% CI 0.74, 1.31)	NS
Buse et al.[163]	**Hazard ratio vs no antipsychotic**		
		3.3 (95% CI 1.4–8.0)	$p = 0.007$
	Hazard ratio vs haloperidol		
		1.31 (95% CI 0.60, 2.86)	NS

For the individuals treated with clozapine, the risk of diabetes compared with typical antipsychotic treatment increased significantly for all patients (OR 1.25; 95% CI 1.07, 1.46; $p < 0.005$) and for those aged <40 years (OR 2.13; 95% CI 1.36, 3.35; $p < 0.002$) and 40–49 years (OR 1.43; 95% CI 1.13, 1.81; $p < 0.003$). In the 60–69-year age group, however, clozapine was associated with a decreased risk of diabetes (OR 0.50; 95% CI 0.26, 0.96; $p < 0.04$).

An analysis of medical and pharmacy data from the Iowa Medicaid program[158] also examined the risk of diabetes in clozapine-treated patients compared with those receiving typical antipsychotic treatment. Unlike the study by Sernyak et al.,[157] this analysis showed no statistically significant difference in overall incidence rates of diabetes between clozapine-treated patients and those receiving typical antipsychotics. Overall, 4.0% of the 531 patients with schizophrenia receiving clozapine therapy developed diabetes (mean follow-up 25.5 months). This compared with 3.4% of the 2296 patients receiving typical antipsychotics (mean follow-up 24.5 months). However, when patients were stratified according to their age, younger patients (20–34 years) showed a statistically significant increase in diabetes incidence with clozapine therapy (5.0%) compared with typical agents (2.0%) [RR 2.5; 95% CI 1.2, 5.4].

A study analysing medical claims data from two health plans encompassing 2.5 million individuals[159] compared the risk of diabetes in clozapine-treated patients with that in untreated individuals. Using data from January 1996 to December 1997, 7933 individuals with psychosis were identified from ICD-CM-9 codes and included in the analysis. Of these, 4308 had received at least 60 contiguous days of antipsychotic therapy (first- or second-generation), and 3625 had received no antipsychotic treatment. These records were then examined for the presence of type 2 diabetes, based on ICD-CM-9 codes or use of antidiabetic medication (except insulin). Patients with pre-existing type 2 diabetes were excluded from the two analyses: one analysis was based on the screening of patients for existing diabetes at 4 months prior to the observation period, the other at 8 months prior to treatment.

Results of regression analyses, based on both 4- and 8-month screening criteria, showed an increased risk of diabetes associated with clozapine therapy. The ORs for clozapine therapy (modelled on treatment duration) were 1.079 (4-month) and 1.182 (8-month) compared with no antipsychotic therapy; this was statistically significant for the 8-month value ($p = 0.01$). Based on the 4-month period, 63 patients received clozapine therapy, four of whom developed diabetes. When the 8-month period was studied, 3 of the 39 patients receiving clozapine therapy developed diabetes. Using the 8-month analysis, which was considered more likely to exclude relatively mild pre-existing cases of diabetes, the OR represents an estimated increased risk of diabetes, compared with no treatment, of 18.2% after 1 month of clozapine treatment. After 12 months of exposure to clozapine, the OR was 7.44 compared with no treatment, and 8.45 compared with risperidone ($p < 0.05$).

A case control study using data from the California Medicaid system compared the risk of developing diabetes in schizophrenic patients treated with first- and second-generation antipsychotics.[160] Among data from more than 129 000 patients with schizophrenia, obtained from 1 January 1997 to 31 December 2000, 3102 cases of newly diagnosed diabetes were identified for inclusion in the analysis (i.e. patients aged ≥18 years receiving continuous therapy with only one antipsychotic during the 12 weeks prior to diabetes diagnosis). These cases were matched for age (±5 years) and sex with 8271 non-diabetic patients with schizophrenia. Logistic regression analysis, controlling for ethnicity and other diabetes-inducing medication, was used to evaluate the risk of type 2 diabetes with each second-generation antipsychotic (clozapine, olanzapine, risperidone and quetiapine) compared with first-generation antipsychotic therapy. This analysis showed that the risk of diabetes was significantly higher with clozapine therapy than with first-generation antipsychotic treatment (OR 1.43; 95% CI 1.19, 1.69; $p < 0.001$).

Another smaller, case control study compared the risk of developing diabetes in patients receiving first- or second-generation antipsychotics using drug prescription data from inpatient facilities operated by the New York State Office of Mental Health.[161] Cases of newly diagnosed diabetes were identified from a new prescription for insulin or an oral hypoglycaemia agent and were matched to 10 control cases. Among the 4923 individuals included in the analysis, there were 58 cases of diabetes. The risk of diabetes was statistically significantly greater for those receiving second-generation antipsychotics compared with those treated with first-generation agents (OR 3.15; 95% CI 1.12, 8.91). Among the second-generation agents, clozapine treatment was associated with the highest risk of diabetes (OR 7.61; 95% CI 2.36, 24.55), with the risk compared with first-generation antipsychotic therapy also increased for treatment with risperidone, olanzapine and quetiapine.

In contrast to the previous studies, a case control study of patients enrolled in Medicaid or government-sponsored drug benefit programmes in New Jersey showed that clozapine treatment was not associated with an increased risk of diabetes.[162] Using a different approach from the studies reported above, this analysis identified patients (>20 years) diagnosed with psychiatric disorders and with newly treated diabetes (n = 7227) or without diabetes (matched control group, n = 6780). Patient records were then examined for clozapine use during the 6 months before diabetes diagnosis. The OR, adjusted for demographic and clinical variables, healthcare use and other medications, showed that clozapine use was not related to the risk of developing diabetes (adjusted OR 0.98; 95% CI 0.74, 1.31). Further analysis by mean daily clozapine dose or duration of clozapine treatment showed no significant increase in the risk of diabetes in any dose or duration quartile, or any consistent increases in OR with increasing dose or treatment duration. In contrast, analysis of other antipsychotic use showed an increased risk of diabetes with the typical agents chlorpromazine (adjusted OR 1.31) and perphenazine (adjusted OR 1.34), but no increase in risk with haloperidol or risperidone.

In another database analysis,[163] involving prescription claims data for patients receiving antipsy-

chotic monotherapy, clozapine-treated patients showed a significant increase in the risk of diabetes compared with individuals not receiving antipsychotic therapy (3.3; 95% CI 1.4, 8.0; p = 0.007), but not compared with those treated with haloperidol (1.31; 95% CI 0.60, 2.86; p = 0.496). It is, however, unclear whether the limited number of patients receiving clozapine (n = 277) who developed diabetes during clozapine treatment (n = 7) may have made the findings uninterpretable, given the large numbers of patients treated with other second-generation agents (overall n = 38 969) and haloperidol (n = 8476) in the study.

6.2.5 Controlled Clinical Studies

Several studies have examined the effects of clozapine treatment on glucose regulation through direct assessments of blood glucose levels rather than retrospective analyses of the surrogate measures described above, with these prospective studies including control group(s) as well as direct measures of glucose metabolism.

Statistically significant increases in FBG levels were observed with clozapine in a prospective 14-week study of antipsychotic treatment in patients with either schizophrenia or schizoaffective disorder.[164] Glucose data were available for 101 patients, randomised to treatment with clozapine (n = 28), olanzapine (n = 26), risperidone (n = 22) or haloperidol (n = 25). Patients in the clozapine group showed a significant mean increase in FBG levels (17.1 mg/dL; p < 0.01) from baseline at week 8; the mean increase at week 14 (4.4 mg/dL) was not statistically significant. Although mean glucose levels remained within normal limits, six clozapine-treated patients experienced abnormally high FBG levels during the 14-week study. ANCOVA analysis indicated no relationship between weight gain (mean change with clozapine +4.8kg) and change in glucose levels at endpoint. This study was limited by potential differences in baseline and endpoint adiposity across the different treatment groups, which were not addressed in the analysis.

Preliminary results from a prospective 16-week study showed elevated glucose levels both at fasting and following an OGTT in 7 of 13 patients receiving clozapine treatment.[165] Significant increases in insulin resistance indices were also reported with clozapine therapy. In contrast, no elevations in fasting or post-OGTT glucose levels or in insulin resistance measures were observed among the 12 patients receiving amisulpride treatment.

In further studies that were designed to assess drug effects on glucose metabolism that might occur independent of changes in adiposity, oral and intravenous glucose tolerance tests were used to examine the response of clozapine-treated patients to a glucose load. Using a frequently sampled modified OGTT, Newcomer et al.[62] compared glucose regulation in non-diabetic patients with schizophrenia treated with first- or second-generation (clozapine, olanzapine or risperidone) therapy and untreated healthy volunteers. Patient groups were well matched for age and BMI and balanced for sex and ethnicity. Despite the exclusion of patients with diabetes and matching for adiposity, data analysis for the nine clozapine-treated patients showed significant elevations in plasma glucose levels at fasting, and at 75 minutes after the glucose load compared with those treated with typical antipsychotics (n = 17) and untreated healthy volunteers (n = 31) [all comparisons p < 0.005]. Calculation of insulin resistance, based on FPG and insulin levels, showed a modest increase with clozapine treatment compared with typical antipsychotics. Similar findings were reported by Henderson and colleagues at the NCDEU 2000 meeting (reviewed by Haupt and Newcomer[54]) in a study using frequently sampled intravenous glucose tolerance tests. Non-diabetic patients receiving long-term treatment, matched for adiposity, age, sex and ethnicity, showed higher postload plasma glucose values with clozapine and olanzapine treatment than with risperidone. Insulin sensitivity was significantly reduced in clozapine- and olanzapine-treated patients compared with those treated with risperidone. Both of these studies were limited by adiposity matching that used BMI val-

ues, which may fail to capture potentially treatment-related differences in abdominal fat mass (i.e. despite equal BMI, some treatment groups may have larger abdominal fat mass), leading to differences in insulin sensitivity that are predictably driven by differences in fat mass rather than some unique adiposity-independent mechanism.

6.2.6 Discussion

Considered together, the various case reports, the majority of database analyses and controlled experimental studies including randomised clinical trials provide largely consistent evidence that clozapine treatment increases the risk of significant weight gain, insulin resistance, hyperglycaemia and diabetes mellitus. The risk of acute complications such as diabetic ketoacidosis may also be increased; however, these infrequent events are more difficult to study and quantify beyond case series.

Although these various reports consistently point to an adverse effect of clozapine treatment on bodyweight and metabolic parameters, their findings carry different value. As discussed earlier (see Levels of Evidence), case reports, chart reviews and open, observational studies provide uncontrolled and largely anecdotal evidence, whereas controlled clinical studies are designed to address specific questions. The retrospective database analyses provide a higher level of evidence than uncontrolled reports, although their value may be limited by the methodology and study endpoints used. In particular, the reliance on surrogate markers rather than direct metabolic measurements for the presence of diabetes is likely to lead to signal-to-noise problems that may affect the ability to reliably detect differences between medications or across groups. However, the full evaluation and ranking of each of these studies according to their limitations, although of interest, is beyond the scope of this review.

Two large database analyses showed that the risk of developing diabetes was statistically significantly greater with clozapine than with typical antipsychotic treatment[157] or with no antipsychotic therapy or with risperidone.[159] A case-controlled database analysis also showed a higher risk of diabetes compared with typical antipsychotic treatment.[158] Two observational studies reported a high incidence of diabetes in patients treated with clozapine. In the 5-year study,[113] 36.6% of clozapine-treated patients were diagnosed with new-onset diabetes, while in the study by Hägg et al.,[146] blood glucose analysis showed that 22% of patients treated with clozapine had IGT or diabetes.

Not all of the database studies showed an increased risk of diabetes with clozapine. Buse and colleagues[163] showed no statistically significant increase in the risk of diabetes with clozapine compared with haloperidol, although diabetes risk was statistically significantly higher in clozapine-treated individuals than in the general population. These findings are, however, limited by the small number of clozapine prescriptions and diabetes cases. The study of Iowa Medicaid data[158] showed no statistically significant increase in the prevalence of diabetes in patients treated with clozapine compared with those receiving typical antipsychotic agents in the overall study population, although patients aged 20–34 years had a statistically significantly higher incidence of diabetes with clozapine (5.0%) than with typical agents (2.0%). This result is consistent with the analysis by Sernyak et al.,[157] which reported an increased risk of diabetes among younger (<40 years) clozapine-treated patients, suggesting the possibility that drug effects could increase risk to a level normally observed only in older individuals. The apparently greater effect of clozapine on the risk of diabetes in younger individuals could also be a factor in the lack of effect observed by Wang and colleagues.[162] The mean age of patients in this study was over 60 years, compared with 37–50 years in the positive studies. Sernyak et al.[157] reported either no statistically significant increase or a statistically significant reduction in the risk of diabetes with clozapine compared with typical therapy in the older patient age groups (50–59, 60–69 and ≥70 years). In the general population, increasing age is a major risk factor for type 2 diabetes,[23,166] so drug effects and age effects may become more difficult to disentangle in elderly samples.

A number of factors identified among the cases from the FDA MedWatch System[69] and from Medline suggests a relationship between clozapine therapy and diabetes. The number of cases, their temporal relationship to the initiation of clozapine therapy, the impact of clozapine withdrawal, the lack of family history in a significant minority and the younger age of patients involved all suggest that clozapine affects the risk of developing diabetes. The large number of case reports in the literature of diabetes or ketoacidosis with clozapine contrasts, for example, with the few reports associated with risperidone therapy, despite the more widespread use of risperidone treatment. The rapid onset of diabetes or ketoacidosis following the initiation of clozapine therapy provides intriguing if circumstantial evidence. Over a quarter of cases of new-onset diabetes identified from the MedWatch-related report occurred within 1 month of starting clozapine therapy, and over half (54%) occurred within 3 months. Furthermore, the majority of patients (78%) who withdrew from clozapine experienced improved glycaemic control following withdrawal.[69] Details from the various other published case reports are consistent with these findings.

The high proportion of younger patients among the cases of diabetes and ketoacidosis was particularly notable and perhaps consistent with findings from the two database analyses that examined a wide range of age groups.[157,158] The mean age among the definitive new-onset diabetes cases from the report that included FDA MedWatch cases was 39 (±11) years, and more than 75% of patients were younger than 50 years. Hägg et al.[145] reported that 10 of the 13 clozapine-treated patients diagnosed with diabetes or IGT were aged ≤45 years. In contrast, population surveys show that the vast majority of patients newly diagnosed with type 2 diabetes are older than 44 years, with most cases observed in the 65–74-year age range.[166]

The large percentage of cases of diabetic ketoacidosis is also unusual among patients with type 2 diabetes. Diabetic ketoacidosis is typically an indicator of insulin deficiency and is therefore commonly thought of in association with type 1 diabetes rather than with type 2 disease. Furthermore, while diabetic ketoacidosis can be observed as a first manifestation of type 2 diabetes, this is not typical, as type 2 disease is characterised initially by peripheral insulin resistance and hyperinsulinaemia, followed by gradual and progressive decline of beta-cell function with diabetic ketoacidosis typically occurring in the later phases of the disease if at all. While most type 2 diabetes patients do not experience diabetic ketoacidosis, most cases of diabetic ketoacidosis in the population in fact occur in type 2 rather than type 1 diabetes, related to the higher frequency of type 2 disease and the contributions of acute insults to beta-cell function such as glucose toxicity (discussed above, see Type 2 Diabetes). With this background it is notable that more than 20% of the cases of hyperglycaemia reported in the study of FDA MedWatch cases were associated with metabolic acidosis or ketosis,[69] with the majority of these cases (91%) occurring in patients with new-onset diabetes. The rapid onset of diabetic ketoacidosis following the initiation of clozapine and the young age of many of these patients suggests an association between clozapine therapy and diabetic ketoacidosis in those individuals. This is also supported by the number of case reports of diabetic ketoacidosis with clozapine therapy, although the novelty of the cases may have contributed to reporting.

The association between clozapine treatment and weight gain is well documented,[59,167] and weight gain and obesity are established risk factors for diabetes. This raises the possibility that the increased risk of diabetes with clozapine therapy could be partly related to treatment effects on bodyweight. While the contributions of weight gain are likely to play a role in observed population effects and individual risk for many patients, a number of observations argue that weight gain may not be a factor in a substantial minority of cases. In some reported cases of diabetes or diabetic ketoacidosis, patients showed no increase in bodyweight. The rapid occurrence of diabetes following treatment initiation in some patients also does not support a primary role for weight gain in those cases.

Adiposity-related increases in insulin resistance occur as an early step in the pathogenesis of diabetes.[31] Clozapine-induced increases in weight and adiposity, perhaps in combination with adiposity-independent effects, may contribute to observed changes in plasma insulin and glucose. Insulin resistance, impaired insulin sensitivity and elevated insulin levels have all been reported with clozapine treatment.[54,62,122,149,150,165] Melkersson and colleagues[151,152] report a statistically significant correlation between clozapine concentrations and insulin levels in two studies, suggesting that clozapine could induce concentration-dependent insulin resistance. Effects on plasma insulin levels reported with clozapine therapy could herald progressive glucose intolerance and the development of diabetes. Several studies showed statistically significant increases in FBG levels from baseline with clozapine therapy[146,147,164] even when diabetes mellitus criteria were not met over the duration of the observation period. Discussed above, elevated plasma glucose and insulin levels following a glucose challenge were observed in non-diabetic, adiposity-matched patients treated with clozapine compared with typical antipsychotic therapy.[62] Even though these patients did not have diabetes, glucose elevations of a similar magnitude to those observed have been associated with long-term increases in cardiovascular morbidity and mortality.[168–170]

6.3 Lipid Levels

The effect of clozapine therapy on serum lipid levels has been examined in prospective studies and retrospective chart reviews. In addition, one analysis of healthcare data compared the incidence rates for hyperlipidaemia between clozapine and typical antipsychotic therapy.

6.3.1 Chart Reviews

Four retrospective reviews of patient records report increases in triglyceride levels with clozapine therapy. An analysis of 39 clozapine-treated patients[146] showed significant increases from baseline in fasting mean triglyceride (34%; $p = 0.01$) and maximum triglyceride (42%; $p = 0.02$) levels. Mean triglyceride levels during treatment were statistically significantly higher than for patients receiving haloperidol treatment. According to now conservative ADA guidelines, 56% of patients in the clozapine group had elevated triglyceride levels (≥200 mg/dL). Analysis of other fasting lipid parameters showed that total cholesterol levels increased slightly from baseline (5%), while LDL and HDL both showed minimal change (4% and 6% decreases, respectively) with clozapine. Minimum HDL levels were, however, significantly lower compared with baseline (–13%; $p = 0.02$). Overall, six patients (15%) in the clozapine-treatment group initiated cholesterol-lowering therapy after starting clozapine.

A retrospective review of patient records[171] examined triglyceride and total cholesterol levels for 222 inpatients receiving either clozapine ($n = 177$) or haloperidol ($n = 45$) treatment. Triglyceride levels increased from baseline in 116 male (mean 88.8 mg/dL; percentage change 48%) and 43 female (58.4 mg/dL; 35%) patients over the course of clozapine treatment (mean duration: male 615 days; female, 526 days); this increase from baseline was statistically significant in male patients ($p < 0.01$) with mean increases of a clinically significant magnitude in both males and females. In haloperidol-treated patients, triglyceride concentrations decreased in 30 male patients (–34.4 mg/dL; –17%) and increased in 9 female patients (81.8 mg/dL; 51%) during treatment (mean duration: male 413 days; female 595 days). No statistically significant changes in total cholesterol were observed with clozapine or haloperidol treatment in either male or female patients.

Another retrospective review[172] showed a significant increase in mean serum triglycerides from baseline (1.8 ± 1.0 mmol/L) after 6 months of clozapine treatment (2.5 ± 2.1 mmol/L; $p < 0.005$) in 70 patients with treatment-resistant schizophrenia. In contrast, 30 patients with chronic schizophrenia treated with typical antipsychotics showed nonsignificant changes in mean serum triglycerides (baseline 2.0 ± 1.1 mmol/L; month

6, 2.1 ± 1.1 mmol/L). Mean total cholesterol levels increased significantly with typical antipsychotic therapy ($p < 0.05$), but not with clozapine treatment. These findings are consistent with a previous study in patients with chronic schizophrenia treated with clozapine for 1 year.[105] This showed significantly higher fasting triglyceride levels in the 30 clozapine-treated patients compared with 30 patients receiving typical antipsychotic therapy ($p < 0.001$). Statistically significantly higher fasting triglyceride levels were also reported with clozapine therapy compared with typical antipsychotics in an incidence study of metabolic parameters in patients with schizophrenia treated with antipsychotic therapy for at least 3 months.[153]

Baymiller and co-workers[144] examined the effects of long-term clozapine treatment in 50 patients with schizophrenia or schizoaffective disorder. Patients participated in a 12-month follow-up of open-label clozapine therapy following a 10-week, double-blind study comparing clozapine and haloperidol therapy. Half of the patients received concomitant β-adrenergic antagonist therapy (atenolol n = 15; propranolol n = 10) during the study. Mean nonfasting serum triglyceride levels increased significantly from pre-clozapine baseline values (+54.7 mg/dL; $p = 0.001$), a mean increase of 41.8%. At the end of the study, 19 patients had elevated triglyceride levels (>199 mg/dL) compared with seven patients at baseline. Mean nonfasting total cholesterol levels also increased significantly from baseline (+14.4 mg/dL; $p < 0.001$), a 7.5% increase. At the end of the study, 30 patients had elevated cholesterol levels compared with 22 patients at baseline, using published norms (>199 mg/dL). Nonfasting HDL- and LDL-cholesterol levels did not change significantly during treatment. Changes in nonfasting triglyceride and total cholesterol levels were greater with concomitant atenolol and propranolol treatment than with clozapine alone, although increases from baseline were significant for all three subgroups ($p < 0.01$). The change in triglyceride level was significantly associated with an increase in bodyweight (mean, +5.5kg) seen during clozapine therapy ($p = 0.005$).

Fasting lipid levels were evaluated in 18 outpatients with schizophrenia or related psychoses treated with clozapine for at least 6 months.[151] Elevated triglyceride, total cholesterol and LDL-cholesterol levels were recorded for eight (44%), seven (39%) and three patients (17%), respectively. Only one clozapine-treated patient had HDL-cholesterol levels below normal. There was a positive correlation between triglyceride levels (but not other lipid levels) and serum clozapine concentration.

Case reports from four patients showed that elevated serum triglyceride levels decreased following the switch from clozapine to risperidone therapy.[173] In two of these patients, serum triglycerides increased following the switch back to clozapine treatment. The increased level of serum triglycerides observed during clozapine is consistent with a previous study of 67 patients by the same authors,[174] which reported higher levels associated with clozapine therapy than with typical antipsychotic treatment. In this study, the risk of abnormally elevated triglycerides was 12.4 times greater with clozapine than with typical antipsychotic therapy.

6.3.2 Retrospective Database Analysis

An analysis of medical and pharmacy data from the Iowa Medicaid program[158] compared the risk of hyperlipidaemia in schizophrenia patients treated with clozapine and those receiving typical antipsychotics. Overall cumulative incidence rates for hyperlipidaemia (based on an appropriate ICD-9-coded medical claim or pharmacy claim for lipid-lowering medication) did not differ significantly between the groups. In all, 26 (5.0%) of the 518 patients treated with clozapine developed hyperlipidaemia (mean follow-up 25.5 months), compared with 93 (3.9%) of the 2373 patients treated with typical antipsychotics (mean follow-up 24.5 months). However, when patients were stratified according to their age, incidence rates for hyperlipidaemia were statistically significantly greater among younger patients (20–34 years) with clozapine therapy (4.6%) compared with typical agents (2.0%), a RR of 2.4 (95% CI 1.1, 5.2).

Similar to the more reliable detection of clozapine-related risk of diabetes in younger patients noted above, several explanations are possible. Again, these include the possibility that age-related increases in the incidence of dyslipidaemia may confound the detection of drug effects in older individuals, or drug effects may produce an increase in risk that is similar in magnitude to, but not additive with, age effects.

6.3.3 Controlled Clinical Studies

Three controlled clinical studies have examined changes in fasting lipid parameters in patients receiving clozapine therapy. In a prospective 14-week study, inpatients with either schizophrenia or schizoaffective disorder were randomised to treatment with clozapine (n = 28), olanzapine (n = 26), risperidone (n = 22) or haloperidol (n = 25).[164] Patients receiving clozapine treatment showed a significant increase in fasting plasma cholesterol level from baseline during the initial 8 weeks of the study (14.7 mg/dL; $p < 0.02$). Analysis of data for the entire 14-week study period showed a similar mean increase in fasting cholesterol from baseline (16.3 mg/dL), although this change did not reach statistical significance. Mean values were within normal limits. Clozapine-treated patients showed significant weight gain over the study period (mean, 4.8kg; $p < 0.0003$). There was a statistically significant correlation between weight gain and increased cholesterol, even after adjustment for initial cholesterol levels and baseline weight.

Another randomised study examined changes in fasting plasma triglyceride and leptin levels in 56 schizophrenia patients treated with clozapine, risperidone, olanzapine or quetiapine for 6 weeks.[175] A control group of 11 patients with psychiatric disorders not receiving antipsychotic medication was included in the study. Mean plasma triglyceride showed no significant differences between the groups at baseline. Triglyceride levels increased significantly from baseline with clozapine treatment at week 6 (36.28 mg/dL; $p < 0.001$). The increase was similar to that seen with olanzapine treatment and contrasted with minimal changes in the risperidone and no therapy groups. Clozapine-treated patients also showed significant mean increases from baseline in bodyweight (6.52kg; $p < 0.01$) and BMI (23.06 to 26.91; $p < 0.05$) over the 6-week study. The changes in triglyceride levels with clozapine showed a significant correlation with increases in bodyweight ($p < 0.01$).

In a small prospective study,[176] eight patients with treatment-resistant schizophrenia (i.e. showing no clinical response to at least two typical antipsychotics) were treated with clozapine for 12 weeks. An 11% increase in fasting plasma triglyceride level was observed from baseline after 12 weeks of clozapine treatment, with no statistically significant changes in fasting total, LDL- or HDL-cholesterol levels. These findings may be limited by the small sample size.

6.3.4 Discussion

Results of clinical studies and chart reviews suggest that clozapine therapy is associated with increases in plasma triglyceride levels. Statistically significant increases in mean plasma triglyceride from baseline were observed with clozapine therapy in one controlled clinical trial,[175] four retrospective chart reviews[105,146,171,172] and a 12-month open-label study in patients with schizophrenia or schizoaffective disorder.[144] Two other studies[151,176] reported increased triglyceride levels with clozapine treatment, and Ghaeli and Dufresne[174] report an increased risk of elevated triglyceride levels with clozapine treatment compared with typical antipsychotic therapy. This is consistent with a healthcare database analysis showing an increased risk of hyperlipidaemia in younger patients.[158]

The effects of clozapine treatment on total cholesterol levels are less clear and more difficult to interpret. Although two studies report statistically significant increases in total cholesterol levels from baseline with clozapine treatment,[144,164] other studies report no statistically significant changes from baseline.[146,171,172,176] Changes in bodyweight may also affect changes in cholesterol levels. Lindenmayer and co-workers[164] report a statistical-

ly significant correlation between increased cholesterol and weight gain in their study. In general, the interpretation of total cholesterol levels is more difficult than that for individual lipid fractions. In population studies, plasma triglyceride, LDL-cholesterol and total cholesterol tend to track together and tend as a group to track with adiposity. In smaller studies and in individuals, insulin resistance occurring in the setting of increased adiposity can be preferentially expressed as an increase in plasma triglyceride, as insulin resistance at the adipocyte can lead to a relative failure in shutting off lipolysis or the release of FFA (i.e. triglyceride + glycerol). Large discrepancies between changes in plasma triglyceride, total cholesterol and LDL-cholesterol remain difficult to account for.

6.4 Conclusion

Clozapine treatment is associated with significant increases in weight and adiposity over both short- and long-term treatment. Studies using a variety of methodologies indicate, with few exceptions, that clozapine treatment is associated with an increased risk of developing diabetes mellitus and elevations in plasma triglyceride levels. While case reports initially suggested the association between clozapine treatment and increased risk of abnormalities in glucose and lipid metabolism, database analyses and controlled clinical studies indicate significant increases in the risk of insulin resistance, hyperglycaemia, dyslipidaemia and diabetes during clozapine treatment.

7. Olanzapine

Olanzapine was the third second-generation antipsychotic approved for use in the US and has been widely used since its introduction in 1996. A large body of literature exists examining the association between olanzapine therapy and diabetes mellitus, hyperglycaemia, and abnormal glucose and lipid regulation. This includes case reports, FDA MedWatch Drug Surveillance information, retrospective database analyses and controlled experimental studies including randomised clinical trials.

7.1 Bodyweight

Olanzapine treatment is associated with marked short- and long-term weight gain, similar in magnitude to that observed with clozapine, with similar implications for long-term patient health. A meta-analysis of 81 published studies reported weight gain of approximately 4kg over 10 weeks of olanzapine treatment.[59] Mean weight gain of over 4kg was also reported with olanzapine in a 10-week comparison study versus clozapine.[110]

As with clozapine treatment, long-term treatment with olanzapine is associated with additional weight gain, with increases from baseline of 6–12kg reported with treatment lasting between 6 and 12 months. In a small retrospective study,[177] olanzapine-treated patients reported a mean weight gain of 10.0kg over a mean treatment duration of 28 weeks. Data from randomised, double-blind registration studies lasting up to 1 year showed a dose-related increase in bodyweight among patients receiving olanzapine.[178] Olanzapine-treated patients receiving 12.5–17.5 mg/day showed a mean increase of approximately 12kg after 1 year of treatment. In the same sample, only the patient group receiving subantipsychotic doses of olanzapine (1 mg/day) experienced a more moderate increase in weight of approximately 3kg, with higher-dose groups generally associated with greater mean increases in weight. Although weight increases were greatest over the initial treatment period, weight gain occurred throughout the 1-year treatment period. The prolonged weight gain is consistent with the study by Wirshing et al.,[113] which showed mean maximum weight gain of 8.0kg with olanzapine treatment at a mean treatment duration of just over 21 weeks.

The marked weight gain seen with olanzapine is also apparent when the proportion of patients experiencing clinically significant weight gain (≥7% increase from baseline) is assessed. Package insert data for olanzapine report that 29% of patients taking olanzapine for 6 weeks experience clinically significant weight gain, compared with 3% receiving placebo, for a cumulative incidence estimate of approximately ten times the placebo

rate. The percentage of patients gaining ≥7% of baseline bodyweight increased to 56% with long-term therapy. Analysis of combined safety data from more than 2400 patients reported that 41% of patients experienced ≥7% increase in weight with olanzapine therapy, compared with 3% for placebo and 12% for haloperidol.[179] These data are consistent with initial findings from an ongoing drug-monitoring programme, which reported that 20% of patients receiving olanzapine experienced a greater than 10% increase in bodyweight from baseline during the first 10 weeks of treatment.[180] As with clozapine therapy, the marked increases in weight seen with olanzapine treatment have implications for long-term patient health, particularly with respect to the risk of cardiovascular disease, diabetes and dyslipidaemia.

Limited data confirm that the weight gain with olanzapine is mostly due to increased fat mass, as would be expected in adult populations where lean muscle mass tends to remain relatively constant. A significant mean weight increase of 3.3kg from baseline was reported during olanzapine treatment in an 8-week study in 10 patients with schizophrenia ($p = 0.001$).[100] This weight gain was mainly due to increases in body fat. Patients experienced a mean increase in body fat of 2.2kg from baseline ($p = 0.004$), with no statistically significant increase in lean body mass during treatment. Assessment of magnetic resonance imaging-measured adiposity in 16 first-episode, drug-naive patients with schizophrenia showed increased intra-abdominal (visceral) fat levels after 6 months of treatment with olanzapine or risperidone.[63] The increases were greater with olanzapine than with risperidone treatment ($26.9 \pm 12.1 cm^2$ vs $18.2 \pm 11.4 cm^2$), with the difference between the groups approaching 1 SD. This large effect size for the difference between groups did not reach statistical significance, perhaps because of the small sample size; not discussed by the authors, approximately 20–40 individuals per group would be required to provide good to excellent power to detect such an effect with this study design. Subcutaneous and total body fat also increased with both treatments over the study. Similar data from a small preclinical study in dogs showed that olanzapine and risperidone were both associated with increases in adiposity, although weight gain was modest.[181] Such differences in adiposity in the absence of substantial changes in weight may be instructive for the interpretation of studies where insulin resistance or diabetes is observed in the absence of substantial weight gain (see above). In this study, there were marked increases in subcutaneous (+106%) and visceral (+89%) adipose stores from baseline levels with olanzapine. Total fat deposition was statistically significantly greater with olanzapine than with risperidone, while the increased levels of subcutaneous fat seen with olanzapine compared with risperidone showed a trend towards statistical significance. Olanzapine also resulted in hepatic insulin resistance, whereas hepatic insulin resistance was unaffected by risperidone. Increases in visceral and subcutaneous abdominal adiposity are associated with increased risk for dyslipidaemia, glucose intolerance and cardiovascular disease, suggesting that the changes in adiposity observed with olanzapine and, to a lesser extent, risperidone treatment could have a clinically significant effect on patient health.

7.2 Diabetes and Hyperglycaemia

7.2.1 FDA MedWatch Drug Surveillance System

Data from the FDA MedWatch Drug Surveillance System (January 1994 to mid May 2001), published reports (Medline, to mid May 2001) and meetings abstracts over a similar period identified a total of 237 cases of diabetes or hyperglycaemia associated with olanzapine therapy.[70] These reports included 188 cases (79%) of newly diagnosed hyperglycaemia and 44 cases (19%) of exacerbation of pre-existing diabetes. In the remaining five cases, this distinction was unclear. Of the 188 patients with new-onset hyperglycaemia, 153 met diagnostic criteria for diabetes based on blood glucose (fasting >126 mg/dL; non-fasting >200 mg/dL) or HbA_{1c} levels, and 20 were receiving antidiabetic medication and/or were acidotic or ketotic at the time of hyperglycaemia.

For the 153 patients with newly diagnosed diabetes, their mean age at onset of the disease was 39.8 (±12.4) years. Over two-thirds of cases (68%) occurred before patients reached 45 years of age. Among patients experiencing exacerbation of their pre-existing diabetes, mean age was 51.7 ± 15.4 years. Time from initiation of olanzapine therapy to the onset of hyperglycaemia ranged from 2 days to 45 months among the 209 patients with available data. For 73% of patients, onset occurred within 6 months of starting olanzapine. For patients with definitive, newly diagnosed diabetes, 47% of cases occurred within 3 months and 70% within 6 months of starting therapy (figure 3). For patients with exacerbation of disease, 84% of events occurred within 3 months of starting olanzapine therapy. Limited data were available regarding withdrawal and rechallenge with olanzapine. Of 76 cases evaluated, improvement was reported for 60 patients (79%) after the withdrawal of olanzapine. Among ten patients rechallenged with olanzapine therapy, eight experienced worsening glycaemic control. For four patients, this occurred within 8 days of the resumption of olanzapine therapy.

The severity of hyperglycaemia ranged from mild glucose intolerance to diabetic ketoacidosis and hyperosmolar coma. In 69 cases (64 with new-onset diabetes), blood glucose levels ≥700 mg/dL were recorded; in 41 cases (38 with new-onset diabetes), blood glucose values exceeded 1000 mg/dL. Changes in mental state (confusion or obtundation) accompanied hyperglycaemia in 43 cases, while

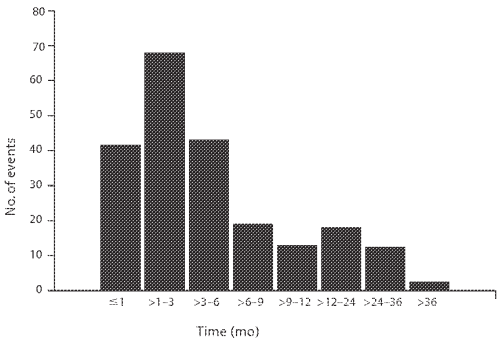

Fig. 3. Time to onset of hyperglycaemia with olanzapine.[56]

for 17 patients, pancreatitis or hyperamylasaemia were associated with hyperglycaemia. Overall, there were 15 deaths reported among identified olanzapine cases, with 13 occurring during or shortly after a hyperglycaemic episode.

Diabetic ketoacidosis was a frequent occurrence in the reported cases of diabetes or hyperglycaemia associated with olanzapine therapy. Metabolic acidosis or ketosis was reported in 80 of the 237 cases (33.8%). The majority of these cases (74; 92%) were new-onset diabetes. In addition, the proportion of deaths among the cases of diabetic ketoacidosis was high (11.3%) relative to the optimal outcomes generally reported in nonpsychiatric samples (e.g. 3–5%), with acidosis or ketosis reported in 9 of the 15 deaths observed in the olanzapine cases.

In an addendum to the paper, the authors report on an additional 52 cases of hyperglycaemia (newly diagnosed n = 35; exacerbation n = 12), identified by extending their FDA MedWatch search to February 2002.[70] Again the incidence of diabetic ketoacidosis was relatively high, with 20 reports of ketosis or acidosis associated with hyperglycaemia (38.5%). There were also five reports of pancreatitis among the cases. In all, 10 deaths occurred among these 52 patients.

In an observational pharmacovigilance study of olanzapine,[182] conducted in the UK between December 1996 and May 1998, prescription event monitoring was used to collect clinical information for 8858 patients recently prescribed olanzapine. Among these patients, there were eight reports of diabetes mellitus considered possibly related to olanzapine treatment.

7.2.2 Case Reports

Medline searches identified 33 published reports detailing associations between olanzapine therapy and diabetes, diabetic ketoacidosis or hyperglycaemia. These reports are summarised in table VI.

In a recent review, Ananth et al.[143] analysed 26 cases of diabetes (male n = 17; female n = 9) associated with olanzapine treatment identified from

Table VI. Case reports of diabetes, ketoacidosis and hyperglycaemia with olanzapine

Reference	Case report details
Torrey & Swalwell[183]	Fatal diabetic ketoacidosis in a 45-year-old male with bipolar disorder and no history of diabetes 1 month after restarting olanzapine therapy
Dewan[184]	A 62-year-old African American man developed hyperglycaemia with olanzapine therapy
Beliard et al.[118]	Development of severe hyperglycaemia in a 16-year-old patient with type 1 diabetes 15 days after starting olanzapine, which resolved on discontinuation
Tavakoli & Arguisola[185]	Acute onset of ketoacidosis and diabetes in a 35-year-old male with bipolar disorder after 18 months of olanzapine
Chang et al.[186]	Two cases of severe hyperglycaemia and hypertriglyceridaemia associated with olanzapine therapy
Azriel Mira[187]	Uncontrolled hyperglycaemia with ketosis associated with olanzapine therapy (original article in Spanish)
Kozian[188]	Olanzapine-induced diabetes mellitus (original article in German)
Straker et al.[189]	Near fatal ketoacidosis with olanzapine treatment
Meatherall & Younes[190]	A 31-year-old male who died from olanzapine-induced hyperglycaemia
Opp & Hildebrandt[191]	Olanzapine-associated type 2 diabetes mellitus
Malyuk et al.[192]	Olanzapine-associated weight gain, hyperglycaemia and neuroleptic malignant syndrome in a 64-year-old woman
Riccitelli & Baker[193]	Weight gain and hyperglycaemia associated with olanzapine
Ramankutty[194]	Olanzapine-induced destabilisation of diabetes in the absence of weight gain
Melkersson & Hulting[195]	Recovery from new-onset diabetes in a schizophrenic man after withdrawal of olanzapine
Ragucci & Wells[196]	A 46-year-old African American woman with no previous history of diabetes mellitus developed diabetic ketoacidosis after being treated with olanzapine
Rojas et al.[197]	A 48-year-old male drinker and cocaine user developed severe diabetes mellitus after 2 months of olanzapine use
Seaburg et al.[198]	A 27-year-old African American male developed new-onset severe hyperglycaemia with ketonuria and acidosis, but no weight gain, 2 years after starting olanzapine
Bechara & Goldman-Levine[199]	A 45-year-old male with well controlled type 2 diabetes mellitus experienced an abrupt worsening of his diabetes after 3 years of olanzapine therapy
Domon & Webber[200]	Development of hyperglycaemia and hypertriglyceridaemia in a male adolescent resolved with discontinuation of olanzapine
Muench & Carey[201]	A 38-year-old schizophrenia patient suddenly developed diabetes mellitus and ketoacidosis 12 months after starting olanzapine
Kropp et al.[202]	Olanzapine-related hyperglycaemia in a nondiabetic woman
Selva & Scott[203]	Acute onset diabetic ketoacidosis presenting in a 16-year-old girl during olanzapine therapy
Bonanno et al.[204]	A 31-year-old African American man and a 44-year-old white man, both with schizoaffective disorder, developed diabetes mellitus within weeks or months of olanzapine initiation
Roefaro & Mukherjee[205]	Olanzapine induced hyperglycaemia leading to a hyperosmolar, hyperglycaemic, nonketonic coma
Rigalleau et al.[123]	Two cases of new-onset diabetes with weight loss and ketosis
Bettinger et al.[206]	A 54-year-old African American woman developed severe glucose dysregulation 12 days after olanzapine initiation
Von Hayek et al.[207]	Two psychotic patients developed hyperglycaemia several weeks after starting olanzapine
Lindenmayer & Patel[208]	Olanzapine-induced ketoacidosis with diabetes mellitus
Goldstein et al.[209]	New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment
Gatta et al.[210]	Diabetic ketoacidosis with olanzapine treatment
Ober et al.[211]	Hyperglycaemia associated with olanzapine
Fertig et al.[212]	Hyperglycaemia associated with olanzapine
Wirshing et al.[133]	Olanzapine-associated new-onset diabetes: 2 cases

the literature. The mean duration of olanzapine treatment prior to detection of diabetes was 18.26 (range 4–68) weeks, with 43% of cases occurring within 12 weeks. The mean age of patients at detection was 41.5 (range 19–56 years); 17 patients (65%) were aged 45 years or younger. Approximately one-third of patients (9 cases) experienced ketoacidosis. Fourteen of the 18 patients who discontinued olanzapine therapy recovered glycaemic control without oral antidiabetic agents or insulin.

Details from other case reports in table VI are consistent with the cases reviewed by Ananth and colleagues.[143] A substantial proportion of reports involve diabetic ketoacidosis, and many patients are younger than is typical for the development of

type 2 diabetes among the general population. Diabetes or ketoacidosis can occur shortly after the initiation of olanzapine therapy and in the absence of weight gain. However, cases also occur after prolonged olanzapine therapy.

One relatively high-profile case of diabetic ketoacidosis, which resulted in death, was reported with olanzapine therapy in a 12-week, double-blind study comparing olanzapine and divalproex sodium for the treatment of acute mania in patients with bipolar disorder.[213] The patient, a 53-year-old man, had no prior history or family history of diabetes and had a normal blood glucose level at baseline (86 mg/dL).

7.2.3 Chart Reviews and Observational Studies

A case series study[214] examined the incidence of diabetes or hyperglycaemia in patients with schizophrenia who had received second-generation antipsychotic treatment (olanzapine n = 45; clozapine n = 38; risperidone n = 51) for 1–3 years. FBG measures showed that three cases of new-onset diabetes (FBG >126 mg/dL) occurred in the olanzapine group since the start of therapy, compared with none in the clozapine or risperidone groups. In addition, four cases of hyperglycaemia (FBG >110–126 mg/dL) occurred in the olanzapine group, four in the clozapine group and none with risperidone therapy.

A chart review examined changes in the use of antidiabetic medication to assess the relationship between diabetic control and antipsychotic medication use in patients treated with first- or second-generation (olanzapine, clozapine, risperidone or quetiapine) antipsychotics for at least 1 year.[215] Among olanzapine-treated patients, 15 of 38 (40%) experienced an increase in antidiabetic medication of at least 50% at an average of 8 months of treatment, and 11 individuals (29%) required additional antidiabetic medication to control their diabetes. This compares with a 50% increase in antidiabetic medication for 1 of 12 patients (8%) receiving typical antipsychotics (average of 276 months of treatment) and 2 of 11 (18%) receiving risperidone (22 months) and additional antidiabetic medications for three (25%) and five (45%) patients receiving typical or risperidone therapy, respectively.

Two retrospective analyses of patient records reported significant increases in fasting glucose levels from pretreatment values with olanzapine. A retrospective study of patient records at Oregon State Hospital[216] compared metabolic outcomes after 1 year of treatment with either olanzapine (n = 47) or risperidone (n = 47) therapy. FBG levels in olanzapine-treated patients showed significant mean increases from baseline for all patients (7.3 mg/dL; p = 0.031) and those younger than 60 years (10.8 mg/dL; p = 0.009; n = 37). These changes were greater than those observed with risperidone (+0.68 and +0.74 mg/dL, respectively), although the difference between the groups reached statistical significance only for non-elderly patients (p = 0.03). Mean bodyweight increased significantly from baseline with olanzapine therapy for all patients (17.5lb [7.9kg]; $p \leq 0.001$) and for non-elderly patients (20.4lb [9.2kg]; $p \leq 0.001$). However, further analysis of the non-elderly patients showed no statistically significant correlation between weight gain and the change in fasting glucose levels in the olanzapine group (see discussion above for limitations on analyses like this one). One case of new-onset diabetes occurred in the olanzapine group during the study period.

A second retrospective chart review examined changes in fasting glucose levels in patients treated with first- or second-generation antipsychotics.[146] Data available for 32 patients receiving olanzapine therapy (mean treatment duration 13.5 months) showed a significant increase in mean glucose levels (21%; p = 0.03) and maximum glucose levels (37%; p = 0.04) from baseline. Two patients who were receiving glucose-lowering agents at baseline required a dose increase to control glucose levels after initiating olanzapine. Of patients with normal FBG levels at baseline, 27% receiving olanzapine developed a clinically significant increase in plasma glucose (≥126 mg/dL) during treatment. In contrast, a study involving 75 patients with schizophrenia or related psychotic disorders treated with first- or second-generation antipsychotic therapy[147] showed no significant change in fasting or 2-hour

postchallenge blood glucose levels from pretreatment values after at least 2 months of olanzapine treatment. No statistically significant change in peripheral insulin resistance was observed with olanzapine therapy.

Changes in fasting insulin levels have also been examined in patients receiving olanzapine, clozapine or typical antipsychotic therapy, mostly for schizophrenia or schizoaffective or schizophreniform disorder.[149] Patients treated with olanzapine had significantly higher median insulin levels than those receiving typical antipsychotics ($p < 0.05$). Median insulin levels were above the upper limit of normal (ULN; >144 pmol/L) in the olanzapine group (234 pmol/L), but not with clozapine (130 pmol/L) or typical antipsychotic (115 pmol/L) treatments. Ten patients (71%) in the olanzapine group had elevated insulin levels compared with 7 (50%) in the clozapine group and 6 patients (32%) treated with typical agents. Two other studies have also examined fasting glucose and fasting insulin levels in patients with schizophrenia or related psychoses treated with olanzapine.[151,217] Elevated fasting insulin levels were reported for 5 (31%) of the 16 olanzapine-treated outpatients included in the study (mean treatment duration 1.2 years).[151] In addition, 7 patients (44%) had elevated fasting C-peptide levels, while 5 patients (31%) had elevated FBG levels. Increasing insulin and C-peptide levels both correlated with an increasing ratio between olanzapine and its metabolite *N*-desmethylolanzapine, but showed an inverse correlation with *N*-desmethylolanzapine concentration. The earlier study reported elevated fasting insulin levels for 10 (71%) of the 14 patients treated with olanzapine.[217] Three of the patients had elevated FBG levels (>6.0 mmol/L [108.1 mg/dL]), while values were normal for the remaining 11 patients. In addition, significant improvements in insulin resistance and beta-cell function were reported for 40 patients with schizophrenia following a switch from olanzapine to risperidone therapy.[218] Data from seven individuals showed a significant decrease in FBG levels following the switch from olanzapine to risperidone therapy (87.7 to 82.3 mg/dL; $p < 0.04$) and a trend towards statistical significance for 2-hour postprandial blood glucose levels (105.5 to 80.0 mg/dL; $p < 0.09$).[219]

A chart review of glucose and lipid parameters in 208 patients with psychotic illness[156] showed no statistically significant difference in the prevalence of diabetes or mean FPG levels between patients treated with clozapine, risperidone, olanzapine, quetiapine or typical antipsychotic monotherapy. In all, 14 of the 83 patients (16.9%) treated with olanzapine had diabetes, and the mean FPG value in the olanzapine group was 110 mg/dL.

7.2.4 Retrospective Database Analyses

Nine analyses of data from epidemiological and health service databases have investigated the association between olanzapine therapy and diabetes (table VII). In all except one of the studies, the risk of developing diabetes was increased significantly with olanzapine treatment.

The largest analysis involved 38 632 outpatients with schizophrenia, treated with first- (n = 15 984) or second-generation (n = 22 648) antipsychotic therapy from the Veterans Health Administration database.[157] Of the patients receiving second-generation antipsychotics, 10 970 (48.4%) were treated with olanzapine. Logistic regression analysis, controlling for demographic, diagnostic and treatment factors, showed that overall, patients receiving olanzapine had a significantly higher risk of diabetes diagnosis than those treated with typical antipsychotics (OR 1.11; 95% CI 1.04, 1.18; $p < 0.002$). When patients were analysed according to their age, patients younger than 40 years (OR 1.64; 95% CI 1.23, 2.21; $p < 0.001$), aged 40–49 years (OR 1.19; 95% CI 1.06, 1.34; $p < 0.001$) and 50–59 years (OR 1.16; 95% CI 1.04, 1.29; $p < 0.001$) all showed a significantly higher risk of diabetes with olanzapine than with typical antipsychotic therapy. Of the other second-generation antipsychotics analysed, treatment with clozapine and quetiapine, but not risperidone, increased the risk of diabetes compared with typical agents. Treatment with all three second-generation agents increased the risk of diabetes for

Table VII. Summary of database analyses investigating association between olanzapine therapy and diabetes

Reference	Risk of diabetes		
Sernyak et al.[157]	**Odds ratio vs typical antipsychotic**		
	All patients	1.11 (95% CI 1.04, 1.18)	p < 0.002
	<40y	1.64 (95% CI 1.23, 2.21)	p < 0.001
	40–49y	1.19 (95% CI 1.06, 1.34)	p < 0.003
	50–59y	1.16 (95% CI 1.04, 1.29)	p < 0.008
	60–69y	0.90 (95% CI 0.77, 1.07)	NS
	≥70y	0.99 (95% CI 0.82, 1.19)	NS
Fuller et al.[220]	**Relative risk vs risperidone**		
	Overall	1.37 (95% CI 1.06, 1.76)	p = 0.016
Gianfrancesco et al.[158]	**Odds ratio[a] vs no antipsychotic**		
	1mo	1.099 (95% CI 1.041, 1.160)	p < 0.001
	12mo	3.10 (95% CI 1.620, 5.934)	p < 0.05
	Odds ratio[a] vs risperidone		
	12mo	3.53	p < 0.05
Gianfrancesco et al.[221]	**Odds ratio vs no antipsychotic**		
	1mo	1.030	p = 0.0247
	12mo	1.426 (95% CI 1.046, 1.955)	
Caro et al.[222]	**Relative risk vs risperidone**		
	Overall	1.20 (95% CI 1.00, 1.43)	p = 0.05
	Month 1–3	1.90 (95% CI 1.40, 2.57)	p < 0.0001
Koro et al.[223]	**Odds ratio vs no antipsychotic**		
	Overall	5.8 (95% CI 2.0, 16.7)	p = 0.001
	Odds ratio vs typical antipsychotic		
	Overall	4.2 (95% CI 1.5, 12.2)	p = 0.008
Lambert et al.[159]	**Odds ratio vs typical antipsychotic**		
	Overall	1.30 (95% CI 1.18, 1.43)	p < 0.001
Farwell et al.[224]	**Diabetes incidence vs typical antipsychotic**		
	Overall	14.3% vs 7.3%	p = 0.015
	Adjusted odds ratio vs typical antipsychotic		
	Overall	3.92 (95% CI 1.0, 15.6)	
Buse et al.[163]	**Hazard ratio vs no antipsychotic**		
	Overall	3.0 (95% CI 2.6, 3.5)	p ≤ 0.0001
	Hazard ratio vs haloperidol		
	Overall	1.09 (95% CI 0.86, 1.37)	NS

[a] Calculated using the 8-month cut-off period.

patients aged 40 or younger.

A smaller retrospective analysis of the VISN-10 Veterans Administration database[220] assessed the risk of developing diabetes in patients receiving olanzapine, risperidone, haloperidol or fluphenazine therapy between the start of 1997 and the end of 2000. Female patients, ethnic groups other than Caucasian or African American, patients treated with clozapine and those with pre-existing diabetes were excluded from the analysis. Diabetes was defined as a diagnosis of diabetes (ICD-9-CM code 250.xx) or prescription of antidiabetic medication. In all, 5837 individuals were analysed, and 368 (6.3%) developed diabetes. Cox regression analysis, controlling for age, race, diagnosis and use of other antipsychotic medication, showed that the risk of developing diabetes was significantly higher with olanzapine therapy than with risperidone (RR 1.37; 95% CI 1.06, 1.76; p = 0.016).

An analysis of medical claims data from two health plans showed that olanzapine treatment was associated with a statistically significant increase in the risk of newly reported diabetes compared with untreated patients.[159] A total of 4308 individuals with psychosis who had received at least 60 contiguous days of antipsychotic therapy (first- or second-generation) and 3625 who received no antipsychotic treatment were identified from the database. Patients with type 2 diabetes diagnosis were then identified. Those with pre-existing disease were excluded from the two analyses, based on screening at either 4 months or 8 months prior

to the observation period. The 1-month ORs for risk of developing diabetes with olanzapine therapy, calculated by logistic regression analysis on the basis of treatment duration, were statistically significant ($p < 0.001$) using both the 4-month (1.082) and 8-month (1.099) cut-off periods. Similarly, analysis according to treatment dose produced a significant OR using both screening periods (4-month 1.161; 8-month 1.222; $p < 0.002$). The 12-month OR for olanzapine, based on the treatment duration and the 8-month cut-off, was 3.10, suggesting that 12 months of treatment increases the odds of diabetes by 210% compared with no treatment. Compared with risperidone therapy, the 12-month OR for olanzapine was 3.53 ($p < 0.05$).

Similar methodology was used in a second study analysing medical claims data from a Blue Cross/Blue Shield database encompassing nearly 2 million individuals.[221] Data available from April 1997 to October 2000 were used to compare the risk of diabetes in patients with psychosis receiving antipsychotic therapy compared with those not receiving treatment. In this study, however, the presence of type 2 diabetes was based solely on prescription claims for anti-diabetic medication, and only an 8-month screening period for existing diabetes was used. Overall, the database analysis identified 6528 individuals with psychosis who had received at least 60 contiguous days of antipsychotic therapy (first- or second-generation), and 10 296 who had received no antipsychotic treatment. Among the 1719 patients treated with olanzapine, 15 developed diabetes. Logistic regression analysis showed that the risk of developing diabetes was statistically significantly greater with olanzapine than with no antipsychotic therapy (OR 1.03; $p = 0.0247$), based on 1 month of treatment. Adjusting this value to 12 months of treatment gave an OR for olanzapine of 1.426 (95% CI 1.046, 1.955), compared again with no antipsychotic therapy, suggesting that the likelihood of diabetes was 42.6% greater with olanzapine than for untreated individuals.

Analysis of healthcare databases managed by the Régie de l'Assurance Maladie du Québec (RAMQ) examined the relative risk of diabetes among patients treated with either olanzapine or risperidone therapy.[222] Patients who had received at least one prescription for either olanzapine or risperidone between 1 January 1997 and 31 December 1999 were included in the study. Those receiving clozapine therapy, diagnosed with diabetes or receiving antidiabetic therapy in the year prior to starting therapy were excluded from the analysis. In all, 19 153 patients treated with olanzapine and 14 793 treated with risperidone were included in the study. Patients receiving olanzapine therapy tended to be younger, more likely to be male, more likely to be diagnosed with schizophrenia (62% vs 39%) and more likely to receive haloperidol treatment (38.1% vs 32.6%) than those treated with risperidone. In all, 317 patients in the olanzapine group and 217 in the risperidone group developed diabetes after the start of treatment. Adjusting for age, sex and haloperidol use, the relative risk of developing diabetes was 20% greater with olanzapine therapy than with risperidone (RR 1.20; 95% CI 1.00, 1.43; $p = 0.05$). A statistically significant interaction between olanzapine and sex was also detected; female patients had a 30% greater risk of diabetes with olanzapine therapy over risperidone, after adjustment for age, schizophrenia diagnosis and haloperidol use (RR 1.30; 95% CI 1.05, 1.65; $p = 0.02$). The duration of treatment also had an effect, with a significantly increased risk of developing diabetes during the first 3 months of treatment with olanzapine compared with risperidone (RR 1.90; 95% CI 1.40, 2.57; $p < 0.0001$).

The effect of olanzapine and risperidone on the risk of diabetes among patients with schizophrenia has also been examined using data from the UK General Practice Research Database.[225] Based on data from June 1987 to September 2000, 19 637 patients diagnosed and treated for schizophrenia were identified for inclusion in the analysis. Of these, 970 patients had received olanzapine treatment and 1683 had received risperidone therapy. Overall, 451 patients developed diabetes during a mean follow-up of 5.2 years, including 9 who had received olanzapine therapy and 23 who had

received risperidone. The overall incidence rate of diabetes among patients receiving antipsychotic therapy was 4.4 per 1000 person-years of treatment. The incidence rate during the first 3 months of treatment was higher for olanzapine (10.0/1000 person-years) than for either risperidone therapy (5.4) or typical antipsychotics (5.1).

Case control analysis, in which each case of diabetes is matched to control cases (i.e. patients with schizophrenia who had not developed diabetes), showed a significant increase in risk of diabetes with olanzapine therapy compared with no antipsychotic therapy (OR 5.8; 95% CI 2.0, 16.7; p = 0.001). Typical antipsychotic therapy (OR 1.4; 95% CI 1.1, 1.7; p = 0.004), and less significantly risperidone treatment (OR 2.2; 95% CI 0.9, 5.2; p = 0.079), was associated with increases in the risk of diabetes compared with no therapy. When compared with typical antipsychotic therapy, olanzapine therapy showed a significant increase in the risk of developing diabetes (OR 4.2; 95% CI 1.5, 12.2; p = 0.008). The level of risk associated with risperidone therapy was not statistically significantly different as compared with that of typical agents (OR 1.6).

An additional two case control studies have reported an increased risk of diabetes with olanzapine therapy. One study, using data derived from the California Medicaid system during 1997–2000, identified cases of new-onset diabetes among patients with schizophrenia treated with first- or second-generation antipsychotics.[160] For inclusion in the analysis, patients had to be aged ≥18 years and receiving continuous antipsychotic monotherapy during the 12 weeks prior to the diagnosis of diabetes. The 3102 cases identified (918 receiving olanzapine treatment) were matched for sex and age (±5 years) with 8271 patients with schizophrenia not diagnosed with diabetes. Logistic regression analysis, controlling for ethnicity and other diabetes-inducing medication, showed a significantly higher risk of developing type 2 diabetes during olanzapine therapy compared with typical antipsychotic treatment (OR 1.30; 95% CI 1.18, 1.43; p < 0.001). Clozapine and quetiapine, but not risperidone, treatment were also associated with a statistically significantly higher risk of diabetes compared with typical antipsychotic treatment.

The other study[224] used data from a number of healthcare providers in Indianapolis, Indiana, to identify patients with schizophrenia receiving antipsychotic treatment (olanzapine n = 1640; risperidone n = 2248; typical n = 6540). Patients aged 18 years or older, with no diabetes prior to antipsychotic treatment, and who had received antipsychotic therapy for at least 1 year were selected for analysis. Among the 744 individuals analysed (olanzapine n = 112; risperidone n = 150; typical n = 482), there were 96 cases of new-onset diabetes. The proportion of patients who developed diabetes was significantly higher with olanzapine treatment (14.3%) than with typical antipsychotic therapy (7.3%; p = 0.015), but did not differ statistically significantly between risperidone and typical antipsychotic treatment. Diabetes cases were matched for age (±2 years), sex and ethnicity with 316 control (non-diabetic) patients. Logistic regression analysis, adjusted for demographic characteristics, comorbid conditions and level of outpatient care, indicated that the risk of diabetes was higher with olanzapine treatment than with typical antipsychotic therapy (adjusted OR 3.92; 95% CI 1.0, 15.6). Compared with typical antipsychotic treatment, olanzapine therapy was also associated with an increased risk of weight gain of 10lb (4.5kg) or more (adjusted OR 2.1; 95% CI 1.0, 4.7).

In a recently published database analysis,[163] the risk of developing diabetes increased significantly in olanzapine-treated individuals compared with the general population, but did not differ significantly compared with haloperidol-treated patients. Using data from the AdvancePCS prescription claims database, the risk of developing diabetes was analysed for patients starting antipsychotic monotherapy between December 1998 and the end of February 2000 and continuing treatment through this period. Overall, 19 782 patients treated with typical antipsychotics and 38 969 treated with second-generation antipsychotics (13 863 with olanzapine) were included in the analysis; patients with pre-existing diabetes, antipsychotic

use in the 6 months before the start of the study period or treatment with more than one antipsychotic during the study period and those younger than 18 years were excluded. Of the 13 863 patients treated with olanzapine, 194 developed diabetes, identified by a prescription claim for antidiabetic medication. Cox proportional hazard regression analysis, adjusting for age, sex and treatment duration, showed a statistically significant increase in the risk of diabetes with olanzapine therapy compared with the general population cohort (hazard ratio [HR] 3.0; 95% CI 2.6, 3.5; $p \leq 0.0001$). The risk of diabetes with olanzapine treatment did not differ significantly from that with haloperidol therapy (HR 1.09; 95% CI 0.86, 1.37; $p = 0.479$).

7.2.5 Controlled Clinical Studies

A number of prospective, controlled clinical studies, including randomised clinical trials, have examined the effect of olanzapine treatment on direct measures of glucose regulation, in contrast to surrogate measures used in the retrospective database analyses, with the majority of the controlled studies reporting significant increases in plasma glucose and/or insulin levels during olanzapine treatment in comparison to different control conditions.

A significant increase in fasting glucose levels was observed during olanzapine therapy in a 14-week prospective study of antipsychotic therapy.[164] Patients with schizophrenia or schizoaffective disorder were randomised to one of four treatments: clozapine, olanzapine, risperidone or haloperidol. Patients in the olanzapine group had a significant mean increase from baseline in fasting glucose after 14 weeks of treatment ($n = 22$; +14.3 mg/dL; $p < 0.02$); this increase was greater than that observed in the other groups. Four patients receiving olanzapine treatment had elevated fasting glucose levels (≥126 mg/dL) during the study. This compared with six patients in the clozapine group, three on risperidone and one on haloperidol. ANCOVA analysis indicated no relationship between weight gain (mean change with olanzapine +7.3kg) and change in glucose levels at endpoint. This study was limited by potential differences in baseline and endpoint adiposity across the different treatment groups, which were not addressed in the analysis.

In studies that were designed to assess drug effects on glucose metabolism that might occur independent of changes in adiposity, oral and intravenous glucose tolerance tests have been used to examine the response of olanzapine-treated patients to a glucose load. Using a frequently sampled modified OGTT, Newcomer et al.[62] compared glucose regulation in non-diabetic patients with schizophrenia treated with first- or second-generation (clozapine, olanzapine or risperidone) therapy and untreated healthy volunteers. Patient groups were well matched for age and BMI; mean age and BMI were 37.4 years and 28.6kg/m^2 in the 12 olanzapine-treated individuals, and groups were also balanced for sex and ethnicity. Despite the exclusion of patients with diabetes, significant elevations in plasma glucose levels were observed in the olanzapine group at fasting and at all timepoints (15, 45 and 75 minutes) after the glucose load, compared with untreated healthy volunteers ($n = 31$) and with patients treated with typical antipsychotics ($n = 17$) [all comparisons $p < 0.005$]. Insulin resistance, calculated from FPG and insulin levels, was increased significantly in association with olanzapine compared with typical antipsychotic treatment ($p < 0.05$). Similar findings were reported by Henderson and colleagues[72] at the NCDEU 2000 meeting (reviewed by Haupt and Newcomer[54]) in a study using frequently sampled intravenous glucose tolerance tests. Chronically treated non-diabetic patients, matched for adiposity, age, sex and ethnicity, showed higher postload plasma glucose values with clozapine and olanzapine treatment than with risperidone. Calculated insulin sensitivity was significantly reduced in clozapine- and olanzapine-treated patients compared with those treated with risperidone.

Ebenbichler and colleagues[73] assessed the effect of olanzapine therapy on measures of insulin resistance/sensitivity. Ten patients with schizophrenia and treated with olanzapine monotherapy

(mean age 30.4 years; mean BMI 22.4 kg/m^2) were evaluated over a mean treatment period of 8.1 weeks. Fasting glucose levels increased significantly from 4.8 mmol/L at baseline to 5.5 mmol/L at endpoint ($p = 0.008$), as did fasting insulin concentrations (baseline 6.09 μU/mL; endpoint 10.64 μU/mL; $p = 0.006$). HOMA index for beta-cell function showed no statistically significant change over the observation period. In contrast, HOMA index for insulin resistance increased significantly ($p = 0.006$), suggesting induction of insulin secretion and insulin resistance in these patients. Bodyweight showed a mean increase of 3.3 (range 1.2–6.5) kg over the assessment period; weight gain was mainly due to an increase in fat mass. No statistically significant changes in any of these parameters were observed in the age- and sex-matched, healthy, untreated comparison group over the observation period.

Glucose, insulin and lipid parameters were also assessed in a randomised, double-blind, 6-week study comparing olanzapine and ziprasidone therapy in 269 inpatients with acute exacerbation of schizophrenia or schizoaffective disorder.[226] No statistically significant changes in FPG levels from baseline were observed with olanzapine or ziprasidone treatment during the study. Significant increases from baseline in median fasting plasma insulin levels ($p < 0.0001$) and HOMA calculated insulin resistance ($p < 0.0001$) were observed with olanzapine therapy, but not ziprasidone. Median bodyweight increased by 7.2lb (3.3kg) from baseline with olanzapine treatment compared with 1.2lb (0.5kg) with ziprasidone; median bodyweight was significantly higher in the olanzapine group than the ziprasidone group at endpoint ($p < 0.0001$). In this relatively young sample, with a significant compensatory hyperinsulinaemia, plasma glucose in the olanzapine-treated individuals did not increase significantly. Statistically significant adverse changes in lipid parameters in the olanzapine group are discussed below. In a 6-month, blinded follow-up study comparing olanzapine ($n = 71$) and ziprasidone ($n = 62$) therapy in patients with schizophrenia or schizoaffective disorder,[227] statistically significant increases from baseline in median fasting glucose and insulin levels were seen with olanzapine therapy. No statistically significant changes were observed with ziprasidone after 6 months of treatment.

Glucose and lipid levels were also assessed in a 28-week, randomised, double-blind comparison study of olanzapine 10–20 mg/day ($n = 277$) and ziprasidone 80–160 mg/day ($n = 271$) therapy in patients with schizophrenia.[228] The proportion of patients with treatment-emergent hyperglycaemia (i.e. those with baseline FPG levels <126 mg/dL who experienced levels ≥126 mg/dL during treatment) did not differ significantly between the two groups (olanzapine 11.5%; ziprasidone 7.4%; $p = 0.159$). However, clinically significant adverse effects on plasma glucose, insulin and lipid levels were observed in the olanzapine treatment arm. Mean bodyweight increased with olanzapine therapy (+3.06kg) and decreased with ziprasidone (–1.12kg) at week 28; the difference between the groups was statistically significant ($p < 0.001$). The changes in glucose levels did not correlate with changes in bodyweight.

Oral glucose tolerance tests were used to assess changes in glucose levels from baseline to endpoint in a small ($n = 30$) randomised, 21-day study of olanzapine 20–40 mg/day therapy.[229] Changes in mean 2-hour OGTT glucose values from baseline did not appear to be dose dependent (20 mg/day 4.68 ± 38.37 mg/dL; 30–40 mg/day 6.4 ± 21.20 mg/dL; 40 mg/day –4.58 ± 33.76 mg/dL). Glucose tolerance worsened in one patient (from IGT to diabetes) and improved in two patients (from IGT to normal) during the study. Other postload timepoints for glucose (i.e. prior to the 2-hour values) and postload insulin values were not reported.

A study of briefly treated healthy volunteers showed an increased insulin response and decreased insulin sensitivity with both olanzapine and risperidone treatments compared with placebo.[230] The change in insulin response correlated with a change in BMI. After adjusting for the effects of weight gain seen with active treatment using regression analyses, no statistically significant changes in insulin response or sensitivity were

detected with olanzapine or risperidone therapy, suggesting that the adverse effects were largely related to changes in adiposity. A more recent study examining insulin sensitivity in healthy volunteers receiving olanzapine (n = 22), risperidone (n = 14) or placebo (n = 19) for 3 weeks, with restricted access to food, showed no statistically significant changes in the insulin sensitivity index from baseline with olanzapine or risperidone therapy.[231] Using two-step, hyperinsulinaemic, euglycaemic clamp methodology, Sowell and colleagues[231] showed no statistically significant difference in the mean change in insulin sensitivity index from baseline between the olanzapine, risperidone and placebo groups at either low or high insulin steady states. Fasting insulin and fasting glucose levels both increased statistically significantly from baseline to endpoint in the olanzapine group, but showed small decreases in the risperidone group.

7.2.6 Discussion

Considered together, the case reports, the majority of the retrospective database analyses and controlled experimental studies including randomised clinical trials consistently suggest that olanzapine treatment increases the risk of significant weight gain, insulin resistance, hyperglycaemia and/or diabetes mellitus. The risk of acute complications such as diabetic ketoacidosis may also be increased; however, these infrequent events are more difficult to study and quantify outside case series.

The majority of the large retrospective database analyses showed a statistically significant increase in the risk of developing diabetes with olanzapine therapy. The risk of diabetes increased significantly with olanzapine therapy compared with no antipsychotic treatment[159,163,221,223] and compared with treatment with typical antipsychotics.[157,160,223,224] Three database analyses also showed a statistically significantly greater risk of developing diabetes with olanzapine therapy compared with risperidone.[159,220,222] In contrast to these findings, one analysis, which used prescription claims data, reported no statistically significant increase in the risk of diabetes with olanzapine treatment compared with haloperidol therapy.[163] The study, however, did show a statistically significantly higher risk of diabetes in olanzapine-treated patients compared with the general population cohort, similar to other first- and second-generation antipsychotics studied.

Analysis of cases identified from the FDA MedWatch system also provides support for an association between olanzapine therapy and diabetes development.[70] The large number of reported cases, the temporal relationship between initiation of olanzapine therapy and onset of hyperglycaemia, the rapid reversibility on treatment discontinuation and the younger age of affected patients are all suggestive. The larger number of olanzapine-treated cases reported to the FDA MedWatch System and in the literature contrasts with the fewer reports of diabetes or hyperglycaemia associated with risperidone therapy. Risperidone was approved for use before olanzapine, with the total number of risperidone prescriptions at the time of the MedWatch reports significantly larger than the total number for olanzapine, so that the number of case reports associated with olanzapine treatment cannot be understood simply as a function of greater exposure.

Further support for a link between olanzapine and diabetes comes from the temporal association between olanzapine treatment and the occurrence of events. Almost half of the cases of diagnosed, new-onset diabetes identified from the MedWatch System occurred within 3 months of the start of treatment, while 70% occurred within 6 months. Six cases were seen within 1 week of starting treatment. Similarly, in a review of published case reports from the literature,[143] 43% of cases occurred within 12 weeks of olanzapine initiation. In addition, the majority of patients recovered glycaemic control following olanzapine withdrawal. Among the MedWatch cases and published case reports,[143] almost 80% of patients experienced improved glycaemic control after discontinuing therapy.

An important feature of the cases analysed by Koller and Doraiswamy[70] was the high proportion

of patients younger than 45 years old. The mean age at onset for newly diagnosed diabetes was 39.8 years, with 68% of cases occurring in those younger than 45 years. This is in contrast to the age distribution of prevalence of diabetes in the US population. Data from the US National Health Interview Surveys (NHIS) show that 81% of diabetes cases occur in individuals aged over 44 years, with prevalence increasing with age.[166] For individuals aged 65–74 years and ≥75 years, 10% and 11%, respectively, have diabetes. An indirect comparison presented by Koller and Doraiswamy[70] showed that the frequency of newly diagnosed diabetes among olanzapine-treated patients aged 0–44 years was twice that in the US population (66% vs 33%). A comparison of the age distributions between the study and US populations showed that the difference was statistically significant ($p < 0.0001$). This suggests that diabetes occurs earlier in olanzapine-treated patients than in the general population, with a marked increase in those younger than 44 years. Analysis of the age distribution for all olanzapine prescriptions suggests that this does not simply reflect large numbers of olanzapine prescriptions in younger individuals.

Published case reports also contain a high proportion of younger individuals. The review by Ananth et al.[143] reported a mean age of patients of 41.5 years, with 65% of patients aged 45 years or younger. Analysis of healthcare data according to age[157] showed that the greatest increase in the risk of diabetes with olanzapine therapy occurred among patients younger than 40 years (OR 1.64).

Another notable feature of the MedWatch study and the case reports was the significant number of cases of diabetic ketoacidosis. Overall, 34.6% of the cases of hyperglycaemia reported in the MedWatch analysis were associated with metabolic acidosis or ketosis.[70] Diabetic ketoacidosis is typically an indicator of insulin deficiency, and is therefore commonly thought of in association with type 1 diabetes rather than with type 2 disease. Diabetic ketoacidosis is not typically observed as a first manifestation of type 2 diabetes, as the disease is characterised initially by peripheral insulin resistance and hyperinsulinaemia, followed by gradual and progressive decline of beta-cell function with diabetic ketoacidosis typically occurring in the later phases of the disease if at all. While most individuals with type 2 diabetes do not experience diabetic ketoacidosis, most cases of diabetic ketoacidosis in the population in fact occur in type 2 rather than type 1 diabetes, given the higher frequency of type 2 disease and the contributions of acute insults to beta-cell function such as glucose toxicity (discussed above, see Type 2 Diabetes). In the MedWatch analysis of olanzapine cases, the majority of cases of diabetic ketoacidosis (92%) were associated with new onset of type 2 diabetes. Published case reports of abnormal glucose regulation with olanzapine therapy also suggest a significant incidence of diabetic ketoacidosis. The clinical significance of diabetic ketoacidosis is illustrated by the number of fatalities in the MedWatch study and among the case reports. Ketosis or acidosis was reported in nine of the deaths reported in the main MedWatch study. Thus, more than 10% of the cases of diabetic ketoacidosis were associated with patient death.

Weight gain and obesity, and increased adiposity in general, are well established risk factors for diabetes. This strongly suggests that the well documented occurrence of marked weight gain with olanzapine therapy[59,167] could be a key factor in the increased risk of diabetes seen with this agent. However, several observations suggest that at least in some cases, weight gain may not play a primary role. A significant minority of reported cases of new-onset diabetes were not accompanied by substantial weight gain or obesity. Among the cases identified from the MedWatch System, 24% of patients did not appear to be overweight or have sustained weight gain. While no significant correlation between weight gain and increased blood glucose levels was reported in the two studies in which this was analysed,[164,216] this may reflect a number of critical host factors (e.g. beta-cell function) that can intervene between changes in weight and plasma glucose. The rapid onset of diabetes following olanzapine initiation and prompt resolution with treatment withdrawal in some cases also

do not suggest that the effects of olanzapine on glucose regulation in these individuals occur simply through actions on weight and adiposity.

Consistent with the increased risk of diabetes with olanzapine therapy, significant increases in blood glucose levels were reported in many but not all studies of patients treated with olanzapine. Chart reviews and more important prospective 8- and 14-week studies, as well as a 6-month follow-up study, showed statistically significant increases in fasting glucose levels with olanzapine compared with pretreatment levels.[73,146,164,216,227] In two of these studies, 18–27% of patients developed clinically significant elevations in FBG (≥126 mg/dL) during olanzapine therapy. A retrospective chart review of 45 olanzapine-treated patients reported three cases of new-onset diabetes (FBG >126 mg/dL) and four cases of hyperglycaemia (FBG >110–126 mg/dL).[214] In a 28-week study,[228] clinically significant increases in plasma glucose were observed in olanzapine-treated patients, although this did not differ statistically significantly from ziprasidone treatment when the hyperglycaemic threshold was set at the level of diabetes (≥126 mg/dL) [11.5% vs 7.4%]. The typical understanding of diabetes in the general population, is a disease characterised initially by peripheral insulin resistance and hyperinsulinaemia, followed by gradual and progressive decline of beta-cell function with resulting progressive increases in plasma glucose that eventually can cross the fasting diagnostic threshold of 126 mg/dL. Thus, studies of younger, non-diabetic individuals (i.e. those who have some degree of beta-cell reserve at baseline) may be better able to detect drug effects by measuring insulin resistance and lower-level hyperglycaemia (e.g. postload hyperglycaemia) rather than testing only for plasma glucose elevations ≥126 mg/dL.

Along these lines, changes in plasma insulin levels have also been reported with olanzapine therapy. Five studies reported significant increases in insulin in comparison to various control conditions,[62,73,149,226,227] while three studies also reported a significant increase in insulin resistance with olanzapine therapy compared with baseline levels.[73,226] Henderson and colleagues[72] reported a significant reduction in insulin sensitivity in non-diabetic olanzapine-treated patients compared with adiposity- and age-matched risperidone-treated individuals (reviewed by Haupt and Newcomer[54]). Two studies reported elevated insulin levels in 31–71% of patients receiving olanzapine treatment,[151,217] while significant improvements in insulin resistance and beta-cell function were also observed in a study of 40 patients with schizophrenia following the switch from olanzapine to risperidone therapy.[218]

Not all studies reported changes in insulin sensitivity with olanzapine therapy. In one study, no statistically significant changes in the insulin sensitivity index were observed in healthy volunteers after 3 weeks of olanzapine therapy.[231] In a second study in healthy volunteers, the changes in insulin sensitivity and insulin response were no longer statistically significant after adjusting for weight gain,[230] suggesting that changes which did occur were largely secondary to weight gain. Another study in patients with schizophrenia or related psychotic disorders showed no statistically significant changes in peripheral insulin resistance after at least 2 months of olanzapine treatment.[147]

7.3 Lipid Levels

Evidence for the effects of olanzapine treatment on lipid levels comes from a similar distribution of uncontrolled case reports and retrospective chart reviews, large-scale database analysis and controlled experimental studies, including randomised prospective clinical trials.

7.3.1 Case Studies and Chart Reviews

Five case reports have reported elevated lipid levels associated with olanzapine therapy (table VIII). Domon and Webber[200] report the development of both hyperglycaemia and hypertriglyceridaemia in a male adolescent that resolved with discontinuation of olanzapine treatment and without dietary changes or the use of antidiabetic therapy. Chang and colleagues[186] reported three cases of severe hypertriglyceridaemia in patients with schizophrenia treated with olanzapine, two of

Table VIII. Case reports of elevated lipid levels with olanzapine

Reference	Case report details
Chang et al.[196]	Three cases of severe hypertriglyceridaemia (2 with hyperglycaemia) associated with olanzapine therapy
Stoner et al.[232]	Severe hypertriglyceridaemia associated with olanzapine
Domon & Webber[200]	Development of hyperglycaemia and hypertriglyceridaemia in a male adolescent resolved with discontinuation of olanzapine
Nguyen & Murphy[233]	Olanzapine and hypertriglyceridaemia
Sheitman et al.[234]	Olanzapine-induced elevation of plasma triglyceride levels

which were also associated with severe hyperglycaemia. For one patient, glucose and triglyceride levels resolved with treatment with the patient continuing on olanzapine therapy. Three other publications reported hypertriglyceridaemia or elevated triglyceride levels with olanzapine therapy.

Significant changes in lipid levels have also been reported in chart reviews and observational studies of olanzapine-treated patients. Fasting plasma lipid levels were examined in a chart review of patients treated with different antipsychotics, including clozapine, olanzapine, risperidone and quetiapine.[146] The analysis included 32 patients treated with olanzapine. Mean triglyceride levels increased significantly from baseline with olanzapine therapy (38%; $p = 0.02$); the resulting mean triglyceride levels (255.0 mg/dL) were significantly higher than those observed with haloperidol therapy ($p = 0.02$). Maximum triglyceride levels also increased from baseline with olanzapine treatment (42%), although this change was not statistically significant. Overall, 39% of olanzapine-treated patients had elevated triglyceride levels (≥200 mg/dL). Minimal changes in mean total cholesterol (6%; NS) and LDL-cholesterol (–14%; $p = 0.03$) levels were observed with olanzapine. However, mean HDL levels also decreased significantly from baseline (10%; $p = 0.03$), and minimum HDL levels were significantly lower than those observed with risperidone treatment ($p = 0.02$). Overall, four olanzapine-treated patients (13%) initiated cholesterol-lowering therapy after starting treatment.

A retrospective study of patient records at Oregon State Hospital compared metabolic outcomes after 1 year of treatment with either olanzapine ($n = 47$) or risperidone ($n = 47$) therapy.[216] Patients in the olanzapine group experienced significant increases from baseline in fasting triglyceride (88.2 mg/dL; $p \leq 0.001$) and fasting total cholesterol (23.6 mg/dL; $p \leq 0.001$) levels. Analysis of patients younger than 60 years also showed statistically significantly greater increases in triglyceride (104.8 mg/dL) and cholesterol levels (30.7 mg/dL) with olanzapine therapy. Comparisons with risperidone-treated patients showed that the increases in both triglyceride and total cholesterol levels with olanzapine were statistically significantly greater than with risperidone for all patients and for those aged less than 60 years ($p < 0.05$). Mean bodyweight increased significantly from baseline with olanzapine therapy for all patients (17.5lb [7.9kg]; $p \leq 0.001$) and for those younger than 60 years (20.4lb [9.1kg]; $p \leq 0.001$). Analysis performed for the non-elderly subgroup showed no statistically significant correlation between weight gain and the change in triglyceride or cholesterol levels.

In an earlier retrospective review of patient records, Meyer[235] analysed 14 cases of severe hypertriglyceridaemia (fasting triglycerides >600 mg/dL) in patients receiving olanzapine ($n = 12$) or quetiapine ($n = 2$) treatment. In the 12 olanzapine cases, the mean fasting peak triglyceride level was 1737 mg/dL. The mean time to peak fasting triglyceride level was 10.0 months, with peak triglyceride levels occurring within 12 months of starting treatment in 9 of the 12 cases. Mean bodyweight increased from 188.0lb (84.6kg) at baseline to 200.3lb (90.1kg) at peak triglyceride levels, while mean BMI increased from 29.33 to 31.46 kg/m^2. Analysis of all 14 cases (including the two treated with quetiapine) showed that the increase in fasting serum triglycerides was not correlated with weight increase or BMI change. Furthermore, the increase in serum triglycerides did not correlate with olanzapine dose.

Changes in fasting triglyceride and cholesterol levels were investigated in a 12-week observational study of olanzapine therapy in 25 inpatients with schizophrenia (n = 13), schizoaffective disorder (n = 4) or other psychoses (n = 8).[236] Olanzapine use was associated with a significant increase in mean fasting triglyceride level (+60 mg/dL; $p < 0.04$) from baseline (162 ± 121 mg/dL) to endpoint (202 ± 135 mg/dL), a 37% increase. This increase was greater when six patients receiving lipid-lowering therapy during the study were excluded from the analysis (+74 mg/dL). In contrast, mean fasting total cholesterol levels showed a minimal change (+3 mg/dL) over the study period. Mean bodyweight also increased significantly during olanzapine treatment (5.4kg; $p < 0.02$), and ANCOVA showed a significant association between weight gain and triglyceride change ($p < 0.02$). Analysis showed that the change in triglyceride levels independent of weight was not statistically significant.

Adverse changes in fasting LDL-cholesterol were reported with olanzapine in a 6-month study involving patients with schizophrenia or schizoaffective disorder.[227] Significant increases in LDL-cholesterol from baseline ($p < 0.01$) occurred in the olanzapine group in this blinded, follow-up study comparing olanzapine and ziprasidone therapy. Increases in triglyceride levels were also reported in an open-label study of olanzapine treatment in patients with schizophrenia conducted in Japan.[237] In all, 20% of the 82 patients experienced abnormally elevated triglyceride levels during treatment.

Fasting lipid levels were evaluated in 16 outpatients with schizophrenia or related psychoses who received olanzapine treatment for at least 6 months.[151] Elevated levels of fasting triglycerides, total cholesterol and LDL-cholesterol were recorded for nine (56%), ten (63%) and six patients (38%), respectively. In addition, one patient had HDL-cholesterol levels below normal. Triglyceride levels (but not other lipid levels) showed a positive correlation with the ratio of olanzapine to its metabolite *N*-desmethylolanzapine.

Two other recent studies have also reported cross-sectional analyses of fasting lipid levels in patients with schizophrenia or related disorders treated continuously with antipsychotic therapy for at least 3 months[153] or 1 year.[238] Chue and Welch[153] reported higher fasting total cholesterol and triglyceride levels for olanzapine-treated patients (n = 18) than those receiving risperidone (n = 16) or typical antipsychotic therapy (n = 17). Hardy and colleagues[238] reported no statistically significant differences in mean fasting total, LDL- or HDL-cholesterol levels between patients treated with olanzapine (n = 67), risperidone (n = 65) or typical antipsychotic therapy (n = 52), although mean fasting triglyceride levels were statistically significantly higher in the olanzapine group than in the risperidone group. However, only patients with normal FBG levels (<110 mg/dL) were included in the analysis, and patients in this study were matched for BMI as well as sex and duration and severity of illness.

7.3.2 Retrospective Database Analysis

Data from the UK General Practice Research Database (GRPD) – a large database including over 6% of the total UK population – were analysed to assess the risk of hyperlipidaemia with risperidone, olanzapine and typical antipsychotic therapy, among patients with schizophrenia.[223] Using data collected between June 1997 and September 2000, 1268 cases of hyperlipidaemia were identified among the 18 309 patients with schizophrenia. Antipsychotic use was defined as antipsychotic treatment in the 3 months before the diagnosis of hyperlipidaemia. On this basis, 16 patients with hyperlipidaemia had been treated with olanzapine, 12 with risperidone, 807 with first-generation antipsychotics, 83 with other newer second-generation agents or more than one agent, and 413 had not been exposed to antipsychotic medication.

The incidence rate for hyperlipidaemia among all patients receiving antipsychotic therapy was 17.04 per 1000 person-years. When rates were determined for individual antipsychotics, the incidence rate for hyperlipidaemia with olanzapine was 26.6 per 1000 person-years (95% CI 17.15, 41.19), compared with 18.52 per 1000 person-

years for typical antipsychotics (95% CI 17.30, 19.82). In comparison, the rate for risperidone was 11.5 per 1000 person-years (95% CI 7.41, 17.81). Patients treated with olanzapine exhibited a 40% increase in the risk of developing hyperlipidaemia compared with those treated with typical antipsychotics (risk ratio 1.4; 95% CI 0.92, 2.22).

Nested case control analysis, involving 7598 matched controls with schizophrenia but no hyperlipidaemia, was used to determine the risk of hyperlipidaemia with olanzapine therapy. Logistic regression analysis, adjusted for age, sex, other medications and disease conditions affecting lipid levels, demonstrated a significant increase in the risk of developing hyperlipidaemia with olanzapine therapy compared with no antipsychotic therapy (OR 4.65; 95% CI 2.44, 8.85; $p < 0.001$) and typical antipsychotic treatment (OR 3.36; 95% CI 1.77, 6.39; $p < 0.001$). In contrast, there was no statistically significant increase in the risk of hyperlipidaemia for patients treated with risperidone, compared with either typical antipsychotic treatment (OR 0.81) or no antipsychotic therapy (OR 1.12).

7.3.3 Controlled Clinical Trials

Significant changes in lipid levels have also been observed during clinical trials of olanzapine therapy. In a prospective, 14-week study, inpatients with either schizophrenia or schizoaffective disorder were randomised to olanzapine, clozapine, risperidone or haloperidol treatment.[164] Data from the 26 patients randomised to olanzapine showed a significant increase in fasting cholesterol level from baseline during the first 8 weeks of the study (12.3 mg/dL; $p < 0.04$) and throughout the 14-week study period ($n = 22$; 16.3 mg/dL; $p < 0.002$). Mean values, however, remained modest (197.6 mg/dL at week 14). Bodyweight increased significantly from baseline with olanzapine therapy (mean 7.3kg; $p < 0.0001$). A significant association was detected between weight gain and cholesterol increase ($p = 0.035$), although this was not statistically significant after adjusting for baseline weight and cholesterol level.

Glick and colleagues[226] examined changes in fasting lipid levels in addition to glucose and insulin measures in a 6-week, double-blind, randomised study comparing the metabolic effects of olanzapine and ziprasidone therapy. Significant increases from baseline in median fasting total cholesterol (20 mg/dL; $p < 0.0001$), LDL-cholesterol (13 mg/dL; $p < 0.0001$) and triglyceride (26 mg/dL; $p = 0.0003$) levels were observed with olanzapine therapy. In contrast, minimal changes were observed with ziprasidone therapy, and median total and LDL-cholesterol and triglyceride levels were significantly higher in the olanzapine group at endpoint ($p < 0.003$). In a further analysis by sex, male schizophrenic patients showed significant increases in total cholesterol, LDL-cholesterol and triglyceride levels with olanzapine treatment compared with ziprasidone therapy ($p < 0.005$), while changes in triglyceride levels tended towards statistical significance with olanzapine versus ziprasidone in female patients.[239] In a 28-week randomised, double-blind comparison study,[228] significantly more olanzapine-treated patients experienced treatment-emergent 'high' triglyceride levels (NCEP criteria: 200–499 mg/dL) than ziprasidone-treated individuals (16.9% vs 2.6%; $p < 0.001$). No statistically significant differences were observed between the treatment groups in the proportion of patients experiencing 'high' or 'very high' total or LDL-cholesterol levels or developing low HDL-cholesterol. In both groups, changes in triglyceride levels correlated significantly with changes in bodyweight.

Significant increases in fasting triglyceride levels with olanzapine therapy were also reported in a 6-week randomised study of clozapine, risperidone, olanzapine and quetiapine therapy in 56 patients with schizophrenia.[175] Patients treated with olanzapine ($n = 13$) showed a significant increase in triglyceride levels from baseline at week 6 (31.23 mg/dL; $p < 0.001$). The mean changes in bodyweight (+8.92kg) and BMI (22.35 to 26.97 kg/m^2) from baseline to study endpoint were also statistically significant with olanzapine therapy ($p < 0.01$ and $p < 0.05$, respectively), and

there was a significant correlation between the changes in triglyceride levels and BMI ($p < 0.01$).

A 12-week double-blind study comparing olanzapine and divalproex sodium for the treatment of acute mania in patients with bipolar disorder examined changes in cholesterol levels.[213] Total and LDL-cholesterol levels increased from baseline with olanzapine treatment (total +13.29 mg/dL; n = 42; LDL +8.78 mg/dL; n = 41) and decreased slightly with divalproex sodium (total –1.69 mg/dL; n = 45; LDL –4.43 mg/dL; n = 42). These changes in cholesterol levels differed significantly between the groups ($p < 0.03$). Mean fasting HDL-cholesterol levels also showed statistically significant adverse changes (i.e. decreases) from baseline in patients receiving olanzapine therapy (n = 9) in a study of 75 individuals with schizophrenia or related psychotic disorders.[147]

Changes in lipid levels were also reported in an 8-week randomised, double-blind study comparing olanzapine and risperidone treatment in 377 patients with schizophrenia or schizoaffective disorder.[240] The ratio of beneficial change (from above-normal baseline value to normal end-of-study value) to adverse change (from normal baseline value to above-normal value at week 8) was presented for both triglycerides and cholesterol. Changes in triglycerides tended to be adverse with olanzapine treatment (ratio 0.45) but beneficial with risperidone therapy (ratio 2.57), so patients treated with risperidone were significantly more likely to experience beneficial changes in triglyceride levels than those receiving olanzapine therapy (risk ratio 5.71; $p = 0.003$). Similarly, adverse changes in cholesterol levels tended to occur with olanzapine (ratio 0.35), whereas beneficial changes were more frequent with risperidone (ratio 1.64), suggesting a significantly greater likelihood of improved cholesterol levels with risperidone treatment than with olanzapine (risk ratio 4.70; $p = 0.005$).

In an 8-week study of olanzapine and risperidone therapy in 50 inpatients with schizophrenia or schizophreniform or schizoaffective disorder,[241] patients receiving olanzapine showed significant increases in triglyceride levels from baseline ($p < 0.001$) but no statistically significant changes in total cholesterol. In addition, significantly more patients in the olanzapine group had clinically significant increases (>7%) in bodyweight from baseline than in the risperidone group (44% vs 4%; $p < 0.01$). No statistically significant changes in lipid levels were observed with risperidone. A randomised study involving 21 female patients with schizophrenia reported statistically significant increases in total cholesterol (17.3%), LDL-cholesterol (31.4%) and VLDL-cholesterol (8.1%) with olanzapine therapy from week 1 to week 6 of treatment ($p < 0.05$).[242] These changes were greater than those observed with quetiapine therapy (total cholesterol 8.0%; LDL-cholesterol 12.2%; VLDL-cholesterol 1.7%). BMI also increased statistically significantly over the study period with olanzapine, but not quetiapine, therapy.

Not all studies have reported significant changes in lipid levels from baseline to endpoint with olanzapine therapy. A 4-month randomised study comparing patients who switched to olanzapine treatment (n = 27) with those remaining on current therapy (either typical antipsychotics or risperidone; n = 27) reported no statistically significant changes in fasting total cholesterol or triglyceride levels at endpoint in patients switched to olanzapine.[243] Mean changes in these fasting lipids did not differ significantly from those observed for patients remaining on prior therapy. However, increases in both total cholesterol and triglyceride levels were observed with olanzapine therapy after 1 month of treatment, with levels returning to baseline at the end of month 2 and month 3, respectively. Furthermore, mean baseline fasting lipid levels, measured prior to randomisation, were either at or above the ULN.

7.3.4 Discussion

Findings from uncontrolled case reports and chart reviews, large-scale database analysis and controlled experimental studies including clinical trials suggest consistent evidence that olanzapine treatment has a potentially adverse effect on plasma lipids, particularly plasma triglyceride. This is

consistent with the effects of increasing abdominal fat mass on insulin sensitivity and lipid metabolism.

Analysis of healthcare data from the UK General Practice Research Database (GPRD) indicates a statistically significantly increased risk of hyperlipidaemia with olanzapine compared with either typical or no antipsychotic therapy in patients with schizophrenia.[223] This finding is supported by the increases in triglyceride levels reported with olanzapine therapy in clinical trials. Statistically significant increases in triglycerides from pretreatment levels were observed with olanzapine therapy in randomised clinical trials and observational studies[175,226,236,241,242] and in two retrospective chart reviews,[146,216] although one randomised study reported no significant change from baseline to endpoint.[243] Increased triglyceride levels were also reported in an open-label study of olanzapine,[237] in four case reports[200] and in cross-sectional analyses of patients receiving olanzapine therapy for at least 3 months.[151,153,238] Statistically significantly more patients developed 'high' triglyceride levels with olanzapine therapy than ziprasidone treatment during a 28-week comparison study.[228] Elevated triglyceride levels, in addition to LDL-cholesterol, are an independent significant risk factor for the exacerbation of coronary artery disease and also appear to precipitate or exacerbate diabetes.[244]

Increases in bodyweight are well documented with olanzapine therapy[59,167] and can be hypothesised to affect the changes in triglyceride levels seen with olanzapine therapy. Osser and co-workers[236] and Hardy et al.[228] reported a statistically significant association between weight gain and triglyceride increases, while Atmaca et al.[175] reported a significant correlation between triglyceride levels and BMI. However, two studies by Meyer[216,235] show no significant correlation between weight gain and changes in triglyceride levels. Again, a number of host factors can intervene in the short term between changes in weight and changes in circulating lipids. In general, increasing adiposity is a well established major modifiable risk factor for dyslipidaemia.

Findings from the analyses of total cholesterol levels were less clear, and total cholesterol in general is more difficult to interpret in comparison to specific lipid fractions (e.g. LDL or HDL). Three studies (one observational study, one chart review and one controlled study) showed minimal changes in total cholesterol levels from baseline.[146,236,243] Four other analyses (one chart review and three controlled studies) reveal statistically significant increases from baseline.[164,217,226,242] In each case, the chart reviews and controlled trials involved similar numbers of patients and patient populations. The effect of bodyweight on cholesterol levels was examined in these studies. The three studies that report increased cholesterol levels also show statistically significant weight or BMI increases from baseline with olanzapine treatment. However, Meyer[216] found no significant correlation between weight gain and increased cholesterol levels, while in the study by Lindenmayer et al.,[164] the correlation was not statistically significant after adjusting for baseline weight and cholesterol levels.

Changes in LDL- and HDL-cholesterol have been little studied. One published report shows statistically significant improvements in LDL-cholesterol levels from baseline with olanzapine therapy.[146] However, these were accompanied by statistically significant adverse changes in HDL-cholesterol levels. In contrast, Simpson et al.,[227] Glick et al.[226] and Ozguven et al.[242] reported statistically significant increases in LDL-cholesterol from baseline during olanzapine treatment.

7.4 Conclusion

Olanzapine treatment is associated with significant increases in weight and adiposity over both short- and long-term treatment. Studies using a variety of methodologies indicate, with few exceptions, that olanzapine treatment is associated with an increased risk of developing diabetes mellitus, based especially on evidence for treatment-related increases in insulin resistance and elevations in plasma triglyceride levels. Evidence from case report analyses, large retrospective database analyses and controlled clinical studies indicate signifi-

cant increases in the risk of insulin resistance, hyperglycaemia, dyslipidaemia and diabetes during olanzapine treatment.

8. Risperidone

Although risperidone has been prescribed extensively since its introduction in the US in 1993, fewer published reports are available concerning the risk of diabetes with risperidone as compared with either clozapine or olanzapine treatment. However, a considerable body of literature is still available examining the potential associations between risperidone therapy and the risk of weight gain, insulin resistance, hyperglycaemia, diabetes and lipid dysregulation.

8.1 Bodyweight

Risperidone therapy is associated with relatively modest weight gain during short-term treatment. In a meta-analysis of published studies,[59] the estimated weight gain over 10 weeks of risperidone therapy was approximately 2kg. Individual studies report weight gain of around 2kg with short-term risperidone treatment.[245] Weight gain with risperidone does not appear to be dose related across doses tested. In an 8-week study comparing five risperidone doses ranging from 1 to 16 mg/day, the mean increase in weight ranged from 0.3 to 1.8kg, with the largest increase reported with the 8 mg/day dose.

Mean increases in bodyweight in the order of 2kg have also been reported with longer-term risperidone treatment. Risperidone-treated patients experienced a mean increase in weight of 2.3kg over the 52-week treatment period in a haloperidol comparison study involving patients with chronic, stable schizophrenia.[246] Similarly, mean weight gain of 2.3kg was observed with risperidone therapy in a 28-week comparison study versus olanzapine treatment.[247] Larger increases in weight have been reported with long-term risperidone therapy. A retrospective analysis of patient records revealed maximum weight gain of 4.1kg with risperidone treatment over a mean treatment duration of approximately 26 weeks.[113] However, not all studies report weight gain with risperidone therapy. A follow-up of schizophrenic patients newly started on risperidone therapy showed a slight mean decrease in bodyweight with risperidone therapy (–0.3kg) over a mean treatment duration of 125.3 days.[248] It may be critical to consider and control for previous medication, as a switch from agents with a higher weight gain liability to those with a lower liability can be associated with weight loss.

The weight gain potential of risperidone is also apparent when the proportion of patients experiencing clinically significant weight gain (≥7% increase) is considered. Package insert data for risperidone report that 18% of risperidone-treated patients gain 7% or more of their bodyweight over 6–8 weeks of treatment compared with 9% of patients receiving placebo, or approximately twice the placebo incidence rate.

8.2 Diabetes and Hyperglycaemia

8.2.1 Case Reports, Chart Reviews and Observational Studies

Data from the FDA MedWatch Drug Surveillance System (1993 to February 2002), published reports (Medline, to February 2002) and selected abstracts from national psychiatric meetings identified a total of 131 cases of diabetes or hyperglycaemia associated with risperidone therapy.[71] Of these reports, 78 cases (60%) involved newly diagnosed hyperglycaemia, 46 cases (35%) described exacerbation of pre-existing diabetes, and 7 cases did not clearly make this distinction. Of the 78 patients with new-onset hyperglycaemia, 55 met diagnostic criteria for diabetes based on blood glucose (fasting ≥126 mg/dL; postload ≥200 mg/dL) or HbA_{1c} levels, and 10 were receiving antidiabetic medication and/or were acidotic or ketotic at the time of hyperglycaemia. In addition, there were a further six reports of acidosis with risperidone treatment that were not associated with hyperglycaemia.

As discussed earlier, it is important to remember that most adverse event reporting happens in

the first 2 years after the launch of a drug, with underreporting generally estimated to be in the range of 1/10 to 1/100 of the actual number of cases. Data for haloperidol collected using the same methodology (FDA MedWatch data, late 1970s to February 2002) identified 13 cases of diabetes or hyperglycaemia (newly diagnosed hyperglycaemia n = 10; exacerbation of pre-existing diabetes n = 2; unknown n = 1) and 11 cases of acidosis not associated with hyperglycaemia. A further seven cases of hyperglycaemia were identified for patients receiving combined risperidone-haloperidol therapy. The reporting rate, based on prescription sales, was 21 times higher for risperidone monotherapy than for haloperidol monotherapy using data from 1981 onwards and 8.5 times greater using data from 1994 onwards.

For risperidone-treated patients with newly diagnosed hyperglycaemia, the mean age at onset was 34.8 (±15.7) years. These patients were significantly younger than risperidone-treated patients with exacerbation of existing diabetes (mean age 48.8 ± 17.5 years; $p < 0.001$) and tended to be younger than haloperidol-treated patients with newly diagnosed hyperglycaemia (50.2 ± 21.7 years; $p = 0.055$). Time from the start of risperidone therapy to the onset of hyperglycaemia ranged from 1 day to 48 months among the 96 patients with available data, and for 65 patients (68%), onset occurred within 6 months of starting treatment (figure 4). Time to onset tended to be shorter for patients experiencing exacerbation of existing disease than for those with new-onset hyperglycaemia, with 71% and 48% of cases, respectively, occurring within 3 months of treatment initiation. Risperidone therapy was withdrawn in 47 patients and reduced in 5 patients. Outcomes data for these patients were limited, although improved glycaemic control was reported for 12 of these patients.

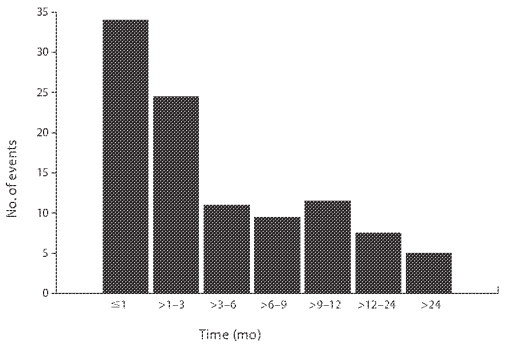

Fig. 4. Time to onset of hyperglycaemia with risperidone.[71]

The severity of hyperglycaemia associated with risperidone treatment ranged from mild glucose intolerance to diabetic ketoacidosis and hyperosmolar coma. Thirty-one patients (24 with new-onset diabetes) experienced blood glucose levels of ≥500 mg/dL. Metabolic acidosis or ketosis was reported for 26 patients treated with risperidone, the majority of whom (n = 22) experienced new-onset diabetes. There were four deaths among patients receiving risperidone monotherapy; three of these patients had acidosis or ketosis. Limited bodyweight data, available for 37 cases, suggested that approximately 20% of patients were not substantially overweight or had significant weight gain.

Diabetes prevalence and plasma glucose levels were examined in a chart review of 208 patients with psychotic illness treated with clozapine, risperidone, olanzapine, quetiapine or typical antipsychotic monotherapy.[156] No statistically significant differences in the prevalence of diabetes or in mean FPG levels were observed between the treatment groups. Nine (19.6%) of the 46 risperidone-treated patients had diabetes; mean FPG level in the risperidone group was 108.9 mg/dL.

In contrast to the large number of published case reports of diabetes or diabetic ketoacidosis associated with clozapine or olanzapine therapy, there have been relatively few case reports of diabetes or hyperglycaemia associated with risperidone treatment in the literature (table IX).

Wirshing and colleagues[250] report a retrospective analysis of two cases in which patients with schizophrenia developed diabetes while receiving risperidone treatment. In both cases, antipsychotic therapy was associated with weight gain. For one patient, the development of diabetes necessitated

Table IX. Case reports of abnormal glucose levels with risperidone

Reference	Case report details
Fukui & Murai[249]	Severe weight gain and diabetes in 1 patient receiving combination treatment with risperidone and paroxetine
Wirshing et al.[250]	Two retrospective cases in which patients with schizophrenia developed diabetes while taking risperidone
Croarkin et al.[251]	Diabetic ketoacidosis associated with risperidone therapy
Mallya et al.[252]	Resolution of hyperglycaemia on risperidone discontinuation

ongoing treatment with insulin. In other reports, Mallya and co-workers[252] document the resolution of hyperglycaemia following discontinuation of risperidone treatment, and Croarkin et al.[251] report a case of diabetic ketoacidosis in a patient with HIV infection, with HIV possibly contributing to risk in this individual.[253] Wilson et al.,[254] in a retrospective chart review, report a case of diabetic ketoacidosis occurring 5 days after clozapine was added to existing risperidone therapy. FBG values decreased when the patient resumed clozapine monotherapy and insulin, and eventually insulin could be discontinued.

A chart review of 215 patients receiving first- or second-generation antipsychotic therapy[146] showed no significant changes in either mean or maximum fasting glucose levels with risperidone treatment compared with pretreatment values. Among the 49 risperidone-treated patients (mean treatment duration 19.2 months), mean glucose levels increased from 118.3 mg/dL at baseline to 122.3 mg/dL on therapy, an increase of 3%. In contrast, significant increases in both mean and maximum fasting glucose values were observed with clozapine, olanzapine and haloperidol (mean only). Excluding patients with abnormal FBG values at baseline, 36% of patients developed clinically significant elevated glucose levels (≥126 mg/dL) during risperidone therapy, similar to the value with haloperidol. However, none of the patients required the initiation of glucose-lowering treatment following the start of risperidone therapy.

Risperidone therapy was also associated with minimal changes in FBG levels from pretreatment values in a review of 47 patients treated for 1 year.[216] The mean increases in glucose were 0.68 mg/dL for all patients and 0.74 mg/dL for the subgroup of patients younger than 60 years (n = 39). These changes were not statistically significant compared with baseline. However, the increase seen in a non-elderly subgroup was significantly less than the increase with olanzapine therapy (10.8 mg/dL; p = 0.03; n = 37). A significant increase in bodyweight from baseline was observed with risperidone treatment for all patients (10.7lb [4.8kg]; p < 0.001) and for the non-elderly subgroup (11.9lb [5.3kg]; p < 0.001). No statistically significant correlation was observed between weight gain and fasting glucose levels in an analysis of non-elderly patients.

Changes in insulin resistance and beta-cell function have also been examined in schizophrenia patients switched to risperidone treatment after at least 30 days of olanzapine therapy.[218] Results for 40 patients showed significant improvements in measures of insulin resistance and beta-cell function following the change to risperidone treatment.

8.2.2 Retrospective Database Analyses

Data analyses of ten healthcare databases have examined the risk of diabetes with risperidone therapy (table X). In two of the studies, the comparison was made against olanzapine treatment. In the other analyses, risperidone therapy was compared with either typical antipsychotics or no antipsychotic treatment.

Analysis of data from the Veterans Affairs databases[157] showed that of the 22 648 outpatients with schizophrenia treated with second-generation antipsychotics, 9903 (43.7%) received risperidone therapy. Logistic regression analysis, controlling for demographic, diagnostic and treatment factors, showed that overall, patients receiving risperidone did not have a significantly greater risk of diabetes diagnosis than patients receiving typical antipsychotics (OR 1.05; 95% CI 0.98, 1.12; p = 0.15). This was in contrast to the findings with clozapine, olanzapine and quetiapine treatment. When patients were stratified according to their age, those

Table X. Summary of database analyses investigating association between risperidone therapy and diabetes

Reference	Risk of diabetes		
Sernyak et al.[157]	**Odds ratio vs typical antipsychotic**		
	All patients	1.05 (95% CI 0.98, 1.12)	NS
	<40y	1.51 (95% CI 1.12, 2.04)	p < 0.008
	40–49y	1.04 (95% CI 0.92, 1.17)	NS
	50–59y	1.13 (95% CI 1.01, 1.26)	p < 0.05
	60–69y	0.94 (95% CI 0.80, 1.10)	NS
	≥70y	1.02 (95% CI 0.86, 1.21)	NS
Fuller et al.[220]	**Relative risk: typical antipsychotic vs risperidone**		
	Haloperidol	0.89 (95% CI 0.67, 1.17)	NS
	Fluphenazine	1.11 (95% CI 0.68, 1.79)	NS
	Relative risk: olanzapine vs risperidone		
	Overall[a]	1.36 (95% CI 1.06, 1.76)	p = 0.017
Gianfrancesco et al.[159]	**Odds ratio vs no antipsychotic**		
	1mo	0.989 (95% CI 0.921, 1.063)	NS
	12mo	0.88 (95% CI 0.372, 2.070)	NS
Gianfrancesco et al.[221]	**Odds ratio vs no antipsychotic**		
	1mo	0.966	NS
	12mo	0.660 (95% CI 0.311, 1.408)	
Koro et al.[223]	**Odds ratio vs no antipsychotic**		
	Overall	2.2 (95% CI 0.9, 5.2)	NS
	Odds ratio vs typical antipsychotic		
	Overall	1.6 (95% CI 0.7, 3.8)	NS
Caro et al.[222]	**Relative risk: olanzapine vs risperidone**		
	Overall[a]	1.20 (95% CI 1.00, 1.43)	p = 0.05
	Month 1–3[a]	1.90 (95% CI 1.40, 2.57)	p < 0.0001
Lambert et al.[160]	**Odds ratio vs typical antipsychotic**		
	Overall	1.10 (95% CI 0.97, 1.23)	NS
Farwell et al.[224]	**Adjusted odds ratio vs typical antipsychotic**		
	Overall	2.22 (95% CI 0.5, 10.6)	
Buse et al.[161]	**Hazard ratio vs no antipsychotic**		
	Overall	3.4 (95% CI 3.1, 3.8)	p ≤ 0.0001
	Hazard ratio vs haloperidol		
	Overall	1.23 (95% CI 1.01, 1.50)	p = 0.040
Cavazzoni et al.[225]	Significantly higher risk of diabetes with risperidone compared with the general population (no data presented in abstract)		

[a] Significantly increased risk with olanzapine over risperidone.

younger than 40 years treated with risperidone had a significantly higher risk of diabetes (OR 1.51; 95% CI 1.12, 2.04; p < 0.008) than those treated with typical antipsychotic therapy, consistent with findings for the other three second-generation agents studied. Risperidone prescription was also associated with a statistically significantly higher risk of diabetes in patients aged 50–59 years, as was olanzapine.

A second retrospective analysis involving a Veterans Administration healthcare database (VISN-10) compared the risk of developing diabetes in patients treated with risperidone, olanzapine, haloperidol or fluphenazine.[220] Male patients of Caucasian or African American ethnicity, treated with any of these four antipsychotics during 1997–2000, were included in the analysis. Diabetes was defined as a diagnosis of diabetes or prescription of antidiabetic medication; those with existing diabetes were excluded. In all, 368 (6.3%) of the 5837 individuals analysed developed diabetes. Multivariate Cox regression analysis showed that the risk of developing diabetes did not differ significantly between patients receiving risperidone treatment (the reference group) and those treated with haloperidol (RR 0.89; 95% CI 0.67, 1.17; p = 0.41) or fluphenazine (RR 1.11; 95% CI 0.68, 1.79; p = 0.61). In contrast, the risk of developing diabetes was significantly greater with olanzapine therapy than with risperidone (RR 1.37; 95% CI 1.06, 1.76; p = 0.016).

Another study analysing health claims data[159]

compared the frequency of newly reported diabetes among patients with psychosis receiving antipsychotic therapy (4308 individuals) with that in untreated patients (3625 individuals). Patients with type 2 diabetes were then identified from the database; those with pre-existing disease were excluded, based on a screening assessment at either 4 or 8 months prior to the start of treatment. This allowed two analyses to be performed.

Based on pre-screening at the 4-month timepoint, 1368 patients received risperidone, of whom 25 developed diabetes; using the 8-month data, 10 patients out of 994 developed diabetes. Logistic regression analysis showed that the risk of developing diabetes with risperidone was not statistically significantly different from the risk with no antipsychotic treatment, whether calculated using 4- or 8-month data on the basis of either treatment duration (4-month OR 1.021; 8-month OR 0.989) or dose (4-month OR 0.909; 8-month OR 0.811). The 12-month OR for risperidone (using the 8-month data) was 0.88 (95% CI 0.372, 2.070); this was not statistically significantly different from the OR with no antipsychotic treatment. In contrast, the odds of diabetes increased statistically significantly with both clozapine and olanzapine compared with no treatment or risperidone therapy.

A second study by Gianfrancesco and colleagues[221] used similar methodology to analyse more recent health claims data. As in the earlier study, they compared the frequency of newly reported diabetes between patients with psychosis receiving antipsychotic therapy (n = 6582) and those who were untreated (n = 10 296). Patients with diabetes were identified on the basis of medical or prescription claims for antidiabetic treatment: those with evidence of diabetes in the 8 months before the start of the observation period were excluded from the analysis. Of the 1675 patients receiving risperidone therapy, five developed diabetes. The risk of developing diabetes with risperidone, calculated using logistic regression analysis, did not differ statistically significantly from that with no treatment (OR 0.966 for 1 month of treatment). Converting this to 12 months of treatment, the OR for risperidone was 0.660 (95% CI 0.311, 1.408). In contrast, the findings showed a statistically significantly greater risk of diabetes with olanzapine therapy than with no antipsychotic therapy.

Two analyses have examined the relative risk of developing diabetes with risperidone and olanzapine therapy. The larger of these analyses used healthcare data from Quebec.[222] Among the 14 793 patients treated with risperidone, 217 developed diabetes after the start of treatment. This compared with 317 cases of diabetes among the 19 153 patients treated with olanzapine. When the data were adjusted for age, sex and haloperidol use, the relative risk of developing diabetes was significantly greater with olanzapine therapy than with risperidone (RR 1.20; 95% CI 1.00, 1.43; $p = 0.05$). The increased risk of diabetes with olanzapine over risperidone was particularly evident during the first 3 months of treatment (RR 1.90; 95% CI 1.40, 2.57; $p < 0.0001$).

In the other analysis, data from the UK GPRD were used to investigate the risk of diabetes among patients with schizophrenia.[225] Out of the 19 637 patients included in the analysis, 1683 had received risperidone therapy and 970 had been treated with olanzapine. Overall, 451 patients developed diabetes during the follow-up period (mean 5.2 years); 23 of these had received risperidone therapy. Case control analyses showed an increased risk of diabetes among schizophrenia patients receiving risperidone treatment compared with those not treated with antipsychotics (OR 2.2; 95% CI 0.9, 5.2), although this increase was not statistically significant. This contrasts with the significant increase in risk seen with olanzapine (OR 5.8; $p = 0.001$). The risk of diabetes with risperidone was also increased compared with typical antipsychotic therapy (OR 1.6; 95% CI 0.7, 3.8), although again this did not reach significance. However, the risk of diabetes increased statistically significantly with olanzapine (OR 4.2; $p = 0.008$) compared with typical antipsychotic therapy.

Case control analysis was also used to examine the risk of developing diabetes with antipsychotic treatment in patients with schizophrenia in the California Medicaid system.[160] Analysis of

records from 1 January 1997 to 31 December 2000 identified 3102 cases of patients with schizophrenia, aged 18 years or older, diagnosed with type 2 diabetes and who had received continuous antipsychotic monotherapy for the 12 weeks prior to diagnosis. These cases were matched for sex and age (±5 years) to 8271 control cases – patients with schizophrenia not diagnosed with diabetes. Logistic regression analysis, controlling for ethnicity and other diabetes-inducing medication, showed that the risk of type 2 diabetes with risperidone therapy did not differ significantly from that with typical antipsychotics (OR 1.10; 95% CI 0.97, 1.23; p = 0.114). In contrast, the risk of diabetes was statistically significantly greater with clozapine (OR 1.43), olanzapine (OR 1.30) and quetiapine (OR 1.45) therapy than with typical antipsychotic treatment.

Another case control study used data from a medical record system covering a number of healthcare providers (including an inner-city public hospital) in Indianapolis, Indiana.[224] In all, 10 428 patients with schizophrenia receiving antipsychotic treatment (risperidone n = 2248; olanzapine n = 1640; typical n = 6540) were identified from the database. Patients aged 18 years or older, with no diabetes prior to antipsychotic treatment, and who had received antipsychotic therapy for at least 1 year were selected for analysis, resulting in a sample of 744 individuals (risperidone n = 150; olanzapine n = 112; typical n = 482). Overall, 96 cases of new-onset diabetes were identified, and these patients were matched for age (±2 years), sex and ethnicity with 316 control (non-diabetic) patients. The proportion of patients who developed diabetes was similar with risperidone therapy (6.7%) and typical antipsychotic therapy (7.3%; p = 0.805). Logistic regression analysis, adjusted for patient demographics, comorbid conditions and level of outpatient care, showed that the risk of diabetes was higher with risperidone treatment than with typical antipsychotic therapy (adjusted OR 2.22; 95% CI 0.5, 10.6). This adjusted OR was numerically less than that observed for olanzapine therapy compared with typical antipsychotics (adjusted OR 3.92; 95% CI 1.0, 15.6).

Two other studies have reported an increased risk of diabetes with risperidone treatment. Buse and co-workers[163] used data from the AdvancePCS prescription claims database, which covers over 50 million individuals (mostly outpatients), to examine the risk of developing diabetes in patients receiving first- or second-generation antipsychotic monotherapy. Patients starting antipsychotic therapy between December 1998 and the end of February 2000 were included in the analysis, unless they had pre-existing diabetes, antipsychotic use in the 6 months before study enrolment, or had received more than one antipsychotic medication during the study period. Overall, 19 782 patients were treated with typical antipsychotics and 38 969 with second-generation antipsychotics. Over 5 million individuals (with no antidiabetic medication or antipsychotic prescription claims) were included in the general population cohort.

New-onset diabetes, identified by a prescription claim for antidiabetic medication, occurred in 951 patients overall (first-generation n = 307; second-generation n = 641). Among the 20 633 risperidone-treated patients there were 400 cases of diabetes. Cox proportional hazard regression analysis, adjusting for age, sex and treatment duration, showed significant increases in the risk of diabetes with all first-generation antipsychotics combined (HR 3.5; 95% CI 3.1, 3.9; p≤0.0001) and all second-generation agents combined (HR, 3.1; 95% CI, 2.9–3.4; p≤0.0001) compared with the general population. Analysis of individual agents showed a statistically significant increase in the risk of diabetes with risperidone compared with the general patient population (HR 3.4; 95% CI 3.1, 3.8; p ≤ 0.0001), consistent with the results for the other first-generation agents (haloperidol and thioridazine) and second-generation agents (clozapine, olanzapine and quetiapine) studied. Risperidone treatment was also associated with a significantly increased risk of diabetes compared with haloperidol treatment (HR 1.23; 95% CI 1.01, 1.50; p = 0.040).

Another analysis of the UK GPRD, presented at the 2002 CINP congress,[255] compared the risk of diabetes among patients prescribed antipsychotic

therapy with a general patient population cohort derived from the GPRD. The analysis included 46 111 patients prescribed first- or second-generation antipsychotics and 266 272 individuals in the general patient population cohort. A Cox proportional hazard regression model was used, including age, sex and the presence or absence of obesity as covariates. Overall, the risk of diabetes was higher in patients receiving antipsychotic therapy than in the general population cohort (HR 1.5; 95% CI 1.1, 1.9). Patients treated with risperidone had a significantly higher risk of diabetes compared with the general population (actual values not in abstract). Assessment of other individual antipsychotics was "limited by the sample size of the cohorts", and data were not presented in the abstract.

8.2.3 Controlled Clinical Studies

Four prospective, controlled, randomised clinical studies have examined changes in blood glucose levels associated with risperidone therapy. Minimal changes in FBG from baseline were observed with risperidone therapy in a 14-week clinical trial of antipsychotic therapy in patients with schizophrenia or schizoaffective disorder.[164] Mean changes from baseline were not statistically significant at week 8 (–1.3 mg/dL) and week 14 (+2.7 mg/dL), unlike the increases observed with clozapine (+17.1 mg/dL) and haloperidol (+8.9 mg/dL) at week 8 and olanzapine at week 14 (+14.3 mg/dL). Three patients receiving risperidone treatment experienced elevated fasting glucose levels (≥126 mg/dL) during the study, fewer than with clozapine (6 patients) or olanzapine (4) treatment, although more than with haloperidol (1).

The second study provided a more detailed assessment of the effects of risperidone on glucose regulation and insulin resistance in patients with schizophrenia, controlling for the effects of differences in adiposity. This study[62] examined the short-term changes in glucose levels seen in response to an OGTT in non-diabetic, age- and BMI-matched schizophrenia patients receiving first- or second-generation antipsychotics and healthy, untreated controls. Evaluation of glucose regulation in 10 patients treated with risperidone showed significant elevations in glucose levels at fasting and at 45 and 75 minutes after glucose load compared with healthy controls only ($p < 0.005$). No statistically significant differences in fasting or postload glucose were found in comparison to the 17 patients treated with typical antipsychotic therapy. The insulin resistance value calculated for the risperidone group did not differ statistically significantly from that for either the typical antipsychotic or untreated control groups. In a similar study involving chronically treated patients, again matched for adiposity (BMI), postload plasma glucose values were higher with clozapine and olanzapine treatment than with risperidone, while insulin sensitivity was significantly reduced with clozapine and olanzapine compared with risperidone.[54]

A recent study examined insulin sensitivity in healthy volunteers receiving risperidone (n = 14), olanzapine (n = 22) or placebo (n = 19) for 3 weeks.[231] Using two-step, hyperinsulinaemic, euglycaemic clamp methodology, Sowell and colleagues[231] showed no statistically significant changes the insulin sensitivity index from baseline with risperidone at either low or high insulin steady states. Fasting insulin and fasting glucose levels showed small decreases from baseline to endpoint in the risperidone group.

8.2.4 Discussion

Together, the individual case reports, database analyses and studies of glucose levels suggest that risperidone treatment is not associated with a consistent increase in the risk of developing diabetes. However, a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity, with risperidone typically producing limited weight gain.

The relative infrequency of published case reports of diabetes or ketoacidosis with risperidone therapy does not indicate a clear link between risperidone treatment and the development of diabetes. Risperidone has been used extensively since its introduction in 1993 and recently accounted for

about 37% of second-generation antipsychotic prescriptions in the US. So the small number of case reports, compared with olanzapine or clozapine therapy, is not simply a consequence of limited usage.

This view is partially supported by data from the FDA MedWatch system.[71] The number of cases of hyperglycaemia reported with risperidone therapy (138) was lower than with clozapine (384)[69] or olanzapine (289),[70] although the estimated years of patient exposure to therapy (based on US prescription data to February 2002) was greater for risperidone (3111.3) than for clozapine (678.7) or olanzapine (2104.6) treatment.[71] From these findings, the authors suggest there may be differences in the diabetogenic potential between the three agents, with clozapine having the highest potential and risperidone the lowest of the three. The reports of hyperglycaemia with risperidone were, however, more numerous than with haloperidol therapy. Furthermore, over half of cases occurred within 3 months of starting risperidone therapy, and the mean age of onset for new cases of hyperglycaemia was relatively low (34.8 years), suggesting that risperidone therapy may unmask or precipitate hyperglycaemia in some individuals.

Results from eight database analyses comparing risperidone either with typical antipsychotic therapy[157,160,220,224,225] or with no antipsychotic treatment,[159,221,225] showed no statistically significant overall increase in the risk of developing diabetes with risperidone compared with the control group. In contrast, in eight studies, olanzapine therapy was associated with a significant increase in the risk of diabetes. In the three studies that analysed clozapine therapy,[157,159,160] clozapine was associated with a statistically significant increase in the risk of diabetes. Furthermore, in the three database analyses that performed direct comparisons of risperidone and olanzapine therapy, the risk of diabetes was statistically significantly greater with olanzapine than with risperidone.[159,220,222] Not all of the database analyses, however, showed that risperidone treatment is not associated with an increased risk of diabetes. Two studies reported a statistically significant increase in the risk of diabetes with risperidone treatment compared with non-antipsychotic-treated individuals from the same database populations.[163,255] In addition, one of these studies showed a statistically significant increase in diabetes risk in risperidone-treated patients compared with those receiving haloperidol.[163]

When the risk of diabetes was assessed according to patients' age,[157] risperidone therapy – in common with clozapine, olanzapine and quetiapine, the other second-generation antipsychotics analysed – was associated with a statistically significant increase in diabetes risk in patients younger than 40 years. The authors suggest that this finding, taken together with the lack of a significant effect of second-generation antipsychotic therapy on diabetes risk in older patients (>60 years), suggests that second-generation antipsychotics could hasten the onset of diabetes. This result is consistent with the early age of onset of hyperglycaemia associated with clozapine, risperidone and olanzapine therapy observed in the FDA MedWatch reports.[69,70] It is possible that patient age could have influenced the findings reported by Buse et al.[163] Regression analysis showed that age was a statistically significant risk factor for the development of diabetes in patients treated with risperidone, olanzapine or haloperidol and in the general population cohort. The mean age of patients in the risperidone group was 62 years, with 56.2% of patients aged 65 years and older, and 24.6% aged 18–44 years. In comparison, the mean age was 72 years for haloperidol-treated patients (18–44 years 11.9%; ≥65 years 72.8%) and 52 years for the general population cohort (18–44 years 36.5%; ≥65 years 24.2%). To what extent variations in the age distribution in the different treatment groups may have affected the results is unclear.

Findings from studies of glucose levels in patients receiving risperidone therapy are largely consistent with the results of the database analyses and case study reports. Minimal increases in fasting glucose levels were observed with risperidone therapy compared with pretreatment values in two chart reviews[146,216] and one controlled study.[164] This is in contrast to significant changes observed

with olanzapine and clozapine therapy. In studies that were designed to assess drug effects on glucose metabolism that might occur independent of changes in adiposity, oral and intravenous glucose tolerance tests have been used to examine the response of risperidone-treated patients to a glucose load. Using a frequently sampled modified OGTT, Newcomer et al.[62] compared glucose regulation in non-diabetic patients with schizophrenia treated with first- or second-generation (clozapine, olanzapine or risperidone) antipsychotics and untreated healthy volunteers. Patient groups were well matched for age and BMI, with groups also balanced for sex and ethnicity. Statistically significant elevations in plasma glucose levels were observed in the risperidone group (n = 10) at fasting and at some but not all timepoints after the glucose load, compared with untreated healthy volunteers (n = 31) only, with no statistically significant differences in plasma glucose at any timepoint in comparison to patients treated with typical antipsychotics (n = 17). Insulin resistance, calculated from FPG and insulin levels, was not increased with risperidone treatment as compared with typical antipsychotic treatment or no treatment in healthy controls. Related findings were reported by Henderson and colleagues at the NCDEU 2000 meeting[72] (reviewed by Haupt and Newcomer[54]) in a study using frequently sampled intravenous glucose tolerance tests. Chronically treated non-diabetic patients, matched for adiposity, age, sex and ethnicity, showed higher postload plasma glucose values with clozapine and olanzapine treatment as compared with risperidone. Insulin sensitivity was significantly reduced in clozapine- and olanzapine-treated patients compared with those treated with risperidone.

Discussed above in the olanzapine section, a clamp study in healthy volunteers showed an increased insulin response and decreased insulin sensitivity with both olanzapine and risperidone treatment compared with placebo.[230] The change in insulin response correlated with a change in BMI. After adjusting for the effects of weight gain seen with active treatment using regression analyses, no statistically significant change in insulin response or sensitivity was detected with olanzapine or risperidone therapy, suggesting that the adverse effects were largely related to changes in adiposity. A more recent study examining insulin sensitivity in healthy volunteers receiving olanzapine (n = 22), risperidone (n = 14) or placebo (n = 19) for 3 weeks showed no statistically significant changes in the insulin sensitivity index from baseline with olanzapine or risperidone therapy.[231] However, fasting insulin and fasting glucose levels both increased statistically significantly from baseline to endpoint in the olanzapine group, while showing small decreases in the risperidone group. Finally, Berry and Mahmoud[218] reported significant improvements in insulin resistance and beta-cell function in schizophrenic patients following a change from olanzapine to risperidone treatment.

8.3 Lipid Levels

The effect of risperidone therapy on lipid levels has been assessed using a combination of case reports, retrospective chart reviews, database analyses and controlled clinical studies, including prospective clinical trials.

8.3.1 Case Studies and Chart Reviews

Changes in lipid levels have been examined in three retrospective reviews of patient records. Meyer[216] evaluated the effects of 12 months of risperidone or olanzapine treatment on lipid parameters from a retrospective review of patient records. In the risperidone group, fasting total cholesterol levels showed small, but not significant, increases from baseline for all 47 patients (7.2 mg/dL) and for those younger than 60 years (n = 39; 7.2 mg/dL). Fasting triglyceride levels increased significantly from baseline for all patients (29.7 mg/dL; p = 0.028) and for the non-elderly (<60 years) subgroup (31.7 mg/dL; p = 0.047). These changes were, however, significantly smaller than the increases in fasting total cholesterol and triglycerides seen with olanzapine therapy in both populations (p < 0.05). Over the 12-month study period, risperidone-treated patients experienced a

significant increase in mean bodyweight from baseline (all 10.7lb [4.8kg]; <60 years 11.9lb [5.3kg]; $p \leq 0.001$). Analysis of the non-elderly subgroup showed no statistically significant correlation between weight gain and changes in triglyceride or cholesterol levels.

In another retrospective review of patient records,[146] which also assessed glucose levels, changes in fasting triglyceride and cholesterol levels were analysed before and after initiating antipsychotic therapy. Significant decreases in mean LDL-cholesterol levels (15%; $p = 0.006$) were observed from baseline with risperidone therapy, similar to the changes observed with clozapine and olanzapine treatment. Small (but not statistically significant) beneficial changes in mean total (–4%) and HDL-cholesterol (+5%) levels from baseline were also observed, while mean triglyceride levels showed a 19% increase from baseline.

Risperidone treatment showed no significant effects on fasting triglyceride or cholesterol levels in a retrospective analysis of 22 children or adolescents (mean age 12.8 years) with behavioural, affective or psychotic disorders.[256] In this chart review, mean fasting triglyceride levels increased by 8.6 mg/dL from pretreatment levels, while fasting total cholesterol levels decreased slightly (1.0 mg/dL). The mean treatment duration was 4.9 months. Bodyweight increased significantly during the study (7.0kg; $p < 0.001$), as did z-score weight (a measure of weight standardised to the normal population) and BMI. There was a statistically significant association between weight gain and triglyceride levels; almost 25% of the variance in triglyceride levels could be explained by weight gain (ANCOVA).

A series of four case studies involving patients with psychotic disorders[173] report that in each of these cases, triglyceride levels decreased following the switch from clozapine to risperidone therapy. The decreases in triglyceride levels ranged from 44 to 145 mg/dL, with final values between 60 and 164 mg/dL (i.e. generally within normal limits). When two of the patients switched back to clozapine treatment, this switch was accompanied by an increase in their serum triglyceride levels.

A cross-sectional analysis of fasting lipid levels in patients with schizophrenia or related disorders treated continuously with risperidone (n = 65), olanzapine (n = 67) or typical antipsychotic therapy (n = 52) for at least 1 year[238] reported no statistically significant differences in mean total, LDL- or HDL-cholesterol levels between the treatments. Mean fasting triglyceride levels were statistically significantly higher in the olanzapine group than in the risperidone group. Patients were matched for sex, BMI, and duration and severity of illness, although only patients with normal FBG levels (<110 mg/dL) were included in the analysis.

8.3.2 Retrospective Database Analyses

The risk of hyperlipidaemia with risperidone therapy was evaluated using data from a large UK-based healthcare database (the UK GPRD).[223] A total of 18 309 patients with schizophrenia were identified using data from June 1997 to September 2000. Among these, 1268 patients were diagnosed or treated for hyperlipidaemia during a mean follow-up of 4.07 years. Antipsychotic use was defined as receipt of antipsychotic treatment in the 3 months before diagnosis of hyperlipidaemia. Of the cases of hyperlipidaemia identified, 12 patients had received risperidone therapy, 16 had received olanzapine, 807 had received typical antipsychotic therapy and 413 had not been exposed to antipsychotic medication.

For the case control analysis, the hyperlipidaemia cases were matched to 7598 controls who had schizophrenia but no hyperlipidaemia. Logistic regression analysis, adjusting for age, sex, and other medications and disease conditions affecting lipid levels, showed no statistically significant increase in the risk of hyperlipidaemia with risperidone therapy compared with no antipsychotic medication (OR 1.12; 95% CI 0.60, 2.11) or compared with typical antipsychotic treatment (OR 0.81; 95% CI 0.44, 1.52). In contrast, there was a statistically significant increase in the risk of hyperlipidaemia with olanzapine therapy compared with no antipsychotic therapy (OR 4.65; $p < 0.001$)

and typical antipsychotic treatment (OR 3.36; $p < 0.001$).

8.3.3 Controlled Clinical Studies

Analysis of fasting lipid levels in a prospective, randomised 14-week study involving inpatients with either schizophrenia or schizoaffective disorder[164] showed minimal mean changes in total cholesterol levels from baseline in patients treated with risperidone (week 8 +4.2 mg/dL; week 14 +9.2 mg/dL). In contrast, statistically significant increases in total cholesterol levels were observed for those receiving either olanzapine or clozapine therapy.

A 6-week randomised study of fasting triglyceride and leptin levels in patients with schizophrenia also showed no statistically significant changes in triglyceride levels with risperidone therapy.[175] Patients were evaluated at baseline and after 6 weeks of treatment with risperidone (n = 13), clozapine (n = 13), olanzapine (n = 13) or quetiapine (n = 14) therapy. Eleven patients with psychiatric disorders and not receiving antipsychotic medication were included as a control group. Fasting triglyceride levels (+3.87 mg/dL), bodyweight (+0.54kg) and BMI (–0.76 kg/m^2) all showed minimal change from baseline with risperidone treatment at week 6. These changes were similar to those in the control group and contrasted with the statistically significant increases in all three parameters seen with clozapine and olanzapine therapy.

Changes in cholesterol and triglyceride levels were also reported in a randomised, double-blind study of risperidone and olanzapine treatment in 377 patients with schizophrenia or schizoaffective disorder.[240] The ratio of beneficial change to adverse change was presented for each parameter, where the change from an above-normal value at baseline to a normal value at week 8 was considered 'beneficial', whereas the change from a normal baseline value to an above-normal value at week 8 was 'adverse'. Overall, 21.9% and 20.1% of patients experienced a change (either beneficial or adverse) in cholesterol and triglyceride levels, respectively. Changes in triglycerides tended to be beneficial with risperidone treatment (ratio 2.57) but adverse with olanzapine therapy (ratio 0.45). Based on this calculation, a beneficial change in triglyceride levels was significantly more likely with risperidone therapy than with olanzapine (risk ratio 5.71; $p = 0.003$). Similarly, changes in cholesterol levels tended to be beneficial with risperidone (ratio 1.64) but not with olanzapine (ratio 0.35), also suggesting a significantly greater likelihood of improvements in cholesterol levels with risperidone than with olanzapine (risk ratio 4.70; $p = 0.005$).

Examination of lipid levels in an 8-week study of risperidone and olanzapine therapy in 50 inpatients with schizophrenia, schizophreniform or schizoaffective disorder also showed no statistically significant changes in triglyceride and total cholesterol levels with risperidone treatment.[241] In contrast, patients receiving olanzapine showed significant increases in triglyceride levels from baseline ($p < 0.001$), although no statistically significant changes in total cholesterol levels were observed.

8.3.4 Discussion

Chart reviews, case reports, database analyses and clinical trials all suggest that risperidone treatment has a limited and not consistently observed adverse effect on plasma lipid levels. In general, evidence does not suggest an adverse effect of risperidone treatment on plasma cholesterol levels, with less consistent but still largely negative results regarding plasma triglyceride levels. In general, a possible increase in risk for dyslipidaemia would be predicted to occur in association with any treatment that produces increases in weight and adiposity, with risperidone typically producing limited weight gain.

Case control analysis of healthcare data from the UK GPRD database showed no increase in the risk of hyperlipidaemia with risperidone therapy in patients with schizophrenia.[225] The use of risperidone did not statistically significantly increase the OR for hyperlipidaemia compared with no antipsy-

chotic therapy or with typical antipsychotic treatment.

A low risk for hyperlipidaemia is supported by studies that measured lipid levels. Minimal changes in total cholesterol levels were found in retrospective analyses of patient records[146,216,256] and clinical study reports.[164,241] One study analysis[240] showed that beneficial changes in cholesterol levels with risperidone therapy outweighed adverse changes. In addition, one study[146] reported beneficial changes in fasting LDL- and HDL-cholesterol levels with risperidone therapy, although only the change in LDL-cholesterol was significant.

Increases in triglyceride levels were reported in three studies, suggesting that risperidone may be linked to adverse changes in triglyceride levels, although these changes were statistically significant in only one study.[216] Furthermore, Atmaca and colleagues[175] reported minimal changes in triglyceride levels, while Conley and Mahmoud[240] reported that changes in triglyceride levels tended to be beneficial. In addition, Ghaeli and Dufresne[171] suggest that their four case studies showing resolution of elevated triglyceride levels following a switch to risperidone therapy provide evidence that risperidone treatment is not associated with increases in triglyceride levels. In general, the direction of effects on lipids in prospective studies may be dependent on the prior treatment condition, with beneficial effects predicted in individuals who are switched from medications associated with greater weight gain or adverse lipid changes.

8.4 Conclusion

Risperidone therapy is associated with modest weight gain during short- and long-term treatment. Risperidone therapy is not associated with a consistent increase in the risk of developing diabetes or dyslipidaemia. However, a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity. Most database analyses showed no statistically significant increase in diabetes risk with risperidone therapy compared with typical antipsychotic treatments or with no antipsychotic therapy. This is supported by the limited number of case reports of diabetes or ketoacidosis associated with risperidone treatment. In controlled studies, minimal changes in plasma glucose levels are reported during risperidone therapy in comparison to typical antipsychotics, with either no differences or modestly increased plasma glucose observed in comparison to untreated healthy controls. Changes in lipid levels also tend to be minimal, although both increases and decreases in fasting triglyceride levels have been observed in a small number of studies.

9. Quetiapine

Quetiapine was introduced in 1998 and is currently among the top three most prescribed second-generation antipsychotics in the US. Its relatively recent introduction does, however, mean that studies and analyses investigating the potential metabolic effects of quetiapine are still limited. Reports examining the possible association between quetiapine treatment and the development of diabetes are currently limited to FDA MedWatch Drug Surveillance information, four analyses of healthcare databases and a few case reports. In addition, changes in glucose levels have been examined in two chart reviews and a naturalistic study involving a small number of quetiapine-treated patients, while the effects on lipid levels are reported from three chart reviews and a 6-week randomised study.

9.1 Bodyweight

Short-term treatment with quetiapine is associated with modest weight gain, which does not appear to be dose related across the antipsychotic dose range. Data from a number of controlled clinical trials show mean increases in bodyweight somewhat above 2kg after 6 weeks of therapy,[257] although one 6-week study reported a mean increase of 5.5kg with quetiapine.[258] In a 6-week study comparing five fixed doses of quetiapine (ranging from 75 to 750 mg/day) with placebo and haloperidol, mean increases in bodyweight ranged

from 0.9 to 2.9kg with quetiapine compared with an increase of 0.3kg with haloperidol and decrease of 0.8kg with placebo.[259] Similarly, mean increases of 1.8 and 1.9kg were reported with quetiapine therapy in 6-week comparison studies involving chlorpromazine[260] and haloperidol,[261] respectively.

Additional increases in bodyweight have been observed with long-term quetiapine treatment. Although one long-term open-label extension study involving 427 patients with schizophrenia reported a mean increase of about 1kg with quetiapine therapy,[262] a larger analysis of weight gain data involving 2216 clinical trial patients showed a mean increase of 2.77kg after 9–12 months of therapy.[74] Analysis of these patients by quetiapine dose revealed mean weight changes ranging from 1.38 to 3.83kg after 9–12 months of treatment, although the changes were not dose related and generally in the 2 to 3.8kg range across the antipsychotic dose spectrum.[74,245] Notably, the most recent analyses of long-term weight gain during quetiapine treatment, restricted to patients with schizophrenia, indicate that among 297 patients with available data after 52 weeks (±30 days) of treatment, mean weight increase was 3.59kg (95% CI: 2.57–4.61).[263] Among 143 patients with available data after 104 weeks of quetiapine treatment (±45 days), mean weight gain was 5.59kg (95% CI: 3.98–7.20).

Package insert data for quetiapine report that almost one-quarter of patients (23%) gained at least 7% of bodyweight after 3–6 weeks of quetiapine treatment, compared with 6% of those receiving placebo, suggesting three to four times the placebo rate. Findings from individual clinical trials are consistent with these data. A review of short-term quetiapine studies[257] reported significant weight gain (≥7% increase) in 11–25% quetiapine-treated patients compared with 4–5% of patients receiving placebo. Small and colleagues[264] observed ≥7% increases in weight for 25% and 16% of patients receiving high-dose (mean 360 mg/day) and low-dose (mean 209 mg/day) quetiapine, respectively, compared with 5% receiving placebo. Similarly, in the multiple fixed-dose study, 11–17% of quetiapine-treated patients experienced clinically significant weight gain (≥7% increase) compared with 4% in the haloperidol group and 6% receiving placebo.[259]

9.2 Diabetes and Hyperglycaemia

9.2.1 Case Reports and Chart Reviews

Although published after the cut-off date for this review (1 January 2004), the report of data from the FDA MedWatch Drug Surveillance System has been included here for comparability and because it contains data collected before the cut-off date. Data from the FDA MedWatch Drug Surveillance System (January 1997 to end July 2002) and published reports (Medline, January 1997 to end July 2002) identified 46 cases of quetiapine-associated diabetes or hyperglycaemia.[265] Of these reports, 34 cases (74%) involved newly diagnosed hyperglycaemia and eight cases (17%) described exacerbation of pre-existing diabetes, while in the remaining four cases this distinction was unclear. Of the 34 patients with newly diagnosed hyperglycaemia, 23 met diagnostic criteria for diabetes based on blood glucose (fasting ≥126 mg/dL; postload ≥200 mg/dL) or HbA_{1c} levels and five were receiving antidiabetic medication. In addition, there were a further nine reports of acidosis with quetiapine treatment that were not associated with hyperglycaemia.

The mean age of onset for patients with newly diagnosed diabetes (31.2 ± 14.8 years; 30 patients with available data) tended to be younger than for patients with exacerbation of existing diabetes (mean age 43.5 ± 16.4 years; n = 8). The time from initiation of quetiapine therapy to diagnosis of hyperglycaemia ranged from 1 day to 21 months in the 36 patients with available data, with 27 patients (75%) experiencing onset of hyperglycaemia within 6 months of starting quetiapine treatment (figure 5). Among patients with newly diagnosed hyperglycaemia, onset occurred within 6 months of starting therapy in 11 of the 27 patients (41%). Time to onset tended to be shorter for patients experiencing exacerbation of existing disease, with six of seven patients (86%) experiencing exacerbation within 3

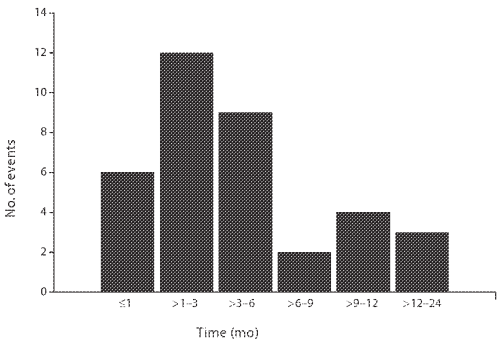

Fig. 5. Time to onset of hyperglycaemia with quetiapine.[265]

months of starting therapy. Quetiapine therapy was reduced in one patient and discontinued in 15 patients. The limited outcomes data available reported improved glycaemic control for seven of these patients. One patient reported a recurrence of hyperglycaemia and ketosis within 2 weeks of a rechallenge.

The severity of hyperglycaemia associated with quetiapine therapy ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. Nineteen patients experienced blood glucose levels of ≥500 mg/dL, and there were 21 reports of diabetic acidosis or ketosis. There were 11 deaths among quetiapine-treated patients; seven occurred among patients with newly diagnosed hyperglycaemia and one occurred following a rechallenge in a patient with pre-existing disease. Seven of the patients who died had acidosis or ketosis.

In an addendum to the paper, the authors report on a further 23 cases of hyperglycaemia (newly diagnosed n = 15; exacerbation n = 6; not clear n = 2) identified by extending their search to the end of November 2003. Again the incidence of diabetic ketoacidosis was high, with eight reported cases of acidosis or ketosis associated with hyperglycaemia (34.8%). There were also two reports of pancreatitis among the cases. In all, there were three deaths among the 23 patients.

A few case reports of diabetes, diabetic ketoacidosis or hyperglycaemia associated with quetiapine treatment have appeared in the literature (table XI). In two published reports,[267,268] quetiapine therapy was associated with development of new-onset diabetes mellitus. In a third report,[266] addition of quetiapine to existing risperidone therapy rapidly led to highly elevated blood glucose levels (300–400 mg/dL), which remained elevated despite antidiabetic treatment. Blood glucose levels normalised with gradual discontinuation of quetiapine therapy and did not increase with subsequent initiation of ziprasidone therapy. In the other report,[269] hyperglycaemia and hypertriglyceridaemia were observed in a patient receiving quetiapine therapy. In addition, Wilson et al.[254] report a patient developing diabetic ketoacidosis with quetiapine treatment, identified from a retrospective chart review of patients receiving second-generation antipsychotic treatment and evaluated or treated for diabetes. The patient experienced acute diabetic ketoacidosis 2 months after switching from risperidone to quetiapine.

The prevalence of diabetes has also been examined in a retrospective chart review of 208 patients with psychotic illness treated with first- or second-generation antipsychotics (clozapine, olanzapine, risperidone or quetiapine).[156] This cross-sectional analysis showed no statistically significant difference in the prevalence of diabetes between the different treatments. Two (11.8%) of the 17 patients treated with quetiapine had diabetes; this compares with an overall prevalence of 16.8%. The mean FPG value in the quetiapine

Table XI. Case reports of abnormal glucose or lipid levels with quetiapine

Reference	Case report details
Sneed & Gonzalez[266]	Rapid onset of severe hyperglycaemia following addition of quetiapine to existing risperidone therapy, which resolved on withdrawal of quetiapine
Procyshyn et al.[267]	New-onset diabetes mellitus associated with quetiapine
Sobel et al.[268]	New-onset diabetes mellitus associated with initiation of quetiapine treatment
Domon & Cargile[269]	Quetiapine-associated hyperglycaemia and hypertriglyceridaemia

group was 109.1 mg/dL, similar to mean values for the other treatment groups (97.3–113.2 mg/dL).

The effects of quetiapine treatment on blood glucose levels are reported in two other studies. In a retrospective chart review of 215 patients treated with either first- or second-generation antipsychotic therapy,[146] data available for the 13 quetiapine-treated patients showed a small change in FBG levels from a mean baseline level of 106.6 mg/dL to 115.7 mg/dL, an increase of 9%. Mean maximum glucose levels remained virtually unchanged (pretreatment 133.4 mg/dL; treatment 133.3 mg/dL). The mean duration of quetiapine treatment was 7.3 months.

A naturalistic study involving 75 patients with schizophrenia or related psychotic disorders receiving first- or second-generation antipsychotic therapy[147] also examined changes in glucose levels and insulin resistance. Data for eight quetiapine-treated individuals showed no significant changes in FBG levels from pretreatment values. However, significant increases were observed in blood glucose levels taken 2 hours after a standard OGTT. No statistically significant changes in peripheral insulin resistance were seen with quetiapine treatment.

9.2.2 Retrospective Database Analyses

The association between quetiapine therapy and diabetes has been examined in four analyses of data from healthcare and prescription claims databases (table XII).

The prevalence of diabetes with quetiapine therapy has been examined in a large database analysis[157] involving more than 38 000 patients treated with first- (41.4%) or second-generation (58.6%) antipsychotics. During the 4-month analysis period, 955 patients received quetiapine therapy. Regression analysis, controlling for demographic, diagnostic and treatment factors, showed that quetiapine was associated with a significant increase in risk of diagnosis of diabetes compared with typical antipsychotic therapy (OR 1.31; 95% CI 1.11, 1.55; $p < 0.002$). The risk of diabetes compared with typical antipsychotic therapy was also statistically significantly increased for all second-generation antipsychotics analysed together (OR 1.09) and for clozapine (OR 1.25) and olanzapine (OR 1.11) treatments, but not risperidone (OR 1.05). When patient data were stratified according to age, the risk of diabetes with quetiapine treatment increased significantly for patients younger than 40 years (OR 1.82; $p < 0.04$), in common with all the other second-generation agents analysed, and for those aged 40–49 years (OR 1.86; $p = 0.0001$) [table XII].

The risk of developing diabetes with quetiapine therapy has also been examined in a matched case control study using data from the Californian Medicaid system obtained during 1997–2000.[160]

Table XII. Summary of database analyses investigating association between quetiapine therapy and diabetes

Reference	Risk of diabetes		
Sernyak et al.[157]	**Odds ratio vs typical antipsychotic**		
	All patients	1.31 (95% CI 1.11, 1.55)	p < 0.002
	<40y	1.82 (95% CI 1.05, 3.15)	p < 0.04
	40–49y	1.86 (95% CI 1.43, 2.41)	p = 0.0001
	50–59y	1.19 (95% CI 0.89, 1.59)	NS
	60–69y	0.90 (95% CI 0.55, 1.46)	NS
	≥70y	0.62 (95% CI 0.30, 1.28)	NS
Lambert et al.[160]	**Odds ratio vs typical antipsychotic**		
	Overall	1.45 (95% CI 1.10, 1.90)	p = 0.006
Buse et al.[163]	**Hazard ratio vs no antipsychotic**		
	Overall	1.7 (95% CI 1.2, 2.4)	p = 0.002
	Hazard ratio vs haloperidol		
	Overall	0.67 (95% CI 0.46, 0.97)	p = 0.033
Gianfrancesco et al.[221]	**Odds ratio vs no antipsychotic**		
	1mo	0.998	NS
	12mo	0.976 (95% CI 0.422, 2.271)	

Overall, the database analysis identified 3102 cases of diabetes among patients with schizophrenia, aged 18 years or older, who were receiving continuous antipsychotic monotherapy during the 12 weeks prior to the diagnosis of diabetes. These cases were matched to 8271 controls – patients with schizophrenia, matched for sex and age (±5 years), not diagnosed with diabetes. Among quetiapine-treated patients, the 94 cases of diabetes were matched with 201 non-diabetic controls. Logistic regression analysis, controlling for ethnicity and other diabetes-inducing medication, showed that the risk of developing type 2 diabetes was significantly higher with quetiapine therapy than with typical antipsychotic treatment (OR 1.45; 95% CI 1.10, 1.90; p = 0.006). The risk of diabetes, compared with typical antipsychotic treatment, was also statistically significantly greater with clozapine (OR 1.43) and olanzapine (OR 1.30) therapy, but not risperidone (OR 1.10).

In contrast to these two analyses, a recent publication by Buse and colleagues[163] reported a reduced risk of diabetes with quetiapine therapy compared with haloperidol treatment. The study, using prescription claims data from the AdvancePCS database, analysed the risk of developing diabetes in patients receiving antipsychotic monotherapy (first- or second-generation). Patients aged 18 years or older, treated with a single first- or second-generation antipsychotic, and without pre-existing diabetes were included in the analysis. There were 40 cases of new-onset diabetes, identified by a prescription claim for antidiabetic medication, among the 4196 patients receiving quetiapine. Cox proportional hazard regression analysis, adjusting for age, sex and treatment duration, showed that, compared with the general population cohort (individuals with no prescription claims for antidiabetic medication or antipsychotics), patients treated with quetiapine had a significantly increased risk of diabetes (HR 1.7; 95% CI 1.2, 2.4; p = 0.002). This was consistent with the increased risk of diabetes seen with other first- and second-generation antipsychotics analysed. However, quetiapine treatment significantly reduced the risk of diabetes compared with haloperidol therapy (HR 0.67; 95% CI 0.46, 0.97; p = 0.033).

Analysis of data from a Blue Cross/Blue Shield claims database showed no statistically significant increase in the risk of diabetes with quetiapine compared with no antipsychotic treatment.[221] Overall, 3 of the 682 patients treated with quetiapine developed diabetes, based on prescription claims for antidiabetic medication. The OR for developing diabetes with quetiapine therapy (0.998) did not differ statistically significantly from that for untreated individuals. Similar findings were observed for typical antipsychotics (OR 1.004) and risperidone (OR 0.966), whereas the risk of diabetes increased significantly with olanzapine treatment (OR 1.030; p = 0.0247).

9.3 Lipid Levels

9.3.1 Chart Reviews

Cases of elevated lipid levels have been reported with quetiapine therapy. Meyer[235] reported 14 cases of severe hypertriglyceridaemia (fasting triglycerides >600 mg/dL) in patients receiving olanzapine or quetiapine treatment, identified from a retrospective review of patient records. This analysis excluded patients previously treated for hypercholesterolaemia or hypertriglyceridaemia or with prior history of severe hypertriglyceridaemia. Analysis of the two patients receiving quetiapine showed peak triglyceride levels of 609 and 1932 mg/dL, occurring 1 and 5 months, respectively, after the initiation of quetiapine, increases of 448 and 1546 mg/dL from baseline. In addition, Domon and Cargile[269] report hypertriglyceridaemia and hyperglycaemia associated with quetiapine therapy in one patient.

Wirshing and co-workers[146] report changes in fasting lipid levels in their retrospective chart review of patients receiving antipsychotic treatment. Clinically beneficial changes in triglyceride levels (a 25% decrease from baseline) and LDL-cholesterol (a 13% decrease) were observed with quetiapine, although only the decrease in LDL-

cholesterol represented a statistically significant change from baseline ($p = 0.04$). Mean total cholesterol (–4%) and HDL-cholesterol (+2%) levels showed minimal changes with quetiapine treatment.

In contrast, Kurt and Oral[147] reported increases in fasting total cholesterol, LDL-cholesterol and triglyceride levels from baseline with quetiapine treatment, although these changes were not statistically significant. The decreases in fasting HDL-cholesterol levels seen with quetiapine did, however, reach statistical significance ($p < 0.05$). An 8-week open-label study of quetiapine treatment in 15 adolescents aged 13–17 (mean 15.1) years with psychotic disorders reported minimal changes in total cholesterol levels from baseline.[270]

9.3.2 Controlled Clinical Trials

A 6-week randomised study of second-generation antipsychotics in 56 patients with schizophrenia[175] showed significant changes in fasting triglyceride levels from baseline with quetiapine therapy. Quetiapine-treated patients ($n = 14$) showed a significant increase in triglyceride levels from baseline at week 6 (11.64 mg/dL; $p < 0.05$), although the increase was less than with clozapine (36.28 mg/dL) or olanzapine (31.23 mg/dL) therapy. Bodyweight also showed a significant mean increase from baseline with quetiapine therapy (+4.41kg; $p < 0.05$), a mean increase that is approximately twice that observed in larger datasets described above. Increases in total cholesterol (8.0%), LDL-cholesterol (12.2%) and VLDL-cholesterol (1.7%) were also reported from week 1 to week 6 of quetiapine therapy ($n = 12$) in a small, single-blind, randomised study involving female patients with schizophrenia.[242] These changes were not statistically significant and were smaller than those reported with olanzapine therapy (total cholesterol 17.3%; LDL 31.4%; VLDL 8.1%; $n = 10$). Pooled laboratory data from the 3- to 6-week placebo-controlled quetiapine clinical trials (quetiapine package insert) report a 17% increase in triglyceride levels and 11% increase in total cholesterol with quetiapine therapy.

9.4 Discussion

The limited amount of data evaluating the metabolic effects of quetiapine therapy and the contradictory nature of some results preclude definitive assessment of the metabolic risks associated with its use. Findings to date suggest that quetiapine therapy is not associated with a consistent increase in the risk of developing diabetes or dyslipidaemia. However, a possible increase in metabolic risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity, with quetiapine typically producing modest weight gain. While the modest weight gain risk clearly appears similar to that with risperidone, the limited availability of metabolic data precludes the same level of confidence that this modest weight gain risk profile (or other drug effects) will similarly yield a low risk of diabetes or dyslipidaemia.

Support for an association between quetiapine treatment and diabetes comes from the FDA MedWatch data and the case reports of new-onset diabetes or diabetic ketoacidosis with quetiapine therapy. In common with the FDA MedWatch reports for clozapine,[69] olanzapine[70] and risperidone,[71] a large proportion (75%) of the cases of hyperglycaemia identified with quetiapine occurred within 6 months of the start of treatment, and the mean age of cases of new-onset hyperglycaemia was relatively low (31.2 years), suggesting that in some individuals, quetiapine therapy may unmask or precipitate hyperglycaemia. The FDA MedWatch System identified a relatively large number of cases of hyperglycaemia with quetiapine therapy (69 cases, 1997 to end November 2003) compared with risperidone (131 cases, 1993 to February 2002) considering the relative usage of the two agents, suggesting that quetiapine may have a higher diabetogenic potential than risperidone, despite similarities in their weight gain potential.

Two database analyses[157,160] showed a statistically significant increase in the risk of diabetes with quetiapine treatment compared with typical antipsychotic therapy, while a third analysis[163]

showed that patients receiving quetiapine were at greater risk of developing diabetes than the general population. However, in contrast to these two studies, the study by Buse et al.[163] showed that quetiapine-treated patients had a statistically significantly *lower* risk of diabetes than haloperidol-treated individuals, and Gianfrancesco et al.[221] reported no increased risk of diabetes with quetiapine treatment compared with no antipsychotic therapy.

All four studies involved analysis of sizeable healthcare databases, suggesting their findings were not skewed as a result of small sample sizes. The study by Sernyak et al.[157] analysed a total of 955 quetiapine-treated patients, similar to the numbers in the clozapine group (n = 1207), while Gianfrancesco and colleagues[221] analysed 682 quetiapine-treated individuals. Similarly, Lambert and co-workers[160] identified 94 cases of new-onset diabetes with quetiapine treatment in their matched case control study, while prescription claims data analysed by Buse et al.[163] revealed 40 cases of new-onset diabetes among more than 4000 quetiapine-treated individuals.

The study by Sernyak and co-workers[157] suggests that age could be an important factor in the risk of developing diabetes. When the data were evaluated according to patient age, quetiapine treatment statistically significantly increased the risk of diabetes compared with typical antipsychotics in patients younger than 40 years and those aged 40–49 years, but not for the older age groups.[157] This is consistent with results for other agents discussed above and with the low mean age of onset for cases of newly diagnosed hyperglycaemia during quetiapine treatment identified by the FDA MedWatch system.[265] In the study by Buse et al.,[163] the mean age of patients receiving quetiapine was 55 years, with 36.0% aged 65 years or older. Patients in the haloperidol group were older; the mean age was 72 years, with 72.8% aged 65 years or older. In addition, the authors noted that the low mean doses and short treatment durations observed in the study (79.9 mg/day and 89 days for quetiapine) may have influenced the risk of developing diabetes. In general, the use of surrogate markers for the presence of diabetes in these database analyses may affect their ability to reliably detect differences between medications or across groups. This may explain some of the variability observed in these studies and suggests that the findings from these studies should be interpreted with caution.

Reports of changes in lipid levels with quetiapine therapy are also limited and somewhat contradictory. The decreases in triglyceride levels reported in the small study by Wirshing et al.[146] contrast with the increases in triglycerides reported for pooled data from the short-term clinical trials and data from a 6-week randomised study[175] and from the case report of hypertriglyceridaemia observed in a patient receiving quetiapine therapy. As discussed by Wirshing, these differences could reflect the recent treatment of some patients with olanzapine (which may have led to elevated baseline triglyceride levels) and/or the small number of patients (n = 13) involved.

In a recent review, Melkersson and Dahl[271] conclude that quetiapine therapy is associated with a moderately high risk of adverse effects on glucose-insulin homeostasis and lipid levels, while the risk with risperidone is described as 'rather low'. However, as the authors point out, the data for quetiapine are limited and come largely from retrospective studies and case reports. The only reliably established treatment-induced risk may be related to treatment-induced weight gain, and only modest weight gain is well described during quetiapine therapy. Conclusions that quetiapine is associated with higher risk than would be predicted from the modest weight gain profile seem to rely on rather limited information, suggesting that more data, particularly from prospective randomised trials, are needed before drawing firm conclusions about the risk of metabolic adverse events associated with quetiapine therapy.

9.5 Conclusion

Quetiapine therapy is associated with moderate weight gain during short- and long-term treatment, somewhat greater than that observed with

risperidone. Quetiapine therapy is not associated with a consistent increase in the risk of developing diabetes or dyslipidaemia. Limited data suggest a possible modest increase in the risk of diabetes and hypertriglyceridaemia with quetiapine treatment. A possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity.

10. Zotepine

Zotepine has been used in Japan since the early 1980s and in Germany since 1990. However, it is not widely used and is currently licensed only in a number of European countries, including Austria and the UK, and in Japan; it is not available in the US. Published data examining the possible association between zotepine therapy and the development of diabetes, hyperglycaemia and/or dyslipidaemia are very limited.

10.1 Bodyweight

The limited number of studies reporting changes in bodyweight with zotepine therapy suggest that it is associated with moderate to substantial increases in bodyweight.[257,272] An 8-week randomised, double-blind schizophrenia study reported a mean increase of 2.32kg with zotepine compared with a mean decrease of 0.81kg with haloperidol therapy ($p < 0.001$). In a retrospective chart review, patients receiving zotepine treatment experienced a mean weight increase of 4.3kg (mean duration 31.9 days), with a maximum reported increase of 17kg.[273] The mean weight gain with zotepine was significantly greater than with typical antipsychotics (0.0–0.5kg) and larger than seen with clozapine (3.1kg). Moderate weight gain has also been reported with zotepine over longer treatment periods. A 1-year naturalistic study of zotepine therapy in patients with schizophrenia reported a mean weight gain of 4.3kg from baseline over the study period, with most weight gain occurring in the first 12 weeks of treatment.[274] Weight gain was the most frequently reported adverse event during the study (27.7% of patients). A review of zotepine studies published largely in the German and Japanese literature reported a mean bodyweight gain of 3.6kg and that 28% of zotepine-treated patients experienced 'bodyweight gain'.[275]

10.2 Diabetes and Hyperglycaemia

There are currently no published reports of the effect of zotepine therapy on blood glucose levels.

10.3 Lipid Levels

Published reports of changes in lipid levels with zotepine therapy are currently limited to a single case report.[276] A female patient with schizophreniform disorder developed elevated serum triglyceride levels (up to 1247 mg/dL) soon after the initiation of zotepine therapy, which normalised after a switch to typical antipsychotic therapy (table XIII).

10.4 Discussion

The almost complete lack of available data in this area makes it difficult to draw conclusions about the risk of diabetes, hyperglycaemia or dyslipidaemia associated with zotepine therapy. Published studies have demonstrated that zotepine shows moderate to substantial weight gain potential, greater than that observed with quetiapine therapy and approaching what has been reported for clozapine and olanzapine. Treatments associated with weight gain and increased adiposity are predicted to increase the risk of adverse metabolic effects, so on this basis, zotepine therapy could be hypothesised to be associated with an increased risk of glucose or lipid dysregulation, but hypothesis-testing studies would be required to test this proposal.

Table XIII. Case report of hyperlipidaemia with zotepine

Reference	Case report details
Wetterling[276]	Hypertriglyceridaemia with zotepine, which resolved after switch to typical antipsychotic therapy

10.5 Conclusion

Zotepine is associated with moderate to substantial weight gain during both short- and long-term therapy. Although the published metabolic data are too limited to draw any conclusions about the risk of glucose or lipid dysregulation with zotepine therapy, a possible increase in risk would be predicted to occur with any treatment that produces increases in weight and adiposity.

11. Amisulpride

Amisulpride has been available in France since 1988, although its launch into other European countries did not start until 1997, and it is not licensed in the US. Although it has been used in France for more than 15 years, limited published data are available examining the possible association between amisulpride therapy and the development of diabetes, hyperglycaemia and/or dyslipidaemia.

11.1 Bodyweight

Amisulpride treatment is associated with relatively low weight gain potential in short-term studies. A pooled analysis of data from 11 short-term, prospective, randomised studies reported an estimated mean weight gain of 0.80kg with amisulpride after 10 weeks of treatment.[275] Mean weight gain from baseline was significantly less for amisulpride-treated patients than for risperidone-treated patients in an 8-week comparison study (0.4 vs 1.4kg; $p = 0.026$).[277]

The low weight gain potential of amisulpride is maintained during long-term treatment. Pooled analysis of three 1-year studies showed a mean weight increase of 1.37kg at endpoint (mean treatment duration 256 days).[75] Among patients who completed 6 months of treatment the mean increase was 1.40kg, while for those completing 1 year of therapy the increase was 2.15kg. This approaches values reported for 1-year weight gain during risperidone and quetiapine treatment. Amisulpride was associated with lower mean weight gain than olanzapine (1.6 vs 3.9kg) in a recent 6-month, randomised comparison study.[278] The incidence of clinically significant weight gain (≥7% increase) was also lower with amisulpride (20.6%) than with olanzapine (35.1%).

11.2 Diabetes and Hyperglycaemia

Published reports of changes in blood glucose levels with amisulpride therapy are limited to preliminary data from a prospective, 16-week study of glucose metabolism in patients with schizophrenia.[165] No elevations in fasting glucose levels or glucose levels following an OGTT were reported among the 12 patients receiving amisulpride treatment, and there were no increases in insulin resistance indices. In contrast, 7 of 13 patients receiving clozapine treatment experienced elevated fasting and post-OGTT glucose levels. Clozapine-treated patients also experienced significant increases in insulin resistance indices.

11.3 Lipid Levels

There are currently no published reports of the effect of amisulpride therapy on blood glucose levels.

11.4 Discussion

The almost complete lack of available data means that it is difficult to draw conclusions about the risk of glucose dysregulation or dyslipidaemia associated with amisulpride treatment. Amisulpride is, however, associated with modest effect on bodyweight. This limited weight gain potential predicts that amisulpride may be associated with a low risk of adverse metabolic events.

11.5 Conclusion

Amisulpride treatment is associated with modest effect on bodyweight during short- and long-term therapy. The limited data make it difficult to draw conclusions about its effect on the risk of developing diabetes, hyperglycaemia or lipid dys-

regulation. A possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity.

12. Ziprasidone

Ziprasidone was approved for use in the US in 2001, and currently accounts for a relatively small proportion of second-generation antipsychotic prescriptions. Limited published data are available examining the possible association between ziprasidone therapy and the development of diabetes, hyperglycaemia and/or dyslipidaemia.

12.1 Bodyweight

Ziprasidone treatment is associated with relatively little weight gain risk. In an analysis of published studies,[59] the estimated weight gain over a 10-week treatment period, using a random effects model, was 0.04kg with ziprasidone therapy. Minimal changes in weight have been reported in randomised, controlled clinical trials with ziprasidone. In a 6-week study involving patients with acute exacerbation of schizophrenia or schizoaffective disorder, treatment with ziprasidone 80 mg/day was associated with a median increase of 1kg, while no change in the median weight was recorded with ziprasidone 160 mg/day or placebo.[279] In a 28-week study of outpatients with stable schizophrenia, the mean changes in weight from baseline to endpoint were similar for ziprasidone (+0.31kg) and haloperidol (+0.22kg) treatment.[280] Ziprasidone-treated patients experienced a small mean decrease in bodyweight (–1.12kg) in a 28-week comparison study with olanzapine therapy.[228] This change was significantly different from the 3.06kg mean increase observed with olanzapine ($p < 0.001$). Small reductions in weight were also reported with ziprasidone in a 1-year study of patients with chronic, stable schizophrenia.[281] Mean decreases of 2.7, 3.2 and 2.9kg from baseline were reported with 40, 80 and 160 mg/day doses of ziprasidone, respectively, approaching the 3.6kg decrease observed with placebo. Statistically significant decreases in mean bodyweight from baseline levels were also reported after 6 weeks of ziprasidone therapy for patients switched from olanzapine (–1.76kg) and from risperidone (–0.86kg) treatments, although patients switched from typical antipsychotics experienced a small increase in weight (0.27kg).[282] The results underscore the effect of previous treatment conditions on current treatment-induced weight changes.

In summary, treatment with this second-generation antipsychotic is associated with minimal risk of clinically significant increases in bodyweight. Package insert data indicate weight gain of 7% or greater in 10% of ziprasidone-treated patients compared with 4% of placebo controls over 4 or 6 weeks of treatment. This is in line with findings from the 28-week comparison study versus olanzapine, in which 9.6% of ziprasidone-treated patients experienced a ≥7% increase in weight from baseline. Although this does represent approximately twice the placebo-related incidence, it is statistically significantly less than the 37.2% reported for the olanzapine group.[228]

12.2 Diabetes and Hyperglycaemia

12.2.1 Case Reports and Chart Reviews

Changes in FPG levels have been examined in a retrospective chart review of patients treated with ziprasidone.[283] In all, 40 patients with mental retardation and behavioural disturbances who had received at least 6 months of ziprasidone treatment were included in the study. Of these, 36 were switched to ziprasidone after excessive weight gain or inadequate response with other second-generation antipsychotics. The majority of patients (n = 28; 70%) had received prior risperidone treatment; five had received quetiapine, two were treated with olanzapine and one with haloperidol/clozapine. Mean fasting glucose levels showed minimal changes during the first 6 months of ziprasidone therapy (baseline 87.0 ± 21.5 mg/dL; 6 months 83.4 ± 16.8 mg/dL). Changes in bodyweight were also reported over the analysis period. Mean bodyweight increased (1.8kg) in the 6 months prior to

Table XIV. Case report of hyperglycaemia with ziprasidone

Reference	Case report details
Yang & McNeely[285]	Rhabdomyolysis, pancreatitis and hyperglycaemia with ziprasidone

the initiation of ziprasidone, then showed a significant mean decrease of 3.6kg during the first 6 months of ziprasidone treatment ($p < 0.001$). In a switching study, nonfasting (random) plasma glucose levels showed no statistically significant change from baseline following 6 weeks of ziprasidone therapy.[284]

To date, one case report of abnormal glucose levels associated with ziprasidone therapy has appeared in the literature (table XIV); in a recent letter, Yang and McNeely[285] report a case of rhabdomyolysis, hyperglycaemia and pancreatitis associated with ziprasidone treatment.

12.2.2 Retrospective Database Analyses

For the period of this literature survey, there have been no published analyses of healthcare data examining the incidence of diabetes associated with ziprasidone treatment.

12.2.3 Controlled Clinical Trials

Glick and colleagues[226] compared the effects of ziprasidone and olanzapine therapy on BMI and metabolic parameters, including FPG, insulin and lipid levels, in a randomised, double-blind study involving 269 inpatients with either schizophrenia or schizoaffective disorder. No statistically significant changes in FPG levels from baseline were observed with ziprasidone or olanzapine treatment over the 6-week study period. Plasma insulin levels and calculated HOMA insulin resistance showed minimal change from baseline with ziprasidone. In contrast, fasting plasma insulin and HOMA insulin resistance, along with fasting lipids discussed below, increased statistically significantly over the 6-week study during treatment with olanzapine (figure 6). At endpoint, the difference in median insulin levels between the treatment groups approached statistical significance (ziprasidone 13.8 μU/mL; olanzapine 16.0 μU/mL; $p = 0.0506$). Changes in median bodyweight from baseline were minimal with ziprasidone, and less than the weight gain observed in the olanzapine group (1.2 vs 7.2lb [0.5 vs 3.3kg]).

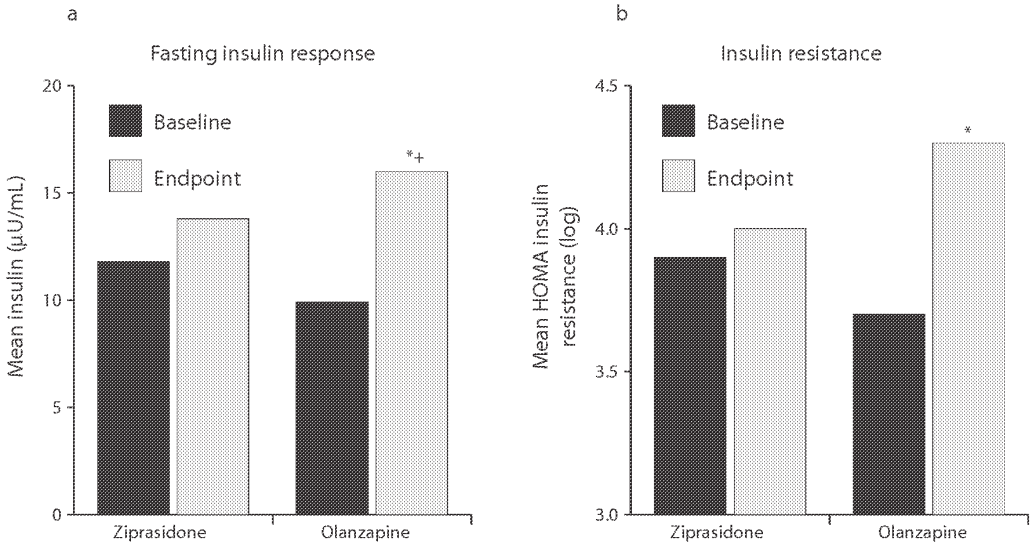

Fig. 6. Fasting insulin response **(a)** and insulin resistance **(b)** in ziprasidone- and olanzapine-treated patients with schizophrenia or schizoaffective disorder.[226] * $p < 0.0001$ vs baseline; + $p < 0.0506$ (NS) ziprasidone vs olanzapine.

The effect of ziprasidone and olanzapine on fasting glucose and lipid levels was also compared in a 28-week randomised, double-blind study involving 548 patients with schizophrenia.[228] Results presented in the abstract showed similar rates of treatment-emergent hyperglycaemia with the two treatments (olanzapine 11.5%; ziprasidone 7.4%; p = 0.159). (Treatment-emergent hyperglycaemia was defined as patients with baseline FPG <126 mg/dL who experienced FPG levels ≥126 mg/dL at any time during the study.) Mean change in weight differed significantly with ziprasidone treatment (–1.12kg) compared with olanzapine (+3.06kg; p < 0.001). Clinically significant increases in fasting plasma insulin occurred during olanzapine treatment. Changes in fasting glucose levels did not correlate with changes in weight. Discussed below, clinically significant increases in fasting plasma lipids were observed during olanzapine but not ziprasidone treatment.

A review of ziprasidone clinical trials[286] reported that there were no reported cases of treatment-emergent diabetes mellitus among the 3834 patients who had received ziprasidone. Analysis of laboratory data from the short-term studies showed that the incidence of abnormal elevations in random glucose measurements was the same in the ziprasidone and placebo groups (8%). In a report of one of these studies,[279] abnormal random glucose elevations (>1.2 × ULN) occurred in 9% and 11% of patients receiving ziprasidone 80 mg/day and 160 mg/day, respectively, compared with 6% receiving placebo.

12.3 Lipid Levels

Published analyses of changes in lipid levels associated with ziprasidone treatment are similarly limited.

12.3.1 Chart Reviews and Observational Studies

The retrospective chart review of 40 patients with mental retardation and behavioural disturbances receiving at least 6 months of ziprasidone treatment also reports changes in lipid levels.[282] Fasting HDL- and LDL-cholesterol levels, available for 19 of the 40 patients, show minimal changes during the first 6 months of ziprasidone therapy. In contrast, significant decreases in mean fasting triglyceride (147.8 to 123.4 mg/dL; n = 29) and total cholesterol (200.5 to 176.4 mg/dL; n = 30) levels were observed during this period (p < 0.04). Significant reductions in nonfasting (random) serum cholesterol (p < 0.001) and triglyceride (p = 0.018) levels from baseline were also reported for 37 patients involved in a switching study following the switch to ziprasidone treatment from other antipsychotics.[284] These changes were independent of changes in BMI. No statistically significant changes in fasting plasma lipid levels were reported with ziprasidone treatment in a 6-month blinded follow-up study in patients with schizophrenia or schizoaffective disorder.[227]

12.3.2 Controlled Clinical Trials

A review of fasting plasma lipid levels from five short-term ziprasidone clinical trials in patients with schizophrenia[287] reported significant decreases in total cholesterol (p < 0.001) and triglyceride (p < 0.001) levels with ziprasidone therapy. Changes in total cholesterol, LDL-cholesterol and triglyceride levels observed with ziprasidone were statistically significant compared with olanzapine (p < 0.01).

In addition to insulin and glucose measures discussed above, Glick et al.[226] examined fasting lipid levels in their 6-week randomised study of ziprasidone (n = 136) and olanzapine (n = 133) therapy. Ziprasidone-treated patients showed minimal changes in median fasting total cholesterol (–1 mg/dL), LDL-cholesterol (–1 mg/dL) and triglyceride (–2 mg/dL) levels from baseline after 6 weeks of therapy. These changes were in contrast to the significant increases in these three parameters from baseline with olanzapine treatment (p ≤ 0.0003). Fasting HDL-cholesterol showed little change from baseline with both ziprasidone and olanzapine treatment. Further analysis showed statistically significantly greater changes in total cholesterol, LDL-cholesterol and triglyceride levels

for male schizophrenic patients with olanzapine treatment than with ziprasidone therapy and a trend towards statistically significant changes in triglyceride levels with olanzapine versus ziprasidone therapy in female patients.[239] Male patients aged 30 years or older showed an increase in the 10-year risk of CHD (calculated using a Framingham-based algorithm) at endpoint with olanzapine therapy compared with a decrease in risk with ziprasidone therapy; the difference between the groups was statistically significant ($p < 0.05$). Changes in CHD risk did not differ significantly between treatments for female patients. Hardy et al.[228] also reported changes in fasting lipid levels in their 26-week comparison study of ziprasidone and olanzapine therapy. Significantly more olanzapine-treated patients experienced treatment-emergent 'high' triglyceride levels (based on NCEP guidelines) than ziprasidone-treated patients (16.9% vs 2.6%; $p < 0.001$). Changes in triglyceride levels positively correlated with changes in weight in both groups. The proportion of patients experiencing 'high' or 'very high' total or LDL-cholesterol levels and the likelihood of low HDL-cholesterol levels did not differ statistically significantly between the groups.

The effect on lipid parameters of switching from other antipsychotics to ziprasidone therapy was examined in 6-week open-label studies involving outpatients with schizophrenia or schizoaffective disorder.[282] Patients experiencing suboptimal efficacy or tolerability with olanzapine (n = 104), risperidone (n = 58) or a typical agent (n = 108) were then switched to flexible dosing with ziprasidone (40–160 mg/day). At the end of the 6-week treatment period, median nonfasting triglyceride levels decreased significantly from baseline in patients switched from olanzapine (–50 mg/dL; $p < 0.0001$) or risperidone (–29 mg/dL; $p < 0.01$) therapy. Median nonfasting total cholesterol levels also decreased significantly from baseline to endpoint in patients receiving prior olanzapine (–17 mg/dL; $p < 0.0001$) or risperidone (–12 mg/dL; $p < 0.005$). Total cholesterol levels decreased for over 70% of patients on each of these prior therapies following the switch to ziprasidone. Small decreases in median nonfasting triglyceride and total cholesterol levels were observed following the switch from typical agents, which were not statistically significant. Following the switch to ziprasidone therapy, both olanzapine- and risperidone-treated patients experienced statistically significant decreases in bodyweight (–1.76 and –0.86kg, respectively) and BMI (olanzapine 31.7 to 31.1 kg/m^2; risperidone 29.6 to 29.3 kg/m^2).

The proportion of patients experiencing abnormal elevations in triglyceride and cholesterol levels was reported in a 6-week ziprasidone study involving 302 patients with acute exacerbation of schizophrenia or schizoaffective disorder.[279] More patients experienced abnormal elevations in cholesterol levels (>1.2 × ULN) in the ziprasidone groups (80 mg/day 25%; 160 mg/day 17%) than with placebo (12%). The percentage of patients experiencing abnormal elevations in triglyceride levels (>1.2 × ULN) was similar in all three groups (ziprasidone 80 mg/day 17%; ziprasidone 160 mg/day 14%; placebo 15%).

12.4 Discussion

The limited availability of data concerning glucose and lipid metabolism prevents firm conclusions regarding the effect of ziprasidone treatment on the risk of developing diabetes, hyperglycaemia or lipid dysregulation. Initial indications from available data, however, suggest that ziprasidone does not have any adverse effect on glucose or lipid levels and may lead to beneficial changes in some lipid parameters, such as triglycerides, especially in patients previously treated with medications that could worsen these measurements.

12.5 Conclusion

Ziprasidone treatment is associated with minimal effect on bodyweight or adiposity. Although published data are somewhat limited, available data suggest that ziprasidone treatment is not associated with an increase in the risk of developing diabetes or dyslipidaemia or any adverse effect on plasma

glucose or lipid levels in treated patients. Limited data suggest that patients whose treatment is switched to ziprasidone from an antipsychotic associated with significant weight gain and increases in plasma glucose and lipids may experience favourable reductions in weight and lipids.

13. Aripiprazole

Aripiprazole is the most recent antipsychotic agent to become available on the market. In the absence of case reports describing metabolic risk or adverse events, or any studies of aripiprazole using retrospective database analyses, the reports of drug effects on weight and possible effects on plasma glucose and lipid levels are all provided by randomised clinical trials.

13.1 Bodyweight

Aripiprazole treatment is associated with minimal changes in bodyweight. Pooled data from five short-term (4- or 6-week) trials in 932 patients treated with aripiprazole showed that aripiprazole was associated with a mean increase in weight of 0.71kg, similar to that reported with haloperidol (0.56kg).[76] The proportion of patients experiencing clinically significant weight gain (≥7% increase) in these studies was modest (8%) in comparison to that seen with placebo (3%).

Minimal changes in weight have also been reported with longer-term treatment. Data from a 52-week double-blind comparison study (n = 1294) of aripiprazole versus haloperidol showed that mean change in weight from baseline to study endpoint (last observation carried forward) was not statistically significantly different between the aripiprazole (1.05kg) and the haloperidol (0.39kg) treatment groups.[288] When stratified by mean BMI at the baseline study visit, only the patients with the lowest baseline BMI (<23 kg/m^2) experienced a statistically significantly greater weight gain with aripiprazole than with haloperidol. Patients with a relatively high BMI (>27 kg/m^2) at baseline lost weight during both aripiprazole (–1.23kg) and haloperidol (–0.78kg) treatment. In a 26-week placebo-controlled study in chronic, stable patients with schizophrenia (n = 310), aripiprazole was associated with a 1.26kg decrease in bodyweight.[289]

The long-term effects of aripiprazole and olanzapine on bodyweight have been compared in two 26-week active-controlled studies.[290,291] The first study was a 26-week multicentre, randomised, double-blind, active-controlled trial in patients with schizophrenia (n = 317), who were in acute relapse and randomised to aripiprazole or olanzapine. At 26 weeks, 14% of aripiprazole-treated patients experienced clinically significant weight gain compared with 37% of olanzapine-treated patients ($p < 0.001$). Among patients remaining on therapy at week 26, there was a mean decrease in weight of 1.37kg with aripiprazole compared with a mean increase of 4.23kg with olanzapine. In a second 26-week study that examined the effects of open-label aripiprazole and olanzapine on cognition in patients with stable schizophrenia or schizoaffective disorder (n = 255),[291] 7% of patients in the aripiprazole group experienced clinically significant weight gain, compared with 27% of the olanzapine-treated patients. The mean change in weight was –0.9kg for aripiprazole versus +3.6kg for olanzapine.[291]

Consistent effects on weight have also been demonstrated in patients with bipolar I disorder. Pooled data from four 3-week placebo-controlled studies in 977 patients presenting with acute mania showed no difference in mean weight change between aripiprazole (0kg) and placebo (–0.2kg).[292]

13.2 Diabetes and Hyperglycaemia

13.2.1 Controlled Clinical Trials

Blood glucose levels have been evaluated in both short- and long-term clinical trials of aripiprazole treatment in patients with schizophrenia or schizoaffective disorder.

Changes in FBG were examined in a 6-week placebo-controlled study of aripiprazole treatment in patients with schizophrenia.[76] Analysis of

pooled data from three aripiprazole groups (10, 15 or 20 mg/day) showed minimal mean changes in blood glucose from baseline (–0.37 mg/dL; n = 120), similar to those observed with placebo (–5.03 mg/dL; n = 34). Random blood glucose measurements pooled from five short-term (4- or 6-week) controlled aripiprazole studies showed that only a small number of patients with normal blood glucose baseline levels (<160 mg/dL) had on-study values of ≥200 mg/dL with aripiprazole treatment (9/648; 1.4%).[76] Similar findings were observed with haloperidol treatment (5/182; 2.7%) and with placebo (4/309, 1.3%).

Data from long-term trials in schizophrenia demonstrate similar neutral effects on blood glucose, comparable to those with placebo. In a 26-week relapse prevention study involving patients with chronic stable schizophrenia,[289] there was no clinically significant change from baseline in fasting glucose levels of aripiprazole-treated and placebo-treated patients (aripiprazole +0.13 mg/dL change; placebo +2.1 mg/dL). However, in a 26-week active-controlled trial of aripiprazole versus olanzapine,[290] there were similarly no statistically significant differences in the change in mean fasting serum glucose levels from baseline to endpoint between the aripiprazole and olanzapine treatment groups (+3 mg/dL for both). Over the course of the study, 5% of patients treated with olanzapine and none treated with aripiprazole exhibited clinically significant elevations in nonfasting serum glucose concentration (≥200 mg/dL). Despite the documented weight gain and hyperglycaemia liability previously discussed with olanzapine, there was no statistically significant difference in mean change in fasting glucose in this 26-week trial. This might be explained by a compensatory increase in insulin secretion in the olanzapine-treated patients over the period of study, but no plasma insulin values are available to validate this hypothesis. In general, pancreatic beta cells can hypersecrete insulin to compensate for reductions in insulin sensitivity. This can be sustained over the lifespan in individuals with no family or personal history of risk for diabetes, whereas individuals at risk can typically sustain the compensatory hyperinsulinaemia for only a limited period before experiencing a gradual, progressive failure of beta-cell function resulting in the progressive onset of plasma glucose elevations.[29]

Comparable effects on fasting serum glucose with aripiprazole and placebo have also been seen in patients with bipolar I disorder. The rates of patients with clinically significant levels of fasting serum glucose (≥110 mg/dL) were similar in both groups.[293]

13.3 Lipid Levels

13.3.1 Controlled Clinical Trials

Lipid levels have also been assessed during short- and long-term aripiprazole treatment. Fasting serum lipid samples were collected in one short-term study in patients with schizophrenia and schizoaffective disorder. The median increase in fasting total cholesterol from baseline observed with aripiprazole treatment was minimal (1.0 mg/dL; median baseline 192 mg/dL; n = 119) and did not differ statistically significantly from that observed with placebo (–5.5 mg/dL; median baseline 194.5 mg/dL; n = 34). In an analysis of fasting and random total cholesterol data from five short-term studies in schizophrenia and schizoaffective disorder,[76] aripiprazole treatment showed minimal changes in total cholesterol levels from baseline. The median increase in total cholesterol levels in the aripiprazole treatment arm (1.0 mg/dL; n = 860) was similar to that in the placebo arm (3.0 mg/dL; n = 392) and less than the increase observed with haloperidol treatment (8.0 mg/dL; n = 190), which differed significantly from placebo ($p \leq 0.01$).

Data from long-term trials in schizophrenia demonstrate neutral effects on serum lipids, comparable to those with placebo. In a 26-week trial, Pigott et al.[289] evaluated changes in fasting total, LDL- and HDL-cholesterol levels and triglycerides in patients with chronic, stable schizophrenia (n = 310). Patients experienced minimal changes in mean HDL-cholesterol (+2.0 mg/dL with aripiprazole and +0.89 mg/dL with placebo) and LDL-cho-

lesterol levels with aripiprazole therapy (–5.1 mg/dL with aripiprazole and –2.9 mg/dL with placebo). There were somewhat larger, favourable mean decreases in total cholesterol (–10.0 mg/dL) and triglyceride levels (–37.2 mg/dL) seen with aripiprazole compared with placebo (–2.7 and –2.9 mg/dL, respectively).

A second long-term aripiprazole study in patients with stable schizophrenia or schizoaffective disorder also reported changes in random total cholesterol levels (including fasting values) from baseline.[291] Total cholesterol levels showed a median decrease of 2.0 mg/dL from baseline with aripiprazole therapy at week 26. In contrast, total cholesterol levels showed a median increase of 20.0 mg/dL with olanzapine therapy at week 26, significantly different from the change observed with aripiprazole ($p < 0.001$).

In a third long-term aripiprazole study, patients with schizophrenia in acute relapse (n = 317) were randomised to 26 weeks of aripiprazole or olanzapine.[290] Changes in fasting plasma levels of HDL-cholesterol and triglycerides were statistically significantly different in the two treatment groups. At week 26, the mean changes in fasting triglycerides were +79.4 mg/dL with olanzapine and +6.5 mg/dL with aripiprazole ($p < 0.05$). The changes in fasting HDL-cholesterol also favoured aripiprazole, with significant differences in changes from baseline to endpoint between the two groups (olanzapine –3.39 mg/dL; aripiprazole +3.61 mg/dL; $p < 0.05$). The difference between changes in fasting total cholesterol (+16.3 mg/dL for the olanzapine group and –1.13 mg/dL for the aripiprazole group) and LDL-cholesterol (+2.27 mg/dL for olanzapine vs –3.86 mg/dL for aripiprazole) did not reach statistical significance ($p = 0.111$). Analysis of the safety dataset revealed statistically significant differences in the incidence of new-onset dyslipidaemias between two treatment groups. In patients with lipid levels within normal range at baseline, treatment with olanzapine resulted in statistically significantly more patients exhibiting clinically significant increases in total cholesterol (>200 mg/dL; 47% with olanzapine and 17% with aripiprazole), LDL-cholesterol (>130 mg/dL; 38% with olanzapine and 19% with aripiprazole) and triglycerides (>150 mg/dL; 50% with olanzapine and 18% with aripiprazole).

Comparable effects on fasting total cholesterol were seen in patients with bipolar I disorder in an acute manic or mixed episode treated with aripiprazole or placebo. The rate of patients with clinically significant levels of fasting total cholesterol (≥200 mg/dL) was similar in both groups.[293]

13.4 Antipsychotic-Induced Metabolic Events

An analysis has recently been published evaluating the risk of developing metabolic syndrome, which is defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III as a key risk factor for development of diabetes and subsequent CHD.[294,295] The NCEP defines the metabolic syndrome as having three or more of the following five risk factors: obesity with a waist circumference >102cm (40in) in men or >88cm (35in) in women; hypertriglyceridaemia defined as triglyceride levels of ≥150 mg/dL; low HDL levels, <40 mg/dL in men and <50 mg/dL in women; hypertension defined as systolic/diastolic blood pressure ≥130/85mm Hg; and elevated FBG levels of >110 mg/dL. Further description of the metabolic syndrome is provided in the Background: Obesity, Insulin Resistance, Diabetes and Dyslipidaemias section of this review. The FDA has recently asked antipsychotic manufacturers to report on drug effects on the ATP III metabolic syndrome as well as on blood lipids and risk of dyslipidaemia, extending an earlier request to report on drug effects on blood glucose and the risk of diabetes. The FDA request regarding ATP III metabolic criteria will be complicated by the lack of waist circumference data in the vast majority of studies conducted to date. A reasonable alternative approach is to substitute BMI criteria for obesity (≥30 kg/m^2) for the ATP III waist circumference obesity threshold. This would allow a number of valuable datasets containing needed fasting lipid and glucose values as well as blood pressure to be

used to calculate treatment-related incidence of the metabolic syndrome, using a modified ATP III approach.

In the first published example of this approach, pooled data from two 26-week double-blind, randomised, controlled trials[289,290] evaluating the efficacy of aripiprazole were used. One trial compared aripiprazole with placebo in stable, chronic schizophrenic patients (n = 310) and the second trial compared aripiprazole with olanzapine in patients in acute relapse of schizophrenia (n = 314). Figure 7 shows a pooled analysis of the two trials.[296] The cumulative incidence (±SE) for worsening of metabolic syndrome during aripiprazole treatment in the two trials was not different (8.3% ± 3.7% vs 6.8% ± 2.8%; p = 0.88). In this analysis, the cumulative metabolic syndrome incidence (±SE) from the pooled data was 19.2% ± 4.0% (olanzapine), 12.8% ± 4.5% (placebo) and 7.6% ± 2.3% (aripiprazole). A log-rank test revealed that there was a significant difference among the three incidence rates (p = 0.003) (aripiprazole vs olanzapine, 69% RR reduction). Based on these results, relative to placebo, aripiprazole does not increase the likelihood for developing or exacerbating metabolic syndrome. Olanzapine statistically significantly increases the likelihood of developing or exacerbating metabolic syndrome relative to aripiprazole.[296,297]

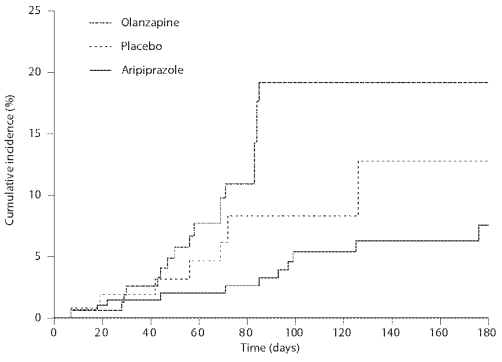

Fig. 7. Kaplan-Meier plot of time to metabolic syndrome in schizophrenic patients: pooled data analysis from two aripiprazole clinical trials.[296] Log-rank test: p = 0.003.

13.5 Discussion

Based on short- and long-term data currently available, aripiprazole treatment has a minimal effect on weight and adiposity and on blood glucose levels. Aripiprazole treatment is associated with neutral effects on serum lipid levels, comparable to those with placebo. In one analysis, aripiprazole was also associated with statistically significantly reduced risk for development of the metabolic syndrome, in comparison to olanzapine, in patients with acute and chronic schizophrenia.

13.6 Conclusion

Aripiprazole treatment is associated with minimal effect on bodyweight or adiposity. Although published data are somewhat limited, available data suggest that aripiprazole treatment is not associated with an increase in the risk of developing diabetes or dyslipidaemia, or adverse effects on plasma glucose or lipid levels in treated patients. Limited data suggest that patients treated with aripiprazole, as compared with olanzapine, may experience a reduced risk of developing the metabolic syndrome.

14. General Discussion

The numerous reports of diabetes, ketoacidosis, hyperglycaemia and lipid dysregulation in schizophrenia patients treated with second-generation antipsychotics provide a strong indication of an association between metabolic effects and some but not all second-generation antipsychotic medications.

Reports of abnormal glucose regulation among individuals with schizophrenia, some of which predate the introduction of antipsychotic therapy, have raised the possibility that observations of diabetes during second-generation antipsychotic therapy could reflect a potential pathophysiological link between schizophrenia and glucose regulation. Three chart reviews reported increased rates of diabetes among patients with schizophrenia compared with the general population. However, another

more recent study reported no increase in the risk of diabetes in patients with schizophrenia, although schizoaffective and bipolar I disorders were associated with significantly higher prevalence rates. Such studies are further complicated by potential confounding factors, for example, prior antipsychotic therapy and lifestyle factors that are likely to influence these results. A small study involving drug-naive patients experiencing first-episode schizophrenia showed higher rates of impaired fasting glucose and more abdominal adiposity than in matched healthy controls, although the use of acutely ill patients with elevated plasma cortisol levels could have influenced some of these findings. Further study is therefore needed to determine whether schizophrenia itself is associated with an increased risk of diabetes. Based on available data, there is no evidence that schizophrenia patients, or patients with any other major mental illness, have *reduced* vulnerability to diabetes or to the adverse effects of increasing adiposity.

Overall, the published findings from case reports, chart reviews, database analyses and clinical trials demonstrate differing metabolic effects with the different second-generation antipsychotics. Evidence is strongest for clozapine and olanzapine, with findings from across the different types of published reports suggesting that olanzapine and clozapine therapy are associated with an increased risk of diabetes. Evidence for the effects of risperidone treatment on the risk of diabetes is less extensive than for clozapine and olanzapine, with similar numbers of database analyses, but fewer chart reviews and observational reports, and fewer controlled studies. These published data do, however, suggest that risperidone treatment is not associated with a consistent increase in diabetes risk. Limited data are available for the other five agents. Findings with quetiapine are somewhat contradictory, and offer relatively less reassuring evidence concerning the relationship between quetiapine treatment and diabetes risk. Initial studies with ziprasidone and aripiprazole suggest that these agents do not adversely affect blood glucose regulation in treated patients. The near absence of data with zotepine and amisulpride makes it difficult to develop rational conclusions about the risk of abnormal blood glucose regulation with these two agents.

Weight gain is a well established side effect of both first- and second-generation antipsychotic therapy. However, this drug-induced adverse event occurs to a markedly different extent among the second-generation agents, with clozapine, olanzapine and less so zotepine therapy associated with a common risk of clinically significant weight gain. Amisulpride, risperidone and quetiapine are associated with mild to moderate weight gain, and ziprasidone and aripiprazole are associated with minimal effects on weight. There is a reasonable hypothesis that much of the effect on glucose regulation observed with the different second-generation agents can be explained simply as a function of their effect on weight and adiposity, although drug effects independent of adiposity have been reported and may add to the effects of adiposity.

Evidence from FDA MedWatch reports and individual case reports suggests that weight gain or obesity may be a factor in approximately 75% of cases of diabetes or hyperglycaemia reported with second-generation antipsychotic therapy. Increased adiposity increases the risk for hyperglycaemia and diabetes in part through adverse effects on insulin sensitivity. Agents that produce the largest rises in adiposity are therefore expected to be associated with the greatest risk of developing diabetes, and this is consistent with the findings of this literature review. However, these reports also suggest that weight gain is not an essential factor in all cases of altered glucose regulation. Available weight gain data from the FDA MedWatch reports[69-71] suggest that 20–25% of cases may occur in the absence of substantial weight gain or obesity. Similarly, in an analysis of individual case reports, Haupt and Newcomer[106] reported that over 25% of the diabetic ketoacidosis cases and 15% of the new-onset hyperglycaemia cases were associated with no weight gain or weight loss (typical of decompensated diabetes). Furthermore, for many patients, the onset of hyperglycaemia occurs shortly after the initiation of treatment, with about 50% of patients experiencing onset within 3 months. Notably, the majority of patients recovered glycaemic control

shortly after discontinuing olanzapine treatment, making it unlikely that adiposity was the sole factor in prompting the changes in glucose regulation in these individuals.

Together these observations suggest that second-generation antipsychotic medications may have a direct (i.e. adiposity-independent) effect on glucose regulation in some individuals. This is supported by results from controlled studies investigating changes in glucose and insulin measures while controlling for confounding factors such as weight, BMI and age. Much speculation has focused on the dibenzodiazepine-derived compounds clozapine, olanzapine, quetiapine and zotepine, which are all structurally related and distinct from the other second-generation antipsychotics. The possible mechanism by which clozapine and olanzapine (and possibly quetiapine and zotepine) may affect glucose regulation independent of adiposity is unclear, and there are currently no structure-function data to support what to date remain essentially *ad hominem* arguments against the subclass. The reports of rapid onset, and often rapidly reversible, diabetic ketoacidosis or severe hyperglycaemia in certain individuals suggests a possible direct effect on beta-cell function in those vulnerable persons.

In this regard, the high proportion of cases of diabetic ketoacidosis reported with clozapine, olanzapine and quetiapine therapy is notable. Although reporting bias toward the more dramatic cases may certainly be present, in the FDA MedWatch studies over 20% of reported cases with clozapine, almost 35% of cases with olanzapine and 42% of cases with quetiapine were associated with metabolic acidosis or ketosis. Similarly, diabetic ketoacidosis featured in a high proportion of published case reports with these agents. In the FDA MedWatch studies, over 90% of the cases of diabetic ketoacidosis seen with clozapine and olanzapine treatment occurred in patients with new-onset type 2 diabetes, suggesting early occurring effects on beta-cell function. Ketosis or metabolic acidosis was reported in at least 60% of the deaths that occurred during or shortly after hyperglycaemic episodes in the FDA MedWatch studies. Overall, death occurred in 10–20% of clozapine- or olanzapine-treated patients and 30% of quetiapine-treated patients reporting ketosis or metabolic acidosis in these studies. In the final analysis, however, the low frequency of these events makes it difficult to definitely establish the extent of differential risk across individual drugs.

As with the differing pattern of drug effects on glucose regulation, the differing effects of different second-generation agents on blood lipid levels suggests that these changes do not reflect a broad class effect of second-generation antipsychotic treatment. Significant increases in triglyceride levels were reported with clozapine and olanzapine therapy, and olanzapine treatment was also associated with a significantly increased risk of hyperlipidaemia. While some increases in triglycerides have been observed with risperidone therapy, other studies have found no effect or only modest, nonsignificant changes. No adverse changes in mean blood lipid levels have been observed with either ziprasidone or aripiprazole therapy; indeed, favourable changes in lipid profiles have been reported in some study cohorts for both treatments. The limited data available for quetiapine have been contradictory. Insufficient data are available for zotepine and amisulpride to draw any conclusions.

The effect of weight gain on lipid profiles is less clear and requires further study. Some studies with olanzapine, clozapine and risperidone report a significant association between weight gain and increased triglyceride levels, while others do not. In general, high correlations between weight and lipids, or glucose as discussed above, should not routinely be expected in small studies given the range of intervening host factors. This is in contrast to the well established relationship between weight or adiposity and metabolic risk in population samples.

The differing effects of the second-generation antipsychotics on bodyweight, glucose regulation and lipid profile presented and discussed in this literature review are in line with the published findings from a recent consensus development conference on antipsychotic drugs, obesity and diabetes.[68] This conference brought together experts

Table XV. Summary of weight gain and metabolic abnormalities with atypical antipsychotics from the 2004 ADA/APA consensus statement[68]

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Ziprasidone[a]	+/–	–	–
Aripiprazole[a]	+/–	–	–

[a]Newer drugs with limited long-term data.
D = discrepant results; + indicates increased effect; – indicates no effect.

from the areas of psychiatry, diabetes and obesity to consider the relationship between second-generation antipsychotics and the development of obesity, diabetes and dyslipidaemia. The published Consensus Statement, based on consideration of all the available evidence, concluded that there are differences between the various second-generation antipsychotics in their effects on bodyweight and risk for diabetes and dyslipidaemia (table XV).

14.1 Guidance for Patient Monitoring

Individuals with mental illnesses, including schizophrenia, bipolar disorder and depression, have increased mortality rates when compared with the general population and are at increased risk of a number of illnesses, including CVD, hypertension and diabetes. The lifestyles of individuals with serious mental illness are likely to be an important contributor to poor overall health, since factors such as obesity, poor diet, lack of exercise, and high rates of smoking and alcohol use are more prevalent in these individuals than in the population as a whole. Furthermore, the antipsychotic agents used to treat these individuals may in some cases contribute to adverse health outcomes by increasing risk factors such as weight, blood glucose and lipids, and the metabolic syndrome.

Growing concerns about the effect of antipsychotic treatment on these risk factors, and the implications for the overall health of a vulnerable patient population, have led to increased interest in careful screening and monitoring of patients to improve their long-term health. This issue was discussed at the recent ADA/APA consensus development conference, and their published statement provides recommendations for the monitoring of patients.[68] Recommended baseline screening measures include weight and height (for BMI calculation), waist circumference, blood pressure, fasting glucose and lipid profile, and personal and family history of obesity, diabetes, dyslipidaemia, hypertension or CVD (table XVI). Second-generation agents with a low propensity for weight gain and glucose intolerance should be considered for patients with diabetes or at increased risk of the disease. Follow-up weight monitoring is recommended 4, 8 and 12 weeks after initiating or switching antipsychotic therapy, then quarterly at routine visits. Glucose and lipid level assessments are recommended 3 months after treatment initiation, then every year for glucose or 5 years for lipids (although the 5-year interval is not consistent with NCEP ATP III guidelines for individuals with anything above minimal risk, a status not characteristic of this population, suggesting the need for annual assessment as with glucose), unless baseline risk or treatment-emergent events indicate the need for increased attention to some or all of these parameters.

Table XVI. Monitoring protocol for patients on atypical antipsychotics, recommended by the 2004 ADA/APA consensus statement;[68] more frequent monitoring may be warranted based on clinical status

Item	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

BMI = body mass index.

The current review suggests that elevated baseline risk and treatment-emergent adverse metabolic events can be expected in many treated patients, suggesting that many patients will have clinical indications for closer and more detailed monitoring. For patients who show weight gain (≥5% increase) or worsening glycaemia or dyslipidaemia, a switch to another second-generation agent not associated with significant weight gain or diabetes risk should be considered along with other interventions.

Similar recommendations for weight, glucose and lipid monitoring come from the Mount Sinai conference, which brought together psychiatrists, endocrinologists and other medical experts to develop guidelines for the routine monitoring of adult schizophrenia patients receiving antipsychotic therapy.[298] These guidelines do, notably, recommend that patients with schizophrenia should be considered at high risk for CHD. Therefore, based on the NCEP guidelines, their lipid profile might need to be monitored more frequently (i.e. every 2 years for normal LDL-cholesterol levels and every 6 months for LDL-cholesterol >130 mg/dL) than is recommended by the ADA/APA consensus statement. The Mount Sinai guidelines suggest that fasting glucose or glycated haemoglobin (e.g. HbA_{1c}) could be used for glucose monitoring, while the ADA recommendations for screening in the general population advise against the use of glycated haemoglobin because of its relative insensitivity as a screening measure.

The introduction of regular routine monitoring should allow for the early detection of changes in these important risk factors, and so improve the overall long-term health of patients with schizophrenia and other mental illnesses.

14.2 Conclusion

Evidence from the published literature indicates that second-generation antipsychotic agents differ in their effects on weight and adiposity and on blood glucose and lipid levels. An extensive body of evidence, including data from prospective clinical trials, shows marked differences in the weight gain liabilities of second-generation antipsychotics. Clozapine and olanzapine, and to a lesser extent zotepine, are all associated with substantial risk of clinically significant weight gain. Amisulpride, risperidone and quetiapine are associated with generally mild to moderate weight gain, increasing across the group as listed. Ziprasidone and aripiprazole are associated with minimal effect on weight.

Studies using a variety of methodologies indicate, with few exceptions, that clozapine and olanzapine treatment are associated with an increased risk of developing diabetes mellitus and elevations in plasma triglyceride levels. Risperidone therapy is not associated with a consistent increase in the risk of developing diabetes or dyslipidaemia. However, a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity. Quetiapine therapy is not associated with a consistent increase in the risk of developing diabetes or dyslipidaemia. However, limited data suggest a possible increase in the risk of diabetes and hypertriglyceridaemia with quetiapine treatment, and a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity. Although published data are somewhat limited, available data suggest that ziprasidone and aripiprazole treatment are not associated with an increase in the risk of developing diabetes or dyslipidaemia or with any adverse effect on plasma glucose or lipid levels in treated patients. The almost complete absence of data makes it difficult to draw any conclusions about the risk of diabetes or dyslipidaemia with zotepine or amisulpride, although the differing weight gain potentials of the two agents suggest a possible increase in risk with zotepine and less so amisulpride therapy.

In general, a possible increase in risk would be predicted to occur in association with any treatment that produces increases in weight and adiposity. In addition to the effects of adiposity, however, limited evidence suggests that certain agents may have a direct effect on glucose regulation independent of adiposity. Further research is needed to improve our understanding of the interactions

between disease states, antipsychotic medications, and glucose and lipid metabolism in patients with psychiatric disorder in order to maximize both psychiatric and medical health outcomes.

Acknowledgements

This work was supported in part by a grant to JWN from the National Institute of Mental Health (NIMH) [MH63985]. In addition, Bristol-Myers Squibb Company/Otsuka Pharmaceutical Co., Ltd provided funding to Ogilvy Healthworld Medical Education, Reading, UK to assist in accessing relevant literature, and to provide production support in the preparation of this manuscript. The author would like to especially thank Andrew Mayhook, PhD, and Rowan Pearce, PhD, at Healthworld for their tireless work.

Disclosure

Dr. Newcomer received grant support in 2004 and 2005 from NIMH, the National Alliance for Research on Schizophrenia and Depression (NARSAD), and the Sidney R. Baer Foundation, as well as investigator-initiated grant support from Pfizer Inc., Janssen Pharmaceutica, and Bristol-Myers Squibb (BMS). In addition, Dr. Newcomer served as a consultant in 2004 for BMS, Pfizer Inc., Janssen Pharmaceutica, AstraZeneca, GlaxoSmithKline, and Wyeth Research. Dr. Newcomer has No Significant Conflict of Interest as defined by the Washington University School of Medicine Conflict of Interest Policy.

References

1. International Obesity TaskForce and the European Association for the Study of Obesity. Obesity in Europe: the case for action. IOTF in collaboration with EASO. London, September 2002 [online]. Available from: URL: www.easoobesity.org [Accessed 23 November 2004]
2. Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999; 341(15): 1097-105
3. NIH/NHLBI guidelines. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults---The Evidence Report. NIH Publication No. 98-4084. Bethesda, MD: National Institutes of Health, 1998 Sep
4. Allison DB, Fontaine KR, Manson JE, et al. Annual deaths attributable to obesity in the United States. JAMA 1999; 282(16): 1530-8
5. Minino AM, Arias E, Kochanek KD, et al. Deaths: final data for 2000. Natl Vital Stat Rep 2002; 50(15): 1-119
6. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. JAMA 1995; 273: 461-5
7. Shaper AG, Wannamethee SG, Walker M. Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. BMJ 1997; 314: 1311-7
8. Shimizu M, Isogai Y. Heart failure due to metabolic heart disorders. Nippon Rinsho 1993; 51: 1362-6
9. Rexrode KM, Hennekens CH, Willett WC, et al. A prospective study of body mass index, weight change, and risk of stroke in women. JAMA 1997; 277: 1539-45
10. Walker SP, Rimm EB, Ascherio A, et al. Body size and fat distribution as predictors of stroke among US men. Am J Epidemiol 1996; 144: 1143-50
11. Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990; 132: 501-13
12. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995; 122: 481-6
13. Brown CD, Higgins M, Donato KA, et al. Body mass index and the prevalence of hypertension and dyslipidemia. Obes Res 2000; 8(9): 605-19
14. Pi-Sunyer FX. Medical hazards of obesity. Ann Intern Med 1993; 119(7 pt 2): 655-60
15. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes and obesity-related health risk factors, 2001. JAMA 2003; 289: 76-9
16. Despres JP. Abdominal obesity as important component of insulin-resistance syndrome. Nutrition 1993; 9(5): 452-9
17. Banjeri M, Chaiken R, Gordon D, Lebowitz H. Does intra-abdominal tissue in black men determine whether NIDDM is insulin-resistant or insulin-sensitive? Diabetes 1995; 44: 141-5
18. Goodpaster BH, Kelly DE, Wing RR, et al. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. Diabetes 1999; 48: 839-47
19. Kelly DE, Goodpaster BH. Skeletal muscle triglyceride. An aspect of regional adiposity and insulin resistance. Diabetes Care 2001; 24(5): 933-41
20. Goldstein BJ. Insulin resistance: from benign to type 2 diabetes mellitus. Rev Cardiovasc Med 2003; 4(Suppl 6): S3–S10
21. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2002. Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention, 2003
22. World Health Organization. Atlas of Health in Europe. Geneva: World Health Organization, 2003
23. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults. Diabetes Care 1998; 21: 518-24
24. DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care 2003; 26: 61-9
25. Gu K, Cowie C, Harris MI. Mortality in adults with and without diabetes in a national cohort of the US population, 1971–1993. Diabetes Care 1998; 21: 1138-45
26. American Diabetes Association. Economic costs of diabetes in the US in 2002. Diabetes Care 2003; 26: 917-32
27. Jonsson B, CODE-2 Advisory Board. Revealing the cost of type II diabetes in Europe. Diabetologia 2002; 45(7): S5-12
28. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20: 1183-97

29. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004; 27 Suppl 1: S5-S10
30. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003; 26 Suppl 1: S5-S20
31. Lebovitz HE. Diagnosis, classification, and pathogenesis of diabetes mellitus. J Clin Psychiatry 2001; 62 Suppl 27: 5-9
32. Schwartz MW. Staying slim with insulin in mind. Science 2000; 289: 2066-7
33. Brüning JC, Gautam D, Burks DJ, et al. Role of brain insulin receptor in control of body weight and reproduction. Science 2000; 289: 2122-5
34. NCEP Expert Panel. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106(25): 3143-421
35. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360(9326): 7-22
36. Sanoski CA. Management of dyslipidemia: an update. Curr Atheroscler Rep 2003; 5(4): 284-90
37. Grundy SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110(2): 227-39
38. Cohn G, Valdes G, Capuzzi DM. Pathophysiology and treatment of the dyslipidemia of insulin resistance. Curr Cardiol Rep 2001; 3: 416-23
39. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. Am J Clin Nutr 1956; 4: 20-34
40. Reaven G. Banting lecture 1988: Role of insulin resistance in human disease. Diabetologia 1988; 30: 1595-607
41. Reaven G. Syndrome X: 10 years after. Drugs 1999; 58 Suppl 1: 19-20; discussion 75-82
42. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002; 287: 356-9
43. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001; 24(4): 683-9
44. Newcomer JW, Nasrallah HA, Loebel AD. The Atypical Antipsychotic Therapy and Metabolic Issues National Survey: practice patterns and knowledge of psychiatrists. J Clin Psychopharmacol 2004; 24 5 Suppl 1: S1-S6
45. Brown S, Birtwistle J, Roe L, Thompson C. The unhealthy lifestyle of people with schizophrenia. Psychol Med 1999; 29: 697-701
46. Baxter DN. The mortality experience of individuals on the Salford case register. I. All-cause mortality. Br J Psychiatry 1996; 168: 772-9
47. Hennekens CH. Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. Circulation 1998; 97: 1095-102
48. Chambers RA, Krystal JH, Self DW. A neurobiological basis for substance abuse comorbidity in schizophrenia. Biol Psychiatry 2001; 50: 71-83
49. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999; 60(4): 215-20
50. Brown S. Excess mortality of schizophrenia. A meta-analysis. Br J Psychiatry 1997; 171: 502-8
51. Ösby U, Correia N, Brandt L, et al. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophr Res 2000; 45(1–2): 21-8
52. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34-38 years. J Affect Disord 2002; 68(2–3): 167-81
53. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord 2002; 72(3): 227-36
54. Haupt DW, Newcomer JW. Abnormalities in glucose regulation associated with mental illness and treatment. J Psychosom Res 2002; 53(4): 925-33
55. Tabata H, Kikuoka M, Kikuoka H, et al. Characteristics of diabetes mellitus in schizophrenic patients. J Med Assoc Thai 1987; 70 Suppl 2: 90-3
56. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996; 37: 68-73
57. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull 2000; 26: 903-12
58. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001; 286: 1195-200
59. Allison DB, Mentore LJ, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156: 1686-96
60. Regenold WT, Thapar RK, Marano C, et al. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. [Erratum in: J Affect Disord 2003; 73(3): 301-2] J Affect Disord 2002; 70: 19-26
61. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug naive patients with schizophrenia. Am J Psychiatry 2003; 160(2): 284-9
62. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Rev Arch Gen Psychiatry 2002; 59: 337-45
63. Ryan MC, Flanagan S, Kinsella U, et al. The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naive patients with schizophrenia. Life Sci 2004; 74(16): 1999-2008
64. Chiba M, Suzuki S, Hinokio Y, et al. Tyrosine hydroxylase gene microsatellite polymorphism associated with insulin resistance in depressive disorder. Metabolism 2000; 49(9): 1145-9
65. Okamura F, Tashiro A, Utumi A, et al. Insulin resistance in patients with depression and its changes during the clinical course of depression: minimal model analysis. Metabolism 2000; 49(10): 1255-60
66. Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. Schizophr Res 2004; 70(1): 1-17
67. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. Acta Psychiatr Scand 1999; 100(1): 3-16
68. American Diabetes Association: American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004; 27(2): 596-601
69. Koller E, Schneider B, Bennett K, Dubitsky G. Clozapine-associated diabetes. Am J Med 2001; 111: 716-23
70. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus [review]. Pharmacotherapy 2002; 22: 841-52
71. Koller EA, Cross JT, Doraiswamy PM, Schneider BS. Risperidone-associated diabetes mellitus: a pharmacovigilance study. Pharmacotherapy 2003; 23(6): 735-44
72. Henderson DC, Cagliero E, Copeland P, et al. Glucose metab-

olism in schizophrenia patients with atypical antipsychotic: a frequent sampled intravenous glucose tolerance test and minimal model analysis. Arch Gen Psychiatry 2005; 62(1): 19-28
73. Ebenbichler CF, Laimer M, Eder U, et al. Olanzapine induces insulin resistance: results from a prospective study. J Clin Psychiatry 2003; 64: 1436-9
74. Jones AM, Rak IW, Raniwalla J. Weight changes in patients treated with quetiapine. Poster presented at the 153rd Annual Meeting of the American Psychiatric Association, May 13–18, 2000, Chicago, IL
75. Leucht S, Wagenpfeil S, Hamann J, Kissling W. Amisulpride is an "atypical" antipsychotic associated with low weight gain. Psychopharmacology 2004; 173: 112-5
76. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term placebo-controlled trials. Schizophr Res 2003; 61: 123-36
77. Boehm G, Racoosin JA, Laughren TP, Katz R. Consensus development conference on antipsychotic drugs and obesity and diabetes: response to consensus statement. Diabetes Care 2004; 27(8): 2088-9
78. Kemner C, Willemsen-Swinkels SH, de Jonge M, et al. Open label study of olanzapine in children with pervasive developmental disorder. J Clin Psychopharmacol 2002; 22: 455-60
79. Ercan ES, Kutlu A, Varan A, et al. Olanzapine treatment of eight adolescent patients with psychosis. Hum Psychopharmacol 2004; 19: 53-6
80. Scahill L, Leckman JF, Schultz RT, et al. A placebo-controlled trial of risperidone in Tourette syndrome. Neurology 2003; 60: 1130-5
81. Patel NC, Kistler JS, James EB, Crismon ML. A retrospective analysis of the short-term effects of olanzapine and quetiapine on weight and body mass index in children and adolescents. Pharmacotherapy 2004; 24: 824-30
82. Aman MG, De Smedt G, Derivan A, et al. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. Am J Psychiatry 2002; 159: 1337-46
83. Gilbert DL, Batterson JR, Sethuraman G, Sallee FR. Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. J Am Acad Child Adolesc Psychiatry 2004; 43: 206-14
84. Gagliano A, Germano E, Pustorino G, et al. Risperidone treatment of children with autistic disorder: effectiveness, tolerability, and pharmacokinetic implications. J Child Adolesc Psychopharmacol 2004; 14: 39-47
85. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002; 347: 314-21
86. Martin A, Scahill L, Anderson GM, et al. Weight and leptin changes among risperidone-treated youths with autism: 6-month prospective data. Am J Psychiatry 2004; 161: 1125-7
87. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. Neuropsychopharmacology 2004; 29: 133-45
88. Visser M, Pahor M, Tylavsky F, et al. One- and two-year change in body composition as measured by DXA in a population-based cohort of older men and women. J Appl Physiol 2003; 94: 2368-74
89. Gallagher D, Ruts E, Visser M, et al. Weight stability masks sarcopenia in elderly men and women. Am J Physiol Endocrinol Metab 2000; 279: E366-75
90. Barak Y, Shamir E, Weizman R. Would a switch from typical antipsychotics to risperidone be beneficial for elderly schizophrenic patients? A naturalistic, long-term, retrospective, comparative study. J Clin Psychopharmacol 2002; 22: 115-20
91. Barak Y. No weight gain among elderly schizophrenia patients after 1 year of risperidone treatment. J Clin Psychiatry 2002; 63: 117-9
92. Goldberg R. Weight variance associated with atypical neuroleptics in nursing home dementia patients. J Am Med Dir Assoc 2001; 2(1): 26-8
93. Madhusoodanan S, Suresh P, Brenner R, Pillai R. Experience with the atypical antipsychotics – risperidone and olanzapine in the elderly. Ann Clin Psychiatry 1999; 11: 113-8
94. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 2000; 57: 968-76
95. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 2003; 28(3): 519-26
96. Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. Lancet 2002; 359(9323): 2086-7
97. Reynolds GP, Zhang Z, Zhang X. Polymorphism of the promoter region of the serotonin 5-HT(2C) receptor gene and clozapine-induced weight gain. Am J Psychiatry 2003; 160(4): 677-9
98. Theisen FM, Hinney A, Bromel T, et al. Lack of association between the -759C/T polymorphism of the 5-HT2C receptor gene and clozapine-induced weight gain among German schizophrenic individuals. Psychiatr Genet 2004; 14(3): 139-42
99. Taylor DM, McAskill R. Atypical antipsychotics and weight gain – a systematic review. Acta Psychiatr Scand 2000; 101(6): 416-32
100. Eder U, Mangweth B, Ebenbichler C, et al. Association of olanzapine-induced weight gain with an increase in body fat. Am J Psychiatry 2001; 158: 1719-22
101. 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(1): 69-80
102. Ardizzone TD, Bradley RJ, Freeman 3rd AM, Dwyer DS. Inhibition of glucose transport in PC12 cells by the atypical antipsychotic drugs risperidone and clozapine, and structural analogs of clozapine. Brain Res 2001; 923(1-2): 82-90
103. Dwyer DS, Donohoe D. Induction of hyperglycemia in mice with atypical antipsychotic drugs that inhibit glucose uptake. Pharmacol Biochem Behav 2003; 75(2): 255-60
104. Elman I, Goldstein DS, Eisenhofer G, et al. Mechanism of peripheral noradrenergic stimulation by clozapine. Neuropsychopharmacology 1999; 20(1): 29-34
105. Spivak B, Roitman S, Vered Y, et al. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. Clin Neuropharmacol 1998; 21: 245-50
106. Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. J Clin Psychiatry 2001; 62 Suppl 27: 15-26; discussion 40-1
107. Thonnard-Neumann E. Phenothiazines and diabetes in hospitalized women. Am J Psychiatry 1968; 124(7): 978-82
108. Clark M, Dubowski K, Colmore J. The effect of chlorpromazine on serum cholesterol in chronic schizophrenic patients. Clin Pharmacol Ther 1970; 11: 883-9
109. Amdisen A. Drug-produced obesity: experiences with chlorpromazine, perphenazine and clopenthixol. Dan Med Bull 1964; 11: 182-9
110. Blin O. A comparative review of new antipsychotics. Can J Psychiatry 1999; 44(3): 235-44

111. Leadbetter R, Shutty M, Pavalonis D, et al. Clozapine-induced weight gain: prevalence and clinical relevance. Am J Psychiatry 1992; 149(1): 68-72
112. Lamberti JS, Bellnier T, Schwarzkopf SB. Weight gain among schizophrenic patients treated with clozapine. Am J Psychiatry 1992; 149(5): 689-90
113. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999; 60: 358-63
114. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000; 157: 975-81
115. Iqbal MM, Rahman A, Husain Z, et al. Clozapine: a clinical review of adverse effects and management. Ann Clin Psychiatry 2003; 15(1): 33-48
116. Bustillo JR, Buchanan RW, Irish D, Breier A. Differential effect of clozapine on weight: a controlled study. Am J Psychiatry 1996; 153(6): 817-9
117. Wehring HJ, Kelly DL, Love RC, Conley RR. Deaths from diabetic ketoacidosis after long term clozapine treatment. Am J Psychiatry 2003; 160(12): 2241-2
118. Beliard S, Valero R, Vialettes B. Atypical neuroleptics and diabetes. Diabetes Metab 2003; 29(3): 296-9
119. Lafayette JM, Pirl WF, Henderson DC. Low-dose clozapine and diabetic ketoacidosis. Psychosomatics 2003; 44(3): 249-52
120. Cohen D, Gispen-de Wied CC. Schizophrenia and diabetes mellitus: not an improbable combination [in Dutch]. Tijdschr Geneeskd 2003; 147(21): 993-6
121. Kristensen SH, Porksen NK. Clozapine and diabetic ketoacidosis [in Danish]. Ugeskr Laeger 2003; 165(5): 475-6
122. Avram AM, Patel V, Taylor HC, et al. Euglycemic clamp study in clozapine-induced diabetic ketoacidosis. Ann Pharmacother 2001; 35: 1381-7
123. Rigalleau V, Gatta B, Bonnaud S, et al. Diabetes as a result of atypical anti-psychotic drugs—a report of three cases. Diabet Med 2000; 17: 484-6
124. 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
125. Isakov I, Klesmer J, Masand PS. Insulin-resistant hyperglycemia induced by clozapine [letter]. Psychosomatics 2000; 41: 373-4
126. Wehring H, Alexander B, Perry PJ. Diabetes mellitus associated with clozapine therapy. Pharmacotherapy 2000; 20: 844-7
127. Brugman NJ, Cohen D, de Vries RH. Diabetes mellitus after treatment with clozapine [in Dutch]. Ned Tijdschr Geneeskd 2000; 144(9): 437-9
128. Maule S, Giannella R, Lanzio M, Villari V. Diabetic ketoacidosis with clozapine treatment [letter]. Diabetes Nutr Metab 1999; 12: 187-8
129. Colli A, Cocciolo M, Francobandiera F, et al. Diabetic ketoacidosis associated with clozapine treatment [letter]. Diabetes Care 1999; 22: 176-7
130. Mohan D, Gordon H, Hindley N, Barker A. Schizophrenia and diabetes mellitus [letter]. Br J Psychiatry 1999; 174: 180-1
131. Smith H, Kenney-Herbert J, Knowles L. Clozapine-induced diabetic ketoacidosis [letter]. Aust N Z J Psychiatry 1999; 33: 120-1
132. Ai D, Roper TA, Riley JA. Diabetic ketoacidosis and clozapine. Postgrad Med J 1998; 74(874): 493-4
133. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998; 44: 778-83
134. Dickson RA, Hogg L. Pregnancy of a patient treated with clozapine. Psychiatr Serv 1998; 49: 1081-3
135. Thompson J, Chengappa KN, Good CB, et al. Hepatitis, hyperglycemia, pleural effusion, eosinophilia, hematuria and proteinuria occurring early in clozapine treatment. Int Clin Psychopharmacol 1998; 13: 95-8
136. Pierides M. Clozapine monotherapy and ketoacidosis. Br J Psychiatry 1997; 171: 90-1
137. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997; 58: 108-11
138. Koren W, Kreis Y, Duchowiczny K, et al. Lactic acidosis and fatal myocardial failure due to clozapine. Ann Pharmacother 1997; 31: 168-70
139. Peterson GA, Byrd SL. Diabetic ketoacidosis from clozapine and lithium cotreatment [letter]. Am J Psychiatry 1996; 153: 737-8
140. Kostakoglu AE, Yazici KM, Erbas T, Guvener N. Ketoacidosis as a side-effect of clozapine: a case report. Acta Psychiatr Scand 1996; 93: 217-8
141. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment [letter]. Am J Psychiatry 1994; 151: 1520-1
142. Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine [letter]. Am J Psychiatry 1994; 151: 1395
143. Ananth J, Venkatesh R, Burgoyne K, Gunatilake S. Atypical antipsychotic drug use and diabetes. Psychother Psychosom 2002; 71: 244-54
144. Baymiller SP, Ball P, McMahon RP, Buchanan RW. Serum glucose and lipid changes during the course of clozapine treatment: the effect of concurrent beta-adrenergic antagonist treatment. Schizophr Res 2003; 59: 49-57
145. Hägg 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: 294-9
146. Wirshing DA, Boyd JA, Meng LR, et al. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002; 63: 856-65
147. Kurt E, Oral ET. Antipsychotics and glucose, insulin, lipids, prolactin, uric acid metabolism in schizophrenia [abstract]. Eur Neuropsychopharmacol 2002; 12 Suppl 3: S276, P.2.049
148. Chae BJ, Kang BJ. The effect of clozapine on blood glucose metabolism. Hum Psychopharmacol 2001; 16: 265-71
149. Melkersson KI, Hulting AL. Insulin and leptin levels in patients with schizophrenia or related psychoses – a comparison between different antipsychotic agents. Psychopharmacology (Berl) 2001; 154: 205-12
150. Yazici KM, Erbas T, Yazici AH. The effect of clozapine on glucose metabolism. Exp Clin Endocrinol Diabetes 1998; 106: 475-7
151. Melkersson KI, Dahl ML. Relationship between levels of insulin or triglycerides and serum concentrations of the atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses. Psychopharmacology (Berl) 2003; 170(2): 157-66
152. Melkersson KI, Hulting AL, Brismar 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
153. Chue P, Welch R. Investigation of the metabolic effects of antipsychotics in patients with schizophrenia [abstract]. Eur Neuropsychopharmacol 2003; 13 Suppl 4: S300, P.2.049
154. Howes OD, Bhatnagar A, Gaughran F, et al. The effect of clozapine on factors controlling glucose homeostasis [abstract]. Schizophr Res 2004; 67: 186, no. 377
155. Sernyak MJ, Gulanski B, Leslie DL, Rosenheck R. Undiagnosed hyperglycemia in clozapine-treated patients with schizophrenia. J Clin Psychiatry 2003; 64(5): 605-8
156. Gupta S, Steinmeyer C, Frank B, et al. Hyperglycemia and hypertriglyceridemia in real world patients on antipsychotic

therapy. Am J Ther 2003; 10(5): 348-55
157. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 2002; 159(4): 561-6
158. Lund BC, Perry PJ, Brooks JM, Arndt S. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Arch Gen Psychiatry 2001; 58(4): 1172-6
159. Gianfrancesco FD, Grogg AL, Mahmoud RA, et al. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. J Clin Psychiatry 2002; 63: 920-30
160. Lambert B, Chou C-H, Chang K-Y, et al. Assessing the risk of antipsychotic-induced type II diabetes among schizophrenics: a matched case-control study [abstract]. Eur Neuropsychopharmacol 2002; 12 Suppl 3: S307, P.2.126
161. Citrome L, Jaffe A, Levine J, et al. Antipsychotic medication treatment and new prescriptions for insulin and oral hypoglycemics [abstract]. Eur Neuropsychopharmacol 2003; 13 Suppl 4: S306, P.2.063
162. Wang PS, Glynn RJ, Ganz DA, et al. Clozapine use and risk of diabetes mellitus. J Clin Psychopharmacol 2002; 22: 236-43
163. Buse JB, Cavazzoni P, Hornbuckle K, et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. J Clin Epidemiol 2003; 56(2): 164-70
164. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am J Psychiatry 2003; 160: 290-6
165. Rettenbacher MA, Baumgartner S, Ebenbichler C, et al. Alterations of glucose metabolism under treatment with clozapine vs. amisulpride [abstract]. Schizophr Res 2004; 67: 191, no. 390
166. Kenny SJ, Aubert RE, Geiss LS. Prevalence and incidence of non-insulin dependent diabetes. In: Harris MI, Cowie CC, Stern MP, et al., eds. Diabetes in America, 2nd ed. Publication no. 95-1468. Bethesda (MD): National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995: 47-67
167. Sussman N. Review of atypical antipsychotics and weight gain. J Clin Psychiatry 2001; 62 Suppl 23: 5-12
168. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999; 22: 233-40
169. Gerstein HC. Is glucose a continuous risk factor for cardiovascular mortality? Diabetes Care 1999; 22: 659-60
170. Temelkova-Kurktschiev T, Henkel E, Schaper F, et al. Prevalence and atherosclerosis risk in different types of non-diabetic hyperglycemia. Is mild hyperglycemia an underestimated evil? Exp Clin Endocrinol Diabetes 2000; 108: 93-9
171. Gaulin BD, Markowitz JS, Caley CF, et al. Clozapine-associated elevation in serum triglycerides. Am J Psychiatry 1999; 156: 1270-2
172. Spivak B, Lamschtein C, Talmon Y, et al. The impact of clozapine treatment on serum lipids in chronic schizophrenic patients. Clin Neuropharmacol 1999; 22: 98-101
173. Ghaeli P, Dufresne RL. Elevated serum triglycerides with clozapine resolved with risperidone in four patients. Pharmacotherapy 1999; 19: 1099-101
174. Ghaeli P, Dufresne RL. Serum triglyceride levels in patients treated with clozapine. Am J Health Syst Pharm 1996; 53: 2079-81
175. Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Serum leptin and triglyceride levels in patients on treatment with atypical antipsychotics. J Clin Psychiatry 2003; 64(5): 598-604
176. Dursun SM, Szemis A, Andrews H, Reveley MA. The effects of clozapine on levels of total cholesterol and related lipids in serum of patients with schizophrenia: a prospective study. J Psychiatry Neurosci 1999; 24: 453-5
177. Gupta S, Droney T, Al-Samarrai S, et al. Olanzapine: weight gain and therapeutic efficacy. J Clin Psychopharmacol 1999; 19(3): 273-5
178. Nemeroff CB. Dosing the antipsychotic medication olanzapine. J Clin Psychiatry 1997; 58 Suppl 10: 45-9
179. Beasley CM, Tollefson GD, Tran PV. Safety of olanzapine. J Clin Psychiatry 1997; 58 Suppl 10)1 3-17
180. Kurzthaler I, Fleischhacker WW. The clinical implications of weight gain in schizophrenia. J Clin Psychiatry 2001; 62 Suppl 7: 32-7
181. Ader M, Catalano KJ, Ionut V, et al. Differential metabolic effects between atypical antipsychotics in normal dogs. Poster presented at the American Diabetes Association 63rd Scientific Sessions, June 13--17, 2003, New Orleans, LA
182. Biswas PN, Wilton LV, Pearcel GL, et al. The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England. J Psychopharmacol 2001; 15: 265-71
183. Torrey EF, Swalwell CI. Fatal olanzapine-induced ketoacidosis. Am J Psychiatry 2003; 160(12): 2241
184. Dewan V. Potential risk of diabetes mellitus with the use of atypical antipsychotic medication. Can J Psychiatry 2003; 48(5): 351-2
185. Tavakoli SA, Arguisola MS. Diabetic ketoacidosis in a patient treated with olanzapine, valproic acid, and venlafaxine. South Med J 2003; 96(7): 729-30
186. Chang HY, Ridky TW, Kimball AB, et al. Eruptive xanthomas associated with olanzapine use. Arch Dermatol 2003; 139(8): 1045-8
187. Azriel Mira S. Uncontrolled hyperglycemia with ketosis associated with olanzapine therapy [in Spanish]. Rev Clin Esp 2002; 202: 672
188. Kozian R. Olanzapine-induced diabetes mellitus [in German]. Psychiatr Prax 2002; 29: 318-20
189. Straker D, Mendelowitz A, Karlin L. Near fatal ketoacidosis with olanzapine treatment [letter]. Psychosomatics 2002; 43: 339-40
190. Meatherall R, Younes J. Fatality from olanzapine induced hyperglycemia. J Forensic Sci 2002; 47: 893-6
191. Opp D, Hildebrandt C. Olanzapine-associated type 2 diabetes mellitus [letter]. Schizophr Res 2002; 56: 195-6
192. Malyuk R, Gibson B, Procyshyn RM, Kang N. Olanzapine associated weight gain, hyperglycemia and neuroleptic malignant syndrome: case report. Int J Geriatr Psychiatry 2002; 17: 326-8
193. Riccitelli G, Baker N. Weight gain and hyperglycaemia associated with olanzapine [letter]. Aust N Z J Psychiatry 2002; 36: 270-1
194. Ramankutty G. Olanzapine-induced destabilization of diabetes in the absence of weight gain. Acta Psychiatr Scand 2002; 105: 235-6; discussion 236-7
195. Melkersson K, Hulting AL. Recovery from new-onset diabetes in a schizophrenic man after withdrawal of olanzapine. Psychosomatics 2002; 43: 67-70
196. Ragucci KR, Wells BJ. Olanzapine-induced diabetic ketoacidosis. Ann Pharmacother 2001; 35: 1556-8
197. Rojas P, Arancibia P, Bravo V, et al. Diabetes mellitus induced by olanzapine: a case report [in Spanish]. Rev Med Chil 2001; 129: 1183-5
198. Seaburg HL, McLendon BM, Doraiswamy PM. Olanzapine-associated severe hyperglycemia, ketonuria, and acidosis: case report and review of literature [review]. Pharmacotherapy 2001; 21: 1448-54
199. Bechara CI, Goldman-Levine JD. Dramatic worsening of type 2 diabetes mellitus due to olanzapine after 3 years of therapy.

Pharmacotherapy 2001; 21(11): 1444-7
200. Domon SE, Webber JC. Hyperglycemia and hypertriglyceridemia secondary to olanzapine. J Child Adolesc Psychopharmacol 2001; 11: 285-8
201. Muench J, Carey M. Diabetes mellitus associated with atypical antipsychotic medications: new case report and review of the literature. J Am Board Fam Pract 2001; 14: 278-82
202. Kropp S, Emrich HM, Bleich S, Degner D. Olanzapine-related hyperglycemia in a nondiabetic woman [letter]. Can J Psychiatry 2001; 46: 457
203. Selva KA, Scott SM. Diabetic ketoacidosis associated with olanzapine in an adolescent patient. J Pediatr 2001; 138: 936-8
204. Bonanno DG, Davydov L, Botts SR. Olanzapine-induced diabetes mellitus. Ann Pharmacother 2001; 35: 563-5
205. Roefaro J, Mukherjee SM. Olanzapine-induced hyperglycemic nonketonic coma. Ann Pharmacother 2001; 35: 300-2
206. Bettinger TL, Mendelson SC, Dorson PG, Crismon ML. Olanzapine-induced glucose dysregulation. Ann Pharmacother 2000; 34: 865-7
207. Von Hayek D, Huttl V, Reiss J, et al. [Hyperglycemia and ketoacidosis associated with olanzapine]. Nervenarzt 1999; 70: 836-7
208. Lindenmayer JP, Patel R. Olanzapine-induced ketoacidosis with diabetes mellitus [letter]. Am J Psychiatry 1999; 156: 1471
209. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics 1999; 40: 438-43
210. Gatta B, Rigalleau V, Gin H. Diabetic ketoacidosis with olanzapine treatment [letter]. Diabetes Care 1999; 22: 1002-3
211. Ober SK, Hudak R, Rusterholtz A. Hyperglycemia and olanzapine [letter]. Am J Psychiatry 1999; 156: 970
212. Fertig MK, Brooks VG, Shelton PS, English CW. Hyperglycemia associated with olanzapine [letter]. J Clin Psychiatry 1998; 59: 687-9
213. Zajecka JM, Weisler R, Sachs G, et al. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. J Clin Psychiatry 2002; 63(12): 1148-55
214. Rubio G, Gómez de la Cámara A, Hawkins F, et al. The risk of developing diabetes in users of atypical antipsychotics: a feasibility pilot study [abstract]. Int J Neuropsychopharmacol 2002; 5 Suppl 1: S168, P.3.W.040
215. Casey D, Matchett JL, Fishman NB, Radmaker SB. The effect of antipsychotic drugs in managing diabetes [abstract]. Int J Neuropsychopharmacol 2002; 5 Suppl 1: S167, P.3.W.039
216. Meyer JM. A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. J Clin Psychiatry 2002; 63: 425-33
217. Melkersson KI, Hulting AL, Brismar 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
218. Berry S, Mahmoud R. Improvement of insulin indices after switch from olanzapine to risperidone [abstract]. Eur Neuropsychopharmacol 2002; 12 Suppl 3: S316, P.2.148
219. Litman R, Peterson SW, Singh I, et al. Glucose metabolism, lipid levels, and body mass indices in olanzapine-treated schizophrenia patients before and after switching to risperidone: a prospective trial [abstract]. Int J Neuropsychopharmacol 2002; 5 Suppl 1: S170, P.3.W.050
220. Fuller MA, Shermock KM, Secic M, Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. Pharmacotherapy. 2003; 23(8): 1037-43
221. Gianfrancesco F, White R, Wang RH, Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. J Clin Psychopharmacol 2003; 23(4): 328-35.
222. Caro JJ, Ward A, Levinton C, Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. J Clin Psychiatry 2002; 63: 1135-9
223. Koro CE, Fedder DO, L'Italien GJ, et al. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry 2002; 59: 1021-6
224. Farwell WR, Stump TE, Wang J, et al. Do olanzapine and risperidone cause weight gain and diabetes? [abstract]. Int J Neuropsychopharmacol 2002; 5 Suppl 1: S170, P.3.W.049
225. Koro CE, Fedder DO, L'Italien GJ, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. BMJ 2002; 325(7358): 243
226. Glick ID, Romano SJ, Simpson G, et al. Insulin resistance in olanzapine- and ziprasidone-treated patients: results of a double-blind, controlled 6-week trial. Presented at: Annual Meeting of the American Psychiatric Association, May 5–10, 2001, New Orleans, LA
227. Simpson GM, Weiden P, Pigott T, et al. Ziprasidone vs olanzapine in schizophrenia: 6-month continuation study [abstract]. Eur Neuropsychopharmacol 2002; 12 Suppl 3: S310, P.2.134
228. Hardy TA, Poole-Hoffmann V, Lu Y, et al. Fasting glucose and lipid changes in patients with schizophrenia treated with olanzapine or ziprasidone. Poster presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology, December 7–11, 2003, San Juan, Puerto Rico
229. Hardy TA, Earley W, Marquez E, et al. Oral glucose tolerance in patients treated with olanzapine 20, 30, or 40 mg/day [abstract]. Schizophr Res 2004; 67: 184, no. 373
230. Sowell MO, Mukhopadhyay N, Cavazzoni P, et al. Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone, or placebo. J Clin Endocrinol Metab 2002; 87: 2918-23
231. Sowell M, Mukhopadhyay N, Cavazzoni P, et al. Evaluation of insulin sensitivity in healthy volunteers treated with olanzapine, risperidone, or placebo: a prospective, randomized study using the two-step hyperinsulinemic, euglycemic clamp. J Clin Endocrinol Metab 2003; 88(12): 5875-80
232. Stoner SC, Dubisar BM, Khan R, Farrar CD. Severe hypertriglyceridemia associated with olanzapine [letter]. J Clin Psychiatry 2002; 63: 948-9
233. Nguyen M, Murphy T. Olanzapine and hypertriglyceridemia [letter]. J Am Acad Child Adolesc Psychiatry 2001; 40: 133
234. Sheitman BB, Bird PM, Binz W, et al. Olanzapine-induced elevation of plasma triglyceride levels [letter]. Am J Psychiatry 1999; 156: 1471-2
235. Meyer JM. Novel antipsychotics and severe hyperlipidemia. J Clin Psychopharmacol 2001; 21: 369-74
236. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry 1999; 60: 767-70
237. Ishigooka J, Murasaki M, Miura S, Olanzapine Early-Phase II Study Group. Efficacy and safety of olanzapine, an atypical antipsychotic, in patients with schizophrenia: results of an open-label multicenter study in Japan. Psychiatry Clin Neurosci 2001; 55: 353-63
238. Hardy T, Sowell E, Marquez E, et al. Cross-sectional comparison of fasting triglycerides in normoglycemic patients with schizophrenia treated with olanzapine, risperidone, or typical antipsychotics [abstract]. Eur Neuropsychopharmacol 2003; 13 Suppl 4: S339, P.2.138
239. Mackell J, Leaderer M. Ziprasidone vs. olanzapine: change in

CHD risk during a 6-week trial [abstract]. Schizophr Res 2004; 67: 189, no. 384
240. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry 2001; 158(5): 765-74
241. Dimelis D, Garyfallos G, Kiouniakis F, et al. Olanzapine vs risperidone: impact on weight gain and blood lipids. Is there any relationship with antipsychotic efficacy? [abstract]. Eur Neuropsychopharmacol 2002; 12 Suppl 3: S328, P.2.175
242. Ozguven HD, Oner O, Baskak B, et al. The metabolic and clinical effects of olanzapine and quetiapine: preliminary findings from a randomized single-blind trial in patients with schizophrenia [abstract]. Schizophr Res 2004; 67: 190, no. 388
243. Ahl J, Kinon B, Liu-Seifert H, Baker R. Longitudinal effect of olanzapine on fasting serum lipids: a randomized, prospective, 4-month study [abstract]. Schizophr Res 2004; 67: 179, no. 361
244. Grundy SM. Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. Am J Cardiol 1998; 81(4A): 18B-25B
245. Nasrallah H. A review of the effect of atypical antipsychotics on weight. Psychoneuroendocrinology 2003; 28: 83-96
246. Csernansky JG, Mahmoud R, Brenner R, Risperidone-USA-79 Study Group. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002; 346(1): 16-22
247. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997; 17: 407-18
248. Ganguli R, Brar JS, Ayrton Z. Weight gain over 4 months in schizophrenia patients: a comparison of olanzapine and risperidone. Schizophr Res 2001; 49(3): 261-7
249. Fukui H, Murai T. Severe weight gain induced by combination treatment with risperidone and paroxetine. Clin Neuropharmacol 2002; 25: 269-71
250. Wirshing DA, Pierre JM, Eyeler J, et al. Risperidone-associated new onset diabetes. Biol Psychiatry 2001; 50: 148-9
251. Croarkin PE, Jacobs KM, Bain BK. Diabetic ketoacidosis associated with risperidone treatment [letter]. Psychosomatics 2000; 41: 369-70
252. Mallya A, Chawla P, Boyer SK, DeRosear L. Resolution of hyperglycemia on risperidone discontinuation: a case report [letter]. J Clin Psychiatry 2002; 63: 453-4
253. Haupt DW, Newcomer JW. Reply to Croarkin et al, Letter to the Editor - Diabetic ketoacidosis associated with risperidone treatment. Psychosomatics 2001; 42: 280
254. Wilson DR, D'Souza L, Sarkar N, et al. New-onset diabetes and ketoacidosis with atypical antipsychotics. Schizophr Res 2002; 59: 1-6
255. Cavazzoni P, Hornbuckle K, Wu J, et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United Kingdom [abstract]. Int J Neuropsychopharmacol 2002; 5 Suppl 1: S168, P.3.W.043
256. Martin A, L'Ecuyer S. Triglyceride, cholesterol and weight changes among risperidone treated youths. A retrospective study. Eur Child Adolesc Psychiatry 2002; 11: 129-33
257. Wetterling T. Bodyweight gain with atypical antipsychotics. A comparative review. Drug Saf 2001; 24(1): 59-73
258. Borison R, Arvanitis LA, Miller BG. USS ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996; 16(2): 158-69
259. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. Biol Psychiatry 1997; 42: 233-46
260. Peuskens J, Link CG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta Psychiatr Scand 1997; 96(4): 265-73
261. Copolov DL, Link CG, Kowalcyk B. A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, 'Seroquel') and haloperidol in schizophrenia. Psychol Med 2000; 30(1): 95-105
262. Brecher M, Rak IW, Melvin K, Jones AM. The long-term effect of quetiapine (Seroquel) monotherapy on weight in the treatment of schizophrenia. Int J Psych Clin Pract 2000; 4(4): 287-91
263. Brecher M, Zukin S, Leong R, Osterling-Koskinen L, Jones M. Long-term weight change with quetiapine treatment in schizophrenia: a comprehensive data review. Poster presented Monday, 13 December 2004 at ACNP 43rd Annual Meeting, 12-16 December 2004, San Juan, Puerto Rico. Abstract in Neuropsychopharmacology 29(Suppl 1): S109
264. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Seroquel Study Group. Arch Gen Psychiatry 1997; 54: 549-57
265. Koller EA, Weber J, Doraiswamy PM, Schneider BS. A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus. J Clin Psychiatry 2004; 65(6): 857-63
266. Sneed KB, Gonzalez EC. Type 2 diabetes mellitus induced by an atypical antipsychotic medication. J Am Board Fam Pract 2003; 16(3): 251-4
267. Procyshyn RM, Pande S, Tse G. New-onset diabetes associated with quetiapine. Can J Psychiatry 2000; 45: 668-9
268. Sobel M, Jaggers ED, Franz MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment [letter]. J Clin Psychiatry 1999; 60: 556-7
269. Domon SE, Cargile CS. Quetiapine-associated hyperglycemia and hypertriglyceridemia [letter]. J Am Acad Child Adolesc Psychiatry 2002; 41: 495-6
270. Shaw JA, Lewis JE, Pascal S, et al. A study of quetiapine: efficacy and tolerability in psychotic adolescents. J Child Adolesc Psychopharmacol 2001; 11: 415-24
271. Melkersson K, Dahl ML. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. Drugs 2004; 64(7): 701-23
272. Taylor DM, McAskill R. Atypical antipsychotics and weight gain – a systematic review. Acta Psychiatr Scand 2000; 101(6): 416-32
273. Wetterling T, Mussigbrodt HE. Weight gain: side effect of atypical neuroleptics? J Clin Psychopharmacol 1999; 19(4): 316-21
274. Palmgren K, Wighton A, Reynolds CW, et al. The safety and efficacy of zotepine in the treatment of schizophrenia: results of a one-year naturalistic clinical trial. Int J Psych Clin Pract 2000; 4: 299-306
275. Prakash A, Lamb HM. Zotepine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of schizophrenia. CNS Drugs 1998; 9: 153-75
276. Wetterling T. Hyperlipidemia: side-effect of the treatment with an atypical antipsychotic (zotepine)? [in German]. Psychiatr Prax 2002; 29(8): 438-40
277. Peuskens J, Bech P, Moller HJ, et al. Amisulpride vs risperidone in the treatment of acute exacerbation of schizophrenia. Amisulpride study group. Psychiatry Res 1999; 88: 107-17
278. Mortimer A, Martin S, Loo H, et al. A double-blind, randomized comparative trial of amisulpride versus olanzapine for 6 months in the treatment of schizophrenia: SOLIANOL Study Group. Int Clin Psychopharmacol 2004; 19: 63-9
279. Daniel DG, Zimbroff DL, Potkin SG, et al., and the

Ziprasidone Study Group. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Neuropsychopharmacology 1999; 20: 491-505
280. Hirsch SR, Kissling W, Bauml J, et al. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. J Clin Psychiatry 2002; 63(6): 516-23
281. Arato M, O'Connor R, Meltzer HY, ZEUS Study Group. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. Int Clin Psychopharmacol 2002; 17(5): 207-15
282. Weiden PJ, Daniel DG, Simpson G, Romano SJ. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. J Clin Psychopharmacol 2003; 23(6): 595-600
283. Cohen S, Fitzgerald B, Okos A, et al. Weight, lipids, glucose, and behavioral measures with ziprasidone treatment in a population with mental retardation. J Clin Psychiatry 2003; 64: 60-2
284. Kingsbury SJ, Fayek M, Trufasiu D, et al. The apparent effects of ziprasidone on plasma lipids and glucose. J Clin Psychiatry 2001; 62: 347-9
285. Yang SH, McNeely MJ. Rhabdomyolysis, pancreatitis, and hyperglycemia with ziprasidone [letter]. Am J Psychiatry 2002; 159: 1435
286. Stimmel GL, Gutierrez MA, Lee V. Ziprasidone: an atypical antipsychotic drug for the treatment of schizophrenia [review]. Clin Ther 2002; 24: 21-37
287. Romano S, Cutler N, Weiden PJ, Simpson GM. Ziprasidone's effects on weight and lipids in patients with schizophrenia [abstract]. Int J Neuropsychopharmacol 2002; 5 Suppl 1: S171, P.3.W.055
288. Kasper S, Lerman MN, McQuade RD, et al. Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. Int J Neuropsychopharmacol 2003; 6(4): 325-37
289. Pigott TA, Carson WH, Saha AR, et al. for the Aripiprazole Study Group. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. J Clin Psychiatry 2003; 64: 1048-56
290. McQuade RD, Stock E, Marcus R, et al. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. J Clin Psychiatry 2004; 65 Suppl 18: 47-56
291. Cornblatt B, Kern RS, Carson WH, et al. Neurocognitive effects of aripiprazole versus olanzapine in stable psychosis. Int J Neuropsychopharmacol 2002; 5 Suppl 1: S185
292. McQuade RD, Marcus R, Sanchez R, et al, Aripiprazole versus placebo in acute mania: safety and tolerability pooled analysis. Poster presented at the 5th International Conference on Bipolar Disorder, June 12–14, 2003, Pittsburgh, PA
293. Keck Jr PE, Marcus R, Tourkodimitris S, et al., Aripiprazole Study Group. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry 2003; 160(9): 1651-8
294. Lorenzo C, Okoloise M, Williams K, et al.; San Antonio Heart Study. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. Diabetes Care 2003; 26(11): 3153-9
295. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003; 108(4): 414-9
296. L'Italien GJ. Pharmacoeconomic impact of antipsychotic-induced metabolic events. Prev Med Manag Care 2003; 3 (2 Suppl): S38-S42.
297. Casey D, L'Italian G, Waldeck R, et al. Metabolic syndrome comparison between olanzapine, aripiprazole and placebo. Poster presented at the American Psychiatric Association, May 2003, San Francisco, CA
298. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. Am J Psychiatry 2004; 161: 1334-9

Correspondence and offprints: John W. Newcomer, Department of Psychiatry, Washington University School of Medicine, 660 S. Euclid, St. Louis, MO 63110, USA.
E-mail: newcomerj@psychiatry.wustl.edu

adis INTERNATIONAL

CNS Drugs™ Supplement

Subscription Information

Adis International Ltd
Subscription Administration, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand
Tel: +64 9 477 0700 (ext. 7819); +44 1829 771 155 (UK); +1 267 757 3400 (USA)
Fax: +64 9 477 0766
E-mail: subs@adis.com; **Online:** www.adisonline.info

Subscription Agent: Japan – LWW Igaku-Shoin Ltd
Shoei Bldg - 7F, 3-23-14, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
Tel: +81 3 5689 5400
Fax: +81 3 5689 5402
E-mail: bsales@lwwis.co.jp

Terms and Conditions

12 issues of *CNS Drugs* are published annually. The annual 2005 institutional subscription price for print and online is $US2405 and for online only is $US2145. The personal subscription price for print and online is $US240 and for online only is $US235. All online subscriptions include access to online archived articles. Subscription orders must be prepaid. Printed in Singapore by Craft Print International Limited.

Electronic Table of Contents E-Mail Alerting Service

Join our free e-mail alerting service and we will send you the table of contents for each new issue. Signing up could not be easier; it takes only a few minutes to register your e-mail address. Choose which journals or newsletters interest you and we will send you the tables of contents (with links to abstracts, and full text with subscription) each time a new issue is published. The AdisOnline eTOC service is available to subscribers and non-subscribers. You may change or amend your selections or cancel the service at any time. Register for the eTOC service at www.adisonline.info

Order Form

Subscriber information

Name: .....

Job title: .....

Postal Address (for journal delivery): .....

.....

Zip code: ..... Country: .....

Tel: ..... Fax: .....

E-mail: .....

Payment details (payable to Adis International Ltd)

Please invoice my Company/Library quoting reference/order number: .....

Please charge my (circle one): American Express Mastercard Visa

Card number: .....

Cardholder name: .....

Signature: ..... Expiry date: .....

Wolters Kluwer Health
Adis International

Argentina, Chile, Paraguay and Uruguay
Juncal 2826 - PB "B", 1425 Buenos Aires, **Argentina**
Tel: +54 11 4823 2985
Fax: +54 11 4824 1527

Brazil
Rua Américo Brasiliense, 2171, CJ 1304, Chac. Sto. Antonio, 04715-005, São Paulo - SP, **Brazil**
Tel: +55 (11) 5181 6901
Fax: +55 (11) 5181 6911

France
4 avenue Hoche, 75008 Paris, **France**
Tel: +33 (1) 56 99 97 00
Fax: +33 (1) 56 99 97 10

Germany
Hauptstrasse 19, D-82319 Starnberg, Munich, **Germany**
Tel: +49 (8151) 555 060
Fax: +49 (8151) 555 0666

Italy
via Lanino 5, 20144 Milan, **Italy**
Tel: +39 (02) 423 4562
Fax: +39 (02) 422 1200

Japan
Shin-Osaka Prime Tower, 3F, 6-1-1, Nishinakajima, Yodogawa-ku, Osaka, 532-0011, **Japan**
Tel: +81 (06) 6304 7227
Fax: +81 (06) 6304 7230

Shoei Bldg - 10F, 3-23-14 Hongo, Bunkyo-ku, Tokyo, 113-0033, **Japan**
Tel: +81 3 5805 5812
Fax: +81 3 5805 5830

New Zealand
41 Centorian Drive, Mairangi Bay, Auckland 1311, **New Zealand**
Tel: +64 (09) 477 0700
Fax: +64 (09) 477 0784

Spain
Adis International Ediciones Medicas, S.A., Calle Orense, 16-8°F, 28020 Madrid, **Spain**
Tel: +34 (91) 555 7689
Fax: +34 (91) 555 7689

Adis International Ediciones Medicas, S.A., Príncipe de Asturias, 63-65, 4°- 4°, 08012 Barcelona, **Spain**
Tel: +34 (93) 218 8866
Fax: +34 (93) 415 2173

North America
770 Township Line Road, Suite 300, Yardley, PA 19067, **USA**
Tel: +1 (0) 267 757 3400
Toll Free: 877 872 2347; 877 USA ADIS
Fax: +1 (0) 267 757 3490
Toll Free: 877 234 7329; 877 ADIS FAX

UK/Rest of the World
Chowley Oak Lane, Tattenhall, Chester, CH3 9GA, **England**
Tel: +44 (1829) 77 1155
Fax: +44 (1829) 77 0330

Publisher of:

- American Journal of Cancer
- American Journal of Cardiovascular Drugs
- American Journal of Clinical Dermatology
- American Journal of Drug Delivery
- American Journal of PharmacoGenomics
- Anti-infectives Today
- Applied Bioinformatics
- Applied Health Economics and Health Policy
- BioDrugs
- Cancer Today
- Clinical Drug Investigation
- Clinical Pharmacokinetics
- Clinical Trials Insight
- CNS Disorders Today
- CNS Drugs
- Disease Management & Health Outcomes
- Drug Safety
- Drugs
- Drugs & Aging
- Drugs & Therapy Perspectives
- Drugs in R&D
- Evidence-Based Integrative Medicine
- High Blood Pressure and Cardiovascular Prevention
- Inpharma® Weekly
- International Journal of Pharmaceutical Medicine
- Molecular Diagnosis
- Paediatrics Today
- Pediatric Drugs
- Pharmaceutical & Diagnostic Innovation
- PharmacoEconomics
- PharmacoEconomics & Outcomes News
- PharmaNewsFeed.com
- R&D Insight
- Reactions Weekly
- Sports Medicine
- Thérapie
- Toxicological Reviews
- Treatments in Endocrinology
- Treatments in Respiratory Medicine

ISSN 1172-7047

All articles published in this journal from 1998 onwards are available online at **www.ingenta.com**

CNS Drugs • 2005, Vol. 19, Suppl. 1, pp. 1-93

Second-Generation (Atypical) Antipsychotics and Metabolic Effects

Adis