Metabolic Consequences of Antipsychotic Therapy: Preclinical and Clinical Perspectives on Diabetes, Diabetic Ketoacidosis, and Obesity

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Abstract Antipsychotic drugs, particularly second-generation antipsychotics (SGAs), have reduced the burden to society of schizophrenia, but many still produce excessive weight gain. A significant number of SGAs also act directly to impair glycemic control causing insulin resistance, impaired glucose tolerance and type 2 diabetes, and also rarely diabetic ketoacidosis (DKA). Schizophrenia itself is almost certainly causal in many endocrine and metabolic disturbances, making this population especially vulnerable to the adverse metabolic consequences of treatment with SGAs. Hence, there is an urgent need for a new generation of antipsychotic drugs that provide efficacy equal to the best of the SGAs without their

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liability to cause weight gain or type 2 diabetes. In the absence of such safe and effective alternatives to the SGAs, there is a substantial clinical need for the introduction of new antipsychotics without adverse metabolic effects and new antiobesity drugs to combat these metabolic side effects. We discuss the adverse metabolic consequences of schizophrenia, its exacerbation by a lack of social care, and the additional burden placed on patients by their medication. A critical evaluation of the animal models of antipsychotic-induced metabolic disturbances is provided with observations on their strengths and limitations. Finally, we discuss novel antipsychotic drugs with a lower propensity to increase metabolic risk and adjunctive medications to mitigate the adverse metabolic actions of the current generation of antipsychotics.

Keywords Antipsychotics • Diabetes • Diabetic ketoacidosis • Metabolic dysfunction • Obesity • Weight gain

Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
DKA	Diabetic ketoacidosis
FGA	First-generation antipsychotic
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide-1
HDL-C	High-density lipoprotein-cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
IOTF	International obesity task force
LDL-C	Low-density lipoprotein-cholesterol
SGA	Second-generation antipsychotic
SSRI	Selective serotonin reuptake inhibitor

1 Introduction

Numerous studies have reported that natural and unnatural deaths are increased significantly in schizophrenia. Cardiovascular disease (CVD) is a common cause of mortality, accounting for more than 30 % of deaths in these subjects. Studies report CVD mortality to be increased nearly fourfold in schizophrenia patients aged 18–49 years (Mortensen and Juel 1993; Osborn et al. 2007), demonstrating that CVD risk in schizophrenia has an early onset, together with a doubling of risk in 50–75 year olds. Patients with schizophrenia are particularly at risk from the CVD risk factors of obesity, hyperglycemia, dyslipidemia, and smoking-related disease, because they are more likely to have an unhealthy lifestyle (lack of exercise and poor diet) than the general population (Brown et al. 1999). They are reported to

have around three times more intra-abdominal fat than control subjects (Ryan et al. 2004) and 40–80 % have a body mass index (BMI) $\geq$ 20 % above normal. An estimated 75 % of schizophrenic patients are smokers (Newcomer 2005).

This review describes the effects of antipsychotic drugs on various metabolic risk factors, including weight, adiposity, and glycemic control. The contribution from these metabolic factors to the unacceptably high rates of cardiovascular morbidity and mortality suffered by patients with schizophrenia and related disorders is discussed. Since much has already been written about the relationship between antipsychotics and weight gain (e.g., Allison et al. 1999a, b; Newcomer 2005; Lieberman et al. 2005; Reynolds and Kirk 2010; De Hert et al. 2011c) about their metabolic side effects (Reynolds and Kirk 2010; De Hert et al. 2011c), we will focus more on insulin resistance and type 2 diabetes. We review the strengths and limitations of animal models of antipsychotic-induced metabolic disturbances. Finally, we describe the merits of antipsychotic drugs with lower cardiovascular risk and adjunctive medications to mitigate the adverse metabolic actions of the current generation of antipsychotics.

2 Metabolic Dysregulation and Cardiovascular Risk

2.1 Obesity

Obesity predisposes an individual to developing dyslipidemia, hypertension, proinflammatory atherogenesis, prediabetes (i.e., insulin resistance and impaired glucose tolerance), and type 2 diabetes (Mokdad et al. 2001; Pi-Sunyer 2002). Together, they increase cardiovascular morbidity and mortality (Montani et al. 2002; Beckman et al. 2002; Flack et al. 2003; Rashid et al. 2003; Law et al. 2003) and are implicated in cancer (International Obesity Task Force [IOTF] 2010), sleep apnoea, arthritis, gout, and gallstones (Wolk et al. 2003; Felson 1996; Bhole et al. 2010; Heshka and Heymsfield 2001). As discussed in this review, antipsychotic-induced weight gain is a major disincentive to treatment in patients.

2.2 Prediabetes, Type 2 Diabetes, and Diabetic Ketoacidosis

Type 2 diabetes (non-insulin dependent) causes increased cardiovascular morbidity, renal damage, neuropathy, and blindness. Many factors including obesity, visceral adiposity, and release of proinflammatory peptides reduce the ability of insulin to promote uptake of blood glucose into liver and skeletal muscle (insulin resistance). To maintain glucose homeostasis, pancreatic β-cells increase their release of insulin (hyperinsulinemia). As the disease progresses, insulin resistance gradually increases and pancreatic insulin secretion can no longer maintain glycemic control, resulting in

glucose intolerance and type 2 diabetes. In later stages, secretion of insulin by the pancreas declines dramatically (van den Oever et al. 2010; Abdul-Ghani and DeFronzo 2010; DeFronzo 2010; Herman and Kahn 2006). Management of type 2 diabetes with sulphonylurea drugs that promote insulin secretion may also contribute to loss of pancreatic β-cell function. The final stage of Type 2 diabetes is characterised by a profound loss of pancreatic β-cell mass whereby insulin secretion is reduced to the point at which individuals need to use injectable insulin to control blood glucose levels. Hypoinsulinemia also reduces insulin-mediated inhibition of lipolysis in adipose tissue, which can lead to diabetic ketoacidosis (DKA) (Eledrisi et al. 2006). Since type 1 diabetes is characterized by autoimmune-mediated loss of pancreatic β-cell function causing profound insulin deficiency, DKA is far more prevalent in this form of the disease. In the absence of insulin, hepatic glucose production rapidly increases whilst fatty acids are metabolized to ketone bodies, resulting in low blood pH (ketoacidosis). When the liberation of ketone bodies resulting in a low blood pH (ketoacidosis) is combined with glucose-induced osmotic diuresis, which depletes blood of potassium and sodium, it sets up a self-perpetuating, cycle of ionic dysregulation and dehydration that can lead to coma and death. Although DKA is rare, the use of atypical antipsychotic drugs is believed to have increased its incidence (Henderson 2001; Jin et al. 2002; Wilson et al. 2003; Reist et al. 2007).

3 Metabolic Dysregulation Associated with Schizophrenia

Evidence suggests that subjects with schizophrenia and schizo-affective disorders are similarly metabolically compromised in terms of glycemic control (insulin resistance, impaired fasting plasma glucose (FPG) [prediabetes], or type 2 diabetes). Although lifestyle factors and obesity unequivocally contribute, studies in first-degree relatives have shown that there is a strong contribution to impaired glycemic control (Spelman et al. 2007).

In a small clinical study comparing insulin resistance using a glucose tolerance test in drug-free, nondiabetic schizophrenic subjects and healthy volunteers, insulin sensitivity in individuals with schizophrenia was 42 % lower (Cohn et al. 2006). Moreover, a compensatory increase of insulin secretion was not present, indicating they had considerably greater risk of developing type 2 diabetes. Although this finding was not consistent across all studies (e.g., Spelman et al. 2007), the inability of insulin release to compensate for hyperglycemia may explain why schizophrenic subjects are prone to DKA when treated with second-generation antipsychotics (SGAs). Ryan et al. (2003) found that mean FPG and insulin concentrations were significantly higher in young, non-obese schizophrenia sufferers than the controls. Insulin resistance calculated by the homeostasis model assessment (HOMA-IR) was also significantly greater in the schizophrenic subjects. Finally, Spelman et al. (2007) performed a study in young, normal weight subjects, who fulfilled the criteria for first-episode, drug-naïve schizophrenia. Using a glucose challenge

test, plasma glucose and fasting insulin concentrations, insulin secretion, and HOMA-IR were all significantly greater in schizophrenic subjects and first-degree relatives than in controls. Impaired glucose tolerance was present in 11 % of patients with schizophrenia, 18 % of nonschizophrenic relatives, and in none of the healthy control subjects.

Although these studies were performed on small groups of subjects (because the number of newly diagnosed cases of schizophrenia not receiving medication is relatively small), the results consistently show that individuals with schizophrenia are much more likely to be prediabetic or to have type 2 diabetes than the general population. The fact that these metabolic disturbances are not necessarily linked to obesity and are present in nonschizophrenic, first-degree relatives (Spelman et al. 2007) indicates there is a strong genetic component. Moreover, this state of affairs exists even before patients are exposed to the cardiometabolic liabilities of treatment with first-generation antipsychotics (FGAs) or SGAs.

4 Adverse Metabolic Effects Associated with the Use of Antipsychotic Drugs

4.1 Effects of Antipsychotic Drugs on Bodyweight

As long ago as 1974, an Editorial in the British Medical Journal reported unusual patterns of weight gain with chlorpromazine. Interestingly, the article stated that this side effect occurred only rarely when other FGAs were used to treat schizophrenia. In the 1980s, reports of weight gain associated with use of depot formulations of FGAs started to appear (Johnson and Breen 1979; Silverstone et al. 1988). However, it was the introduction of the prototypical SGA clozapine that was linked to a high incidence of obesity (Cohen et al. 1990; Leadbetter et al. 1992). Meltzer's hypothesis that clozapine's unique profile as an antipsychotic drug derived from the ratio of its affinities for D_2 and 5-HT_2 receptors (Meltzer et al. 1989; Meltzer 1989) prompted the rapid discovery and development of the SGAs that currently dominate the treatment of schizophrenia. Allison et al. (1999b) produced the first systematic meta-analysis of the relative propensities of a wide range of FGAs and SGAs to induce weight gain. It established beyond doubt that many SGAs had much greater liability to cause substantial increases in bodyweight than the preceding FGAs. The article by Allison and colleagues contained a widely reproduced graph of corrected mean weight change at 10 weeks with molindone being weight-neutral and olanzapine and clozapine at the opposite end of the weight gain spectrum. Possibly excepting clozapine and ziprasidone, it has been frequently reported that weight gain plateaus on longer term antipsychotic treatment and differences for individual drugs become less pronounced (Stanton 1995; Haddad 2005; Gentile 2006). Although our analysis is not comprehensive, in Fig. 1a we ranked the weight changes for various FGAs and SGAs in studies where treatment ranged from 12 weeks to several years.

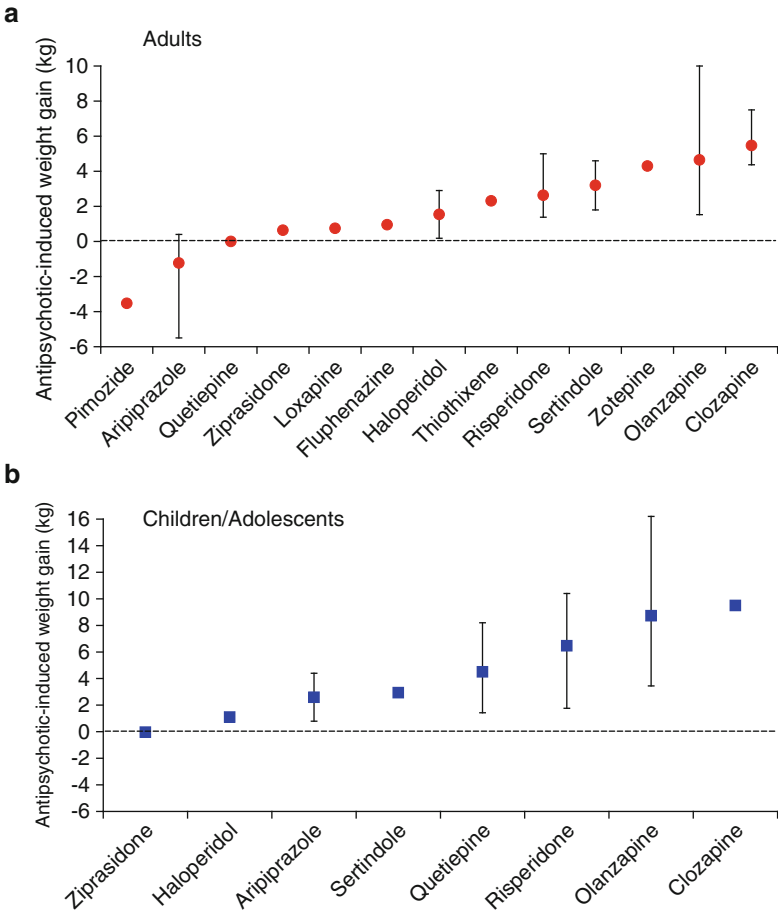

Fig. 1 Liability of various FGAs and SGAs to elicit weight gain. Data for adults are taken from studies with ≥12 week drug exposures. Ranges are shown where results were taken from several sources; Daniel et al. (1998), Allison et al. (1999b), Wetterling (2001), Ratzoni et al. (2002), Bobes et al. (2003), McQuade et al. (2004), Chrzanowski et al. (2006), Keck et al. (2007), De Hert et al. (2007), Kane et al. (2009), Correll et al. (2009), and De Hert et al. (2011a, b)

These results represent a time frame that is different from those reported by Allison et al. (1999b). Our analysis shows that clozapine, olanzapine, sertindole, zotepine, and risperidone cause the greatest weight gain in adults. Taking ≥7 % increases in bodyweight as clinically significant for cardiometabolic risk, Newcomer (2005) revealed that the percentage of subjects meeting this criterion was 41 % for olanzapine, >20 % for clozapine, 23 % for quetiapine, and 18 % for risperidone compared with 12 % for haloperidol. Similar findings were published by Bobes et al. (2003).

Mean bodyweight change data have also given rise to the misconception that certain SGAs, e.g., ziprasidone and aripiprazole, do not cause clinically significant weight gain. As reported by Newcomer (2005), 10 % of patients treated with

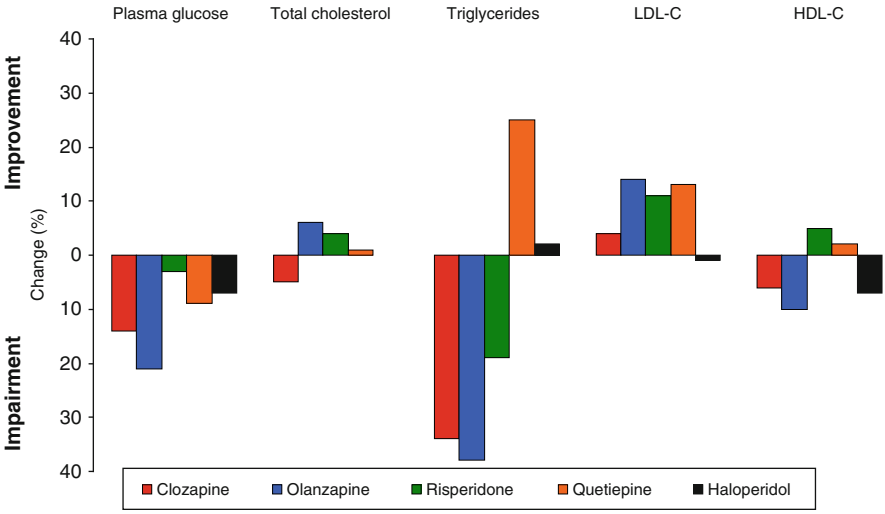

Fig. 2 Impact of various antipsychotic drugs on obesity-related cardiometabolic risk factors. Changes in the parameters are represented as percentage improvements or impairments relative to baseline. Data sourced from Wirshing et al. (2002)

ziprasidone experienced $\geq$7 % weight gain compared with 4 % of subjects on placebo. Similarly, Keck et al. (2006) reported that 13 % of patients on aripiprazole experienced $\geq$7 % weight gain compared with 0 % of control subjects.

Figure 1b shows weight change produced by antipsychotic drugs in children and adolescents. Once again, the drugs causing the greatest weight gain were clozapine and olanzapine. Since the data were taken from different sources, the assumption that clozapine induced more weight gain than olanzapine is misleading. In fact, in the trial by Fleischhaker et al. (2008), the rank order of weight gain was olanzapine $>$ clozapine $>$ risperidone. It is evident that SGAs pose a significant obesity risk in children/adolescents. Results with first-time use of SGAs in children/adolescents are even more troubling. Correll et al. (2009) reported mean increases in bodyweight after 11 weeks treatment of 4.4–8.5 kg for olanzapine, quetiapine, risperidone, and aripiprazole compared with 0.2 kg in the control group.

As obesity exacerbates cardio-metabolic risk factors, antipsychotic-induced weight gain would be predicted to have similar deleterious metabolic effects. However, the SGAs also produce unexpected changes in cardio-metabolic risk factors (Fig. 2). As examples, all of the SGAs reduce plasma LDL-C concentrations, and although clozapine, olanzapine, and risperidone increase plasma triglycerides, paradoxically quetiapine reduces them. In this regard, ziprasidone appears to be relatively benign with small reductions in both the fasting concentrations of glucose and triglycerides and no deleterious effects on waist circumference, blood pressure, or HDL-C (Meyer et al. 2008).

From this representative evidence, the SGAs have much greater propensity to induce clinically significant weight gain than the FGAs. Although some SGAs are worse than others, none is entirely devoid of risk.

4.2 Insights from Animal Models of Antipsychotic-Induced Weight Gain

There has been considerable debate on whether rodent models of antipsychotic-induced weight gain have "construct" and "translational" validity. This is because antipsychotics causing weight gain in humans frequently do not produce this effect in rodents and vice versa. During the development of sibutramine (Meridia®, Reductil®) in the late 1990s, we explored rodent models of neuroleptic-induced weight gain at a very early stage to evaluate whether this antiobesity drug would be effective in treating this adverse event.

We employed adult, outbred (Sprague–Dawley or Wistar), female rats maintained on reversed-phase lighting with free access to high fat diet. The rationale for selecting females was because they are relatively weight stable and a high fat diet was chosen as schizophrenia patients often eat unhealthy "junk food" (Brown et al. 1999). Although in many respects, the experimental conditions that we employed appear very similar to those used by other research groups, as will be discussed in this section, the subtle differences can have a substantial impact on the experimental outcome. The results from published studies and our own work on antipsychotic-induced weight gain in rodents, together with some of the key experimental conditions employed, are reported in Table 1.

As shown in Table 1 and Fig. 3b, administration of olanzapine to female rats consistently produces increases in bodyweight, and in some experiments, hyperphagia and/or increased adiposity. In many of these studies, the translational validity of the model has been tested using ziprasidone, one of the SGAs with the lowest propensity to cause weight gain in the clinic, as the negative control. Although ziprasidone has been reported not to increase the bodyweights of rats and mice in a substantial number of studies, weight gain has been observed in others (Table 1; Fig. 3c). It is important to note that this is often dependent on the dose used and duration of treatment (Fig. 3c). Various other FGAs and SGAs, e.g., haloperidol, sulpiride, and risperidone that cause moderate weight gain have also been studied in rodents. Again, the data are conflicting with most researchers observing weight gain, but a significant minority reporting either no effect or a mixed outcome (Table 1). The effects of these antipsychotics on the comorbid endpoints of hyperphagia and increased adiposity were similarly inconsistent across studies (Table 1). Clozapine is associated with a high risk of substantial weight gain (Allison et al. 1999b; Newcomer 2005), and although it has not been extensively investigated, its effects on hyperphagia, weight gain, and adiposity have also been determined in female rats. Cooper et al. (2008) investigated a wide range of doses (Table 1) and observed that this SGA did not increase bodyweight; at some doses, it even caused weight loss without altering food intake. The only reported adverse metabolic outcome was increased adiposity at certain doses (Cooper et al. 2008). In our model, we also found that clozapine did not cause weight gain but did produce hyperphagia when given acutely (Fig. 3a). Only at very high doses which caused sedation, was weight loss observed (Fig. 3a). Although such findings have

Table 1 Summary of the findings from various rodent models of antipsychotic weight gain

Female rats (juvenile)							
Drug	Dose and route	Duration	Diet	Weight	Hyperphagia	Adiposity	Author
Haloperidol	0.5 mg/kg ip	21 days	HF	↑	±	↑	Fell et al. (2005b)
Olanzapine	4 mg/kg ip	21 days	HF	↑	±	↑	
Risperidone	0.5 mg/kg ip	21 days	HF	↑	±	↑	
Sulpiride	10 mg/kg ip	21 days	HF	↑	↑	↑	
Ziprasidone	2.5 mg/kg ip	21 days	HF	±	±	±	
Female rats							
Drug	Dose and route	Duration	Diet	Weight gain	Hyperphagia	Adiposity	Author
Olanzapine	2 mg/kg ip	22 days	CD	↑	↑	↑ (NS)	Fell et al. (2007)
Risperidone	0.5 mg/kg ip	22 days	CD	±	±	±	
Ziprasidone	2.5 mg/kg ip	22 days	CD	±	±	±	
Olanzapine	0.5, 1, 4 mg/kg ip	21 days	SLC	↑	↑	↑	Fell et al. (2004a)
Olanzapine	2 mg/kg ip	28 days	HF	↑/↓	↑/↓	±	Fell et al. (2008)
Risperidone	0.5 mg/kg ip	28 days	HF	↑/±	↑/↓	±	
Ziprasidone	2.5 mg/kg/ip	28 days	HF	±	±	±	
Olanzapine	1, 2, 4 mg/kg ip bid	20 days	SLC	↑	↑/±	↑/±	Cooper et al. (2005)
Olanzapine	4 → 20 mg/day po	33 days	SLC	↑	↑	↑	Albaugh et al. (2006)
Clozapine	4 → 8 mg/day po	13 days	SLC	±	ND	±	
Olanzapine	1.75 mg/day sc osmotic pump	28 days	SLC	↑	↑	↑	Lykkegaard et al. (2008)
Clozapine	0.25–0.5, 1–4, 6, 12 mg/kg ip bid	20 days	SLC	↓	±	↑	Cooper et al. (2008)
Olanzapine	3 mg/kg po	21 days	HF	↑	↑	ND	RenaSci
Clozapine	1, 3, 10 mg/kg po	21 days	HF	±	↑	ND	
Ziprasidone	3, 10 mg/kg po	21 days	HF	↑/±	±	ND	
Haloperidol	0.1, 0.5, 1.0 mg/kg ip	21 days	SLC	↑	±	ND	Fell et al. (2004b)
Risperidone	0.1, 0.5, 1.0 mg/kg ip	21 days	SLC	↑	↑	ND	
Ziprasidone	1, 2.5 mg/kg ip	28 days	SLC	±	±	ND	Fell et al. (2005a)
Olanzapine	1.75 mg/day sc osmotic pump	14 days	SLC	↑	↑	ND	Wallingford et al. (2008)

(continued)

Table 1 (continued)

Olanzapine	3 mg/kg po bid	24 days	SLC	↑	↑	ND	Stefanidis et al. (2009)
Olanzapine	5, 20 mg/kg po	7 days	LP	↑	±/↑	ND	Pouzet et al. (2003)
Haloperidol	0.08, 0.31 mg/kg po	7 days	LP	↑	±	ND	
Sulpiride	20 mg/kg ip	21 days	HF	↑	↑ (?)	ND	Baptista et al. (1998)
Risperidone	0.5 mg/kg	12 days	HF	↑	↑	ND	Baptista et al. (2002a)
Sulpiride	20 mg/kg	12 days	HF	↑	↑	ND	
Olanzapine	2 mg/kg po bid	7 days	SLC	↑	ND	ND	Kalinichev et al. (2006)
Ziprasidone	2, 6, 10 mg/kg po bid	7 days	SLC	↑	ND	ND	
Olanzapine	4 mg/kg ip bid	20 days	SLC	↑	ND	ND	Goudie et al. (2002)
Male rats							
Drug	Dose and route	Duration	Diet	Weight	Hyperphagia	Adiposity	Author
Risperidone	0.125, 0.25, 0.5 mg/kg sc	16 days	HF	±	±	ND	Baptista et al. (2002a)
Clozapine	10 mg/kg sc	28 days	SLC	↓	↓	±	Smith et al. (2008a)
Haloperidol	0.25 mg/kg sc	28 days	SLC	↓	↓	±	
Quetiapine	10 mg/kg sc	28 days	SLC	±	±	↑	
Sulpiride	20 mg/kg ip	21 days	HF	±	±	±	Baptista et al. (2002b)
Olanzapine	5, 20 mg/kg po	21 days	LP	±/↓	±	ND	Pouzet et al. (2003)
Haloperidol	0.08, 0.31 mg/kg po	21 days	LP	±	±	ND	
Olanzapine	1, 2, 4 mg/kg ip bid	20 days	SLC	↓	±	↑	Cooper et al. (2007)
Olanzapine	0.1, 0.5 2 mg/kg po in diet	42 days	MF	↑	↑	ND	Minet-Ringuet et al. (2006)
Olanzapine	1 mg/kg po in diet	21 says	MF	↑	↑	ND	
Ziprasidone	10 mg/kg po in diet	21 days	MF	±	±	ND	
Haloperidol	1 mg/kg po in diet	21 days	MF	±	±	ND	
Olanzapine	1 mg/kg po in diet	35 days	MF	±	ND	↑	Minet-Ringuet et al. (2007)
Ziprasidone	10 mg/kg po in diet	35 days	MF	±	ND	±	
Haloperidol	1 mg/kg po in diet	35 days	MF	±	ND	±	
Olanzapine	5, 7.5,10 mg/kg po in diet	42 days	MF	↑/±	↑/±	↑	Shobo et al. (2011a)
Olanzapine	0.5, 1,2 mg/kg in diet	Acute	SLC	ND	↑	ND	

Ziprasidone	1.25, 2.5, 5 mg/kg in diet	42 days	MF	±	±	±	
Ziprasidone	0.3, 1, 3 mg/kg ip	Acute	SLC	ND	±	ND	
Female mice							
Drug	Dose and route	Duration	Diet	Weight gain	Hyperphagia	Adiposity	Author
Olanzapine	6 mg/kg po bid	28 days	SLC	↑	↑	↑	Cope et al. (2005)
Quetiapine	15, 30 mg/kg po bid	28 days	SLC	↑	↑	±	
Risperidone	0.125, 0.25 mg/kg po bid	28 days	SLC	↑	↑	±	
Ziprasidone	7, 10.5 mg/kg po bid	28 days	SLC	↑	↑	±	
Olanzapine	4 → 8 mg/day po	18 days	SLC	±	ND	ND	Albaugh et al. (2006)
Clozapine	4 → 8 mg/day po	18 days	SLC	±	ND	ND	
Risperidone	4 mg/kg po bid	21 days	LF	↑	↑	ND	Cope et al. (2009)
Male mice							
Drug	Dose and route	Duration	Diet	Weight gain	Hyperphagia	Adiposity	Author
Olanzapine	1.0, 1.5 mg/kg sc osmotic pump	42 days	MF	±	±	±/↑	Shobo et al. (2011b)

ND not determined, ± no change, ↑ increase, ↓ decrease, *SLC* standard laboratory chow, *HF* high fat diet, *MF* medium fat diet, *CD* cafeteria diet.

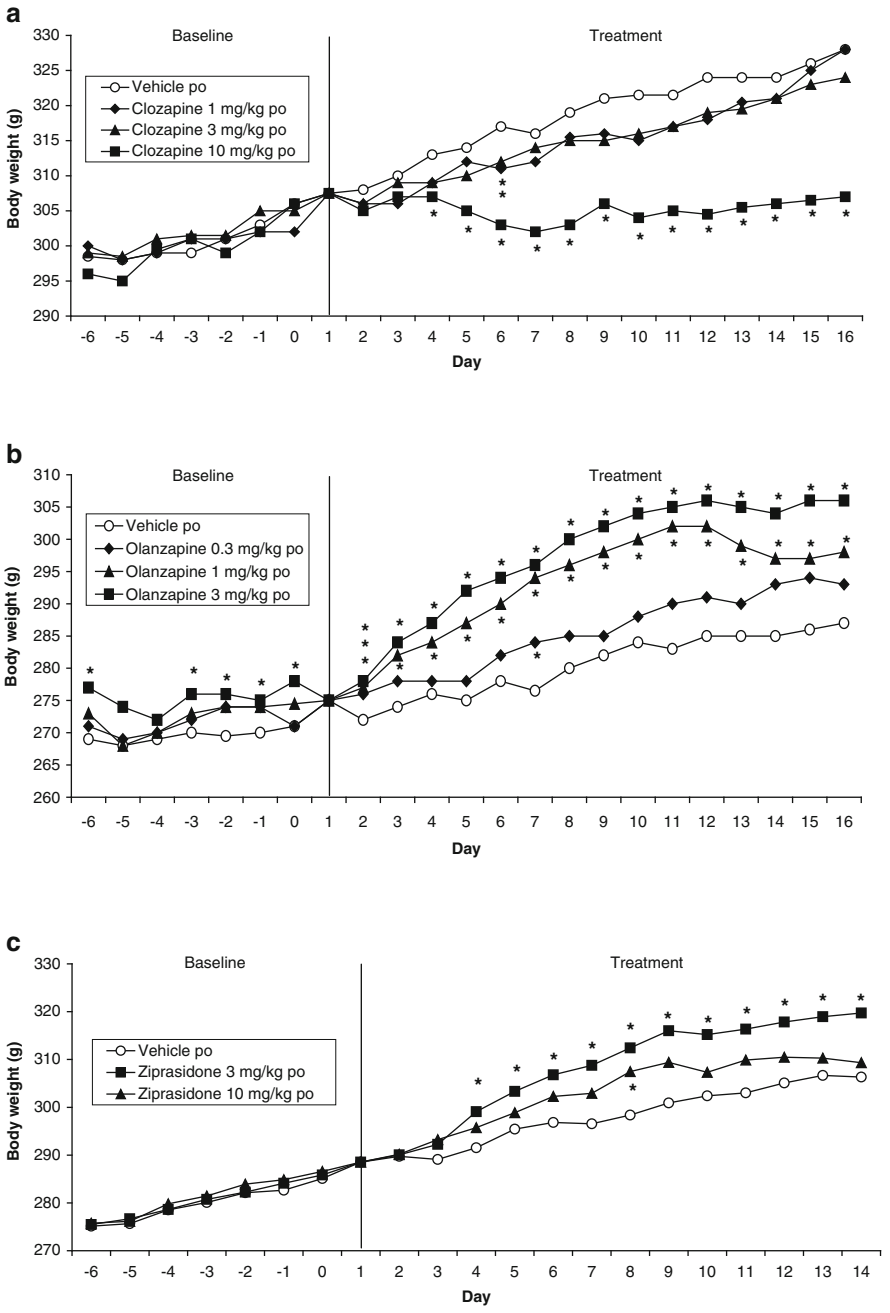

Fig. 3 Effects of repeated administration of (**a**) clozapine, (**b**) olanzapine, or (**c**) ziprasidone on bodyweight in female rats maintained on a high fat diet. Female rats were maintained in reversed-phase lighting and on a high fat diet. Drug treatment commenced Day 1. Results are adjusted means; $n = 10$. Data analyzed by ANCOVA with bodyweight on Day 1 as covariate. Multiple comparisons versus control group by Dunnett's test. Significant differences versus controls $^*p < 0.05$. Data on file RenaSci

prompted many researchers to dismiss rodent models as having little value in predicting the effects of antipsychotic drugs on weight, differences in protocols may have influenced experimental outcomes and contributed to the inconsistencies in the data. In addition to defining the optimal experimental conditions, this analysis has also examined the results to determine whether there are more predictive outcomes than simply measuring changes in bodyweight.

With the exception of studies published by Cope et al. (2005, 2009), Albaugh et al. (2006) and Shobo et al. (2011b), all experiments on weight gain have been conducted in rats. Although data in mice are limited, the observation that all antipsychotics, including ziprasidone, induced weight gain and hyperphagia (Cope et al. 2005) together with the finding that olanzapine failed to induce weight gain in two studies (Albaugh et al. 2006; Shobo et al. 2011b) clearly indicates that there is less differentiation between adverse metabolic actions of antipsychotic drugs in the mouse than in the rat.

When female rats are used, olanzapine consistently produces increases in bodyweight, and in the majority of studies, weight gain is observed with antipsychotics that have a moderate liability for weight gain in humans, e.g., risperidone, haloperidol, and sulpiride. The credibility of the model is generally questioned because ziprasidone has been reported to increase bodyweight or to produce equivocal outcomes (Table 1; Fig. 3c). Clozapine appears to be the most serious anomaly in the model. It causes weight gain in humans, but although it caused hyperphagia, it did not cause weight gain in our hands (Fig. 3a). It has even been reported to induce weight loss (Cooper et al. 2008). Although there are some notable dissentions (Shobo et al. 2011a, b), the majority view is that male rats are not suitable for modeling the effects of antipsychotic drugs on bodyweight because olanzapine and many other antipsychotics known to produce weight gain in man fail to produce this effect in them (Table 1).

The choice of dose, dosing intervals, route of administration, and duration of treatment are all factors that potentially influence experimental outcomes. A wide range of dose routes has been employed including oral, intraperitoneal and subcutaneous, with the drugs being given as discrete doses once or twice daily, or continuously by mixing the drug in the animals' food or via osmotic mini-pumps. The duration of dosing ranged between 7 and 42 days. From the data in Table 1, weight gain with olanzapine has been observed across a wide range of doses and dosing routes. Furthermore, changes in these variables do not provide an obvious explanation for the discordant findings obtained with ziprasidone and antipsychotic drugs that evoke moderate weight gain in humans. However, the duration of dosing does appear to have a significant influence on the outcome. Thus, in the case of ziprasidone, although some initial weight gain does occur in rats, tolerance tends to develop later in the study (Figure 3c), and for this reason drugs should be administered for a period of at least 14 days. With the exception of Fell et al. (2008), all studies report that excessive weight gain is maintained throughout treatment with antipsychotics that cause weight gain in humans. In several studies, (e.g., Pouzet et al. 2003; Cooper et al. 2005), the effects of the antipsychotic drugs on bodyweight and related comorbidities show an inverted U-shaped dose

relationship, which is discussed later. When administered once daily, we observed that the lighting phase influenced the actions of antipsychotic drugs on food intake. When female rats were maintained on reversed-phase lighting and drugs were administered just prior to the dark cycle, they induced hyperphagia, but this effect disappeared when rats were dosed prior to the light cycle. Rats are predominantly nocturnal feeders and these drugs have their greatest effect when given before the animals consume most of their daily diet.

On the basis of the results in Table 1, increased bodyweight in rats is not predictive of whether antipsychotics have potential to cause weight gain in humans. On the basis of the results presented in Table 1, an increase in bodyweight is not a definitive endpoint to determine whether antipsychotic drugs have the potential to cause weight gain in humans. Based on results obtained with olanzapine, antipsychotics with the potential to cause marked weight gain in humans will induce weight gain in rats, together with hyperphagia and/or increased adiposity. Other factors that distinguish olanzapine from antipsychotics with a lower propensity to cause obesity are increased weight gain in rodents across a range of doses and no evidence of tolerance to weight enhancement when the drug is given for prolonged periods. Conversely, antipsychotics with lower potential to induce obesity in humans, e.g., risperidone, haloperidol, and sulpiride, generally induce some degree of weight gain in rodents without producing hyperphagia or increased adiposity. The data reveal that female rats are more susceptible to the weight enhancing actions of antipsychotic drugs than males, but on the other hand, the possibility that hyperphagia will be recorded for an antipsychotic that causes moderate weight gain in humans is increased.

Reduced energy expenditure and/or decreased basal metabolic rate also significantly contribute to weight gain and there is evidence to show that both are influenced by antipsychotic administration. Stefanidis et al. (2009) reported that olanzapine produced a sustained increase in the bodyweight of female rats during 23 days treatment, even though hyperphagia was only apparent for ten of them. However, dark-phase activity and non-shivering thermogenesis in brown adipose tissue were decreased (Stefanidis et al. 2009). Similarly, risperidone-induced weight gain in female mice was associated with increased food intake and reduced locomotor activity (Cope et al. 2009).

Returning to the lack of dose-dependency for the actions of some antipsychotics on bodyweight, because changes in bodyweight are mediated by the effects of these drugs on feeding, locomotor activity and metabolic rate, it is probable that the relative contribution of each varies according to the dose of antipsychotic thereby accounting for the lack of a linear dose-response relationship. For example, although a sedative dose of a SGA is likely to reduce exercise and basal metabolic rate, it may also reduce food intake to such an extent that weight loss not gain occurs.

Finally, when assessing the translational validity of the models, it is important to define the positive and negative control responses. Ziprasidone is mostly used as a comparator with no propensity to cause weight gain in humans. Whilst this assessment is correct based on average data, in reality this drug simply causes less weight gain than most other antipsychotics. Furthermore, there is a significant minority of

ziprasidone-treated subjects whose weight increases substantially (Simpson et al. 2005; Hoffmann et al. 2010).

After taking all of these factors into account, the hypothesis that antipsychotic-induced weight gain in humans can be modeled by measuring the effects of these drugs on bodyweight in rodents must be treated with caution. However, olanzapine-induced weight gain in female rats is dose-dependent, and persistent. In addition, olanzapine and clozapine have been reported to induce hyperphagia when given acutely and increased adiposity when given repeatedly. We hypothesize that if these additional endpoints are employed, particularly induction of hyperphagia, the predictive validity of the model would be much improved. Although not definitively proven, the results in Table 1 suggest that by employing all three criteria, olanzapine can be differentiated not only from ziprasidone but also from antipsychotics that have the potential to cause moderate weight gain.

4.3 Antipsychotic Drugs and Type 2 Diabetes

The negative impact of the FGAs and SGAs on glycemic control can be subclassified into at least two major categories:

1. Indirect induction/exacerbation of hyperinsulinemia and insulin resistance/impaired glucose tolerance (prediabetes) as a secondary consequence of antipsychotic-induced weight gain and dyslipidemia.
2. The idiosyncratic, de novo induction of type 2 diabetes (possibly leading to DKA) by antipsychotic drugs.

Mechanisms responsible for these aspects of impaired glycemic control are probably not identical and reflect multiple pharmacological actions.

There is an increased risk of developing insulin resistance, impaired glucose tolerance, or type 2 diabetes with FGA treatment (Scheen and de Hert 2007; Smith et al. 2008b; De Hert et al. 2008; Yood et al. 2009; Nielsen et al. 2010; Vidarsdottir et al. 2010). A meta-analysis of 11 studies reported that overall relative risk for type 2 diabetes was higher for SGAs compared with FGAs (Smith et al. 2008b). De Hert et al. (2008) reported significantly more subjects with abnormal glucose levels after treatment with SGAs compared with FGAs. However, Nielsen et al. (2010) did observe that the hazard ratio for developing type 2 diabetes was similar for midpotency FGAs compared with clozapine or olanzapine and the chance of developing the disease within 3 months of treatment initiation was similar for low-potency FGAs and the SGAs. Part of the reason for this apparent discordance is because some analyses grouped all SGAs into a single cohort and there are marked differences between them in terms of adverse effects on glycemic control (Table 2). Clozapine and olanzapine have the greatest adverse impact on glycemic control and pose the highest risk of causing type 2 diabetes (Wirshing et al. 2002; Scheen and de Hert 2007; Yood et al. 2009; Nielsen et al. 2010; Newcomer 2005). Ziprasidone and aripiprazole are relatively benign in terms of adverse effects on glycemic control (Newcomer 2005; Scheen and de Hert 2007; Yood et al. 2009;

Nielsen et al. 2010). With midranked SGAs, i.e., quetiapine and risperidone, some studies demonstrate that their negative influence on glycemic control is not substantially different from olanzapine and clozapine (Scheen and de Hert 2007; Lambert et al. 2006), whilst others reported it was similar to the low risk SGAs or the FGAs (Wirshing et al. 2002; Yood et al. 2009).

Obesity is a major causal factor in pre-diabetes and Type 2 diabetes across the whole of the demographic range and it can, therefore, be concluded that antipsychotic-induced weight gain contributes to the increased incidence of glycemic dysregulation in subjects treated with SGAs. This view is supported by the observation that clozapine and olanzapine are not only the SGAs with the greatest liability for weight gain, but also are the most likely to produce glycemic dysregulation and Type 2 diabetes. Although there is a reasonably good association between weight gain and adverse changes in glycemic control and/or newly diagnosed type 2 diabetes (Scheen and de Hert 2007; Haupt et al. 2007; Kim et al. 2010), BMI is thought to contribute only 25–33 % of the variance in insulin resistance in patients treated with SGAs (Kim et al. 2010). Kim et al. (2010) observed that although the slopes of the linear correlation between fasting plasma glucose concentration and BMI were not significantly different for individuals on risperidone or aripirazole compared with controls, the curve for olanzapine deviated significantly, indicating it has a weight-independent action to increase insulin resistance. Where obesity is not linked to drug treatment, progression of insulin resistance and impaired glucose tolerance to type 2 diabetes generally takes several years. Evidence for SGAs as an independent causal factor in the development of glycemic disturbances comes from the finding that many cases of hyperglycemia occur within 6 weeks of starting antipsychotic treatment (Cohen 2004; Newcomer 2005; Saddichha et al. 2008), development of type 2 diabetes is most prevalent in the first 6 months (Cohen 2004), and the disease is frequently reversible when antipsychotic drugs are switched or discontinued (Cohen 2004; De Hert et al. 2007).

Possible direct effects of SGAs on glycemic control have been investigated by hyperinsulinemic/euglycemic clamp studies in human volunteers (Sowell et al. 2002, 2003; Sacher et al. 2008; Vidarsdottir et al. 2010), where they were infused with high levels of insulin to promote glucose tissue disposition together with glucose to maintain plasma glucose concentration. Although the data are not totally consistent, the evidence indicates that SGAs directly impair glycemic control. Vidarsdottir et al. (2010) compared the effects of 8 days administration of the SGA, olanzapine, against the FGA, haloperidol, in young healthy male volunteers. Neither drug altered bodyweight or fasting plasma insulin or FPG. However, in a hyperinsulinemic clamp experiment, subjects receiving olanzapine had significantly decreased glucose uptake, indicating it reduced insulin action and glucose disposal. Haloperidol was without effect. These results suggested that olanzapine impaired glycemic control by a rapid mechanism independent of weight gain. Sacher et al. (2008) compared the effect of 10 days administration of olanzapine or ziprasidone in young healthy male volunteers. At the end of treatment, there was a small (0.6 kg) weight increase in the olanzapine subjects but no change in the ziprasidone group. Fasting plasma concentrations of insulin, but not glucose, were increased by olanzapine. Olanzapine decreased glucose uptake in a hyperinsulinemic clamp, indicating reduced insulin

Table 2 Relative liability of various atypical antipsychotics to cause type 2 diabetes and diabetic ketoacidosis (DKA)

	Warning in the product label		Number of cases[a]			Odds ratio relative to:	
Antipsychotic drug	Hyperglycemia	Diabetes	Type 2 diabetes	DKA	Deaths	FGAs	No drug
Clozapine (Clozaril®)	Yes	Yes	384 (323)[b]	73[b]	23[b]	1.37[c]	7.44[c]
Olanzapine (Zyprexa®)	Yes	Yes	237 (188)[b]	80[b]	15[b]	1.26[c]	2.31[c]
Risperidone (Risperdal®)	Yes	Yes	131 (78)[b]	16[b]	4[b]	1.07[c]	1.20[c]
Quetiapine (Seroquel®)	Yes	Yes	46 (34)[b]	21[b]	11[b]	1.22[c]	1.00[c]
Ziprasidone (Geodon®)	Yes	Yes	ND	0	ND	ND	ND
Aripiprazole (Abilify®)	Yes	Yes	ND	2[d,e]	ND	ND	ND

ND no data, *FGA* first-generation antipsychotic.
[a]Number of de novo cases of type 2 diabetes shown in parentheses.
[b]*Sources*: Newcomer (2005).
[c]Newcomer (2007a, b).
[d]Church et al. (2005).
[e]Reddymasu et al. (2006).

sensitivity and impaired glucose disposal. None of these parameters was altered by ziprasidone, consistent with other findings (Newcomer 2005; Scheen and de Hert 2007; Yood et al. 2009; Nielsen et al. 2010; Vidarsdottir et al. 2010). Sowell et al. (2002) administered olanzapine or risperidone to adults for 15–17 days where they increased bodyweight by ~3 kg and the fasting plasma concentration of insulin but not glucose compared with the placebo group. In a hyperglycemic clamp study, insulin secretion was not impaired by administration of either olanzapine or risperidone. However, insulin sensitivity was reduced 18 % by both drugs, although only olanzapine's effect was statistically significant. Impaired insulin responsiveness and increased fasting insulin support the hypothesis that these SGAs adversely affect glycemic control. Decreased insulin responsiveness and increased fasting plasma insulin concentrations correlated with bodyweight (Sowell et al. 2002), but of itself this does not imply causality, only that SGAs are responsible for both metabolic effects. Olanzapine and risperidone were administered for 21–23 days to healthy volunteers before a hyperinsulinemic clamp (Sowell et al. 2003) and they increased weight by 1.6–2.0 kg. Olanzapine raised fasting plasma insulin and glucose compared with baseline. No changes in glucose uptake were observed in the clamp experiment, but enhanced excursions of meal-induced plasma insulin and glucose were found. Experience of treating first episode psychosis with SGAs mirrors human volunteer studies with reports of clinically meaningful increases in fasting plasma concentrations of glucose and insulin (De Hert et al. 2008; Graham et al. 2008).

The minority of studies where glycemic markers were measured in children/adolescents do not reveal substantial metabolic disturbances (De Hert et al. 2011a).

The risk of schizophrenia patients developing DKA whilst taking SGAs is high for clozapine and olanzapine, moderate for risperidone and quetiapine, and low for ziprasidone and aripiprazole (Table 2). The pharmacological mechanism of the SGAs that is responsible for progression of diabetes to DKA is unlikely to be mediated via weight gain or insulin resistance. It is more likely to be a direct action that rapidly suppresses insulin secretion in susceptible individuals. There is a substantial amount of clinical evidence to support this view. Several studies have reported that pancreatic β-cell function is impaired in schizophrenic subjects and certain SGAs, e.g., clozapine and olanzapine, can further suppress insulin secretion (Henderson et al. 2005a; Cohn et al. 2006; Chiu et al. 2006).

4.4 Insights from Animal Models on the Effects of Antipsychotic Drugs, Pancreatic β-Cell Function and Glycemic Control

Olanzapine and clozapine, but not risperidone or ziprasidone, dose dependently antagonized the carbachol enhancement of glucose-stimulated insulin release from perifused pancreatic islets in vitro; an effect mediated by muscarinic M_3 antagonism (Johnson et al. 2005). In contrast, none of the antipsychotics altered pancreatic insulin secretion in response to normal physiological concentrations of glucose (Johnson et al. 2005; Melkersson and Jansson 2005). In vitro studies have demonstrated that some drugs, particularly clozapine, reduced insulin-stimulated glucose uptake into adipocytes (Vestri et al. 2007). Although *in vitro* experiments have shown that various antipsychotic drugs do not influence glucose-stimulated insulin release from rat pancreatic islets, there is compelling *in vivo* evidence to demonstrate that they have direct actions that have a substantial influence on the release of insulin. In hyperglycemic clamp experiments (Chintoh et al. 2009), clozapine and olanzapine reduced insulin secretion, whilst ziprasidone reduced the first phase of this response. Therefore although pancreatic insulin secretion was normal in response to a physiological glucose concentration (~8.0 mM) (Johnson et al. 2005; Melkersson and Jansson 2005), when faced with a glucose load, β-cell function was clearly impaired (Chintoh et al. 2009).

In vivo hyperinsulinemic/euglycemic clamp experiments and complementary in vitro studies showed that acute administration of various antipsychotics, particularly clozapine and olanzapine, increased peripheral insulin resistance (Vestri et al. 2007; Houseknecht et al. 2007; Chintoh et al. 2009). Houseknecht et al. (2007) reported that clozapine, not other atypical antipsychotics, reduced insulin-stimulated glucose uptake into skeletal muscle in vitro but increased glucose uptake into liver and adipocytes. In contrast, Vestri et al. (2007) reported that clozapine and risperidone decreased insulin-stimulated glucose uptake into adipocytes. Clozapine and olanzapine, but not risperidone, ziprasidone, or haloperidol, were also shown to increase hepatic glucose production in vivo (Houseknecht et al. 2007; Chintoh et al. 2009). Various antipsychotics, especially clozapine, reduced insulin-stimulated

glucose uptake into skeletal muscle in vivo (Houseknecht et al. 2007; Chintoh et al. 2009). Savoy et al. (2010) showed antipsychotic-induced increases in plasma glucose to be inhibited by the ganglionic blocker, hexamethonium, indicating central activation of the sympathetic nervous system to the liver (Savoy et al. 2010) and/or muscarinic antagonism of parasympathetic drive (Houseknecht et al. 2007).

The results reveal a multiplicity of mechanisms whereby atypical antipsychotics could cause glycemic dysregulation, e.g., increased peripheral insulin resistance, enhanced hepatic glucose production, and reduced pancreatic insulin secretion. Although clozapine, olanzapine, and possibly risperidone appear to carry the greatest risk, other antipsychotic drugs may not be free of safety concerns.

Adverse effects after acute exposure to certain antipsychotics do not appear to ameliorate on repeated treatment. Experiments have investigated the effect of repeated administration where no weight gain occurred, providing insights into their direct effects on glycemic control and also where increased weight and adiposity did contribute to the adverse metabolic effects.

Male rats have generally been used in these experiments because they are generally resistant to the weight promoting effects of the FGAs and SGAs. However, not all studies in female rats have observed weight gain with antipsychotic drugs and they have also made a significant contribution to research in this area. Chintoh et al. (2008) infused olanzapine for 29 days in female rats, and although there was no hyperphagia or weight gain, increased visceral adiposity occurred. Using a hyperinsulinemic/euglycemic clamp, prolonged olanzapine treatment increased hepatic glucose production and decreased peripheral glucose utilization, indicating reduced sensitivity to insulin. In contrast to clinical data, hyperglycemic clamp experiments revealed no increase in insulin secretion, but this is consistent with in vitro observations with olanzapine (Johnson et al. 2005). Cooper et al. (2007) administered olanzapine for 20 days to male rats, which did not increase bodyweight or alter fasting plasma concentrations of glucose or insulin. Although these experiments suggested olanzapine had no deleterious effect on glycemic control independent of weight gain, more sensitive measures of glycemic control, e.g., glucose or insulin challenge tests, were not performed. Several other SGAs, including risperidone, quetiepine, and clozapine, did not induce weight gain in male rats (Baptista et al. 1998, 2002a, b; Smith et al. 2008a, 2009). Glucose tolerance tests revealed that repeated administration of sulpiride, quetiapine, or clozapine, but not risperidone, enhanced plasma glucose and insulin (Baptista et al. 1998, 2002a, b; Smith et al. 2008a, 2009). These results demonstrate that antipsychotic drugs impair glucose tolerance and decrease insulin action, consistent with clamp experiments (Chintoh et al. 2008). Risperidone was the exception because no impairment of glucose tolerance was observed after repeated administration (Baptista et al. 2002a).

Studies where antipsychotics produced weight gain have been mostly performed in female rats. The findings are similar to those where bodyweight was not increased. Repeated administration of olanzapine increased fasting insulin concentrations in female rats (Cooper et al. 2005; Albaugh et al. 2006; Lykkegaard et al. 2008) and male mice (Coccurello et al. 2009). Increased insulin resistance (Cooper et al. 2005; Coccurello et al. 2009) and impaired glucose tolerance were

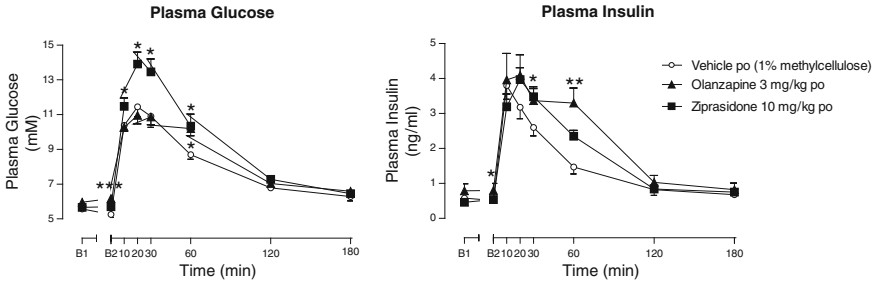

Fig. 4 Effects of repeated administration of olanzapine or ziprasidone on glucose tolerance of female Sprague–Dawley rats maintained on a high fat diet. Female rats were maintained in reversed-phase lighting on a high fat diet. After an overnight fast, (Day 15 of dosing) a baseline blood sample was taken, followed 15 min later by vehicle/drug. A second sample was collected after ~45 min followed by oral glucose challenge (2 g/kg D-glucose). Results are means adjusted for differences in bodyweight on Day 1 and bleeding order ± SEM, $n = 10$. Multiple comparisons versus controls were by a multiple t-test for olanzapine and a Williams' test for ziprasidone. Significant differences versus controls $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$. Data on file RenaSci

also found (Albaugh et al. 2006; Lykkegaard et al. 2008; Coccurello et al. 2009). In obese animals, risperidone, quetiapine, and clozapine all impaired glucose tolerance (Baptista et al. 2002a; Smith et al. 2009). Sulpiride was the exception because although it produced significant weight gain, an oral glucose tolerance test revealed a decrease in the excursion of plasma glucose with no change in plasma insulin (Baptista et al. 2002a). In our laboratory, we repeatedly administered olanzapine, which caused significant weight gain, and ziprasidone, which did not. After 15 days, both SGAs increased fasting plasma insulin and impaired glucose tolerance (Fig. 4). However, with olanzapine, the dysregulation was predominantly due to increased plasma insulin, whereas ziprasidone caused a marked increase of plasma glucose (Fig. 4).

Smith et al. (2009) observed that perturbations in glycemic control caused by quetiapine and clozapine were reversed after 7 days of their withdrawal.

In summary, SGAs have rapid and direct actions to impair glycemic control by mechanisms independent of weight gain. However, increased adiposity and obesity resulting from repeated administration exacerbate the dysregulation in glycemic control.

5 Drug Treatments for Antipsychotic-Induced Metabolic Dysregulation

5.1 Clinical Data

A wide range of pharmacological interventions to manage antipsychotic-induced weight gain have been studied. However, the relatively small size of many studies

is a major difficulty in assessing their relative efficacy. A meta-analysis of 32 placebo-controlled, clinical trials showed that only 5 of 14 drugs produced significant weight loss, i.e., the antiobesity drugs, sibutramine, *d*-fenfluramine, and topiramate, the insulin sensitiser, metformin, and the selective noradrenaline reuptake inhibitor, reboxetine. The average placebo-subtracted weight reductions produced by these drugs was 2.0–3.0 kg (Maayan et al. 2010). However, weight loss was enhanced when drug treatment was combined with behavioral therapy (Wu et al. 2008). In addition to reductions in abdominal obesity, weight-related improvements in glycemic control and plasma lipid profiles were reported (Maayan et al. 2010). The effect of stimulant medication in children and adolescents with ADHD, who were receiving SGAs for management of their behavioral disorders, has been determined (Penzner et al. 2009). The stimulants did not reduce weight gain or improve other cardio-metabolic risk factors. Since stimulants decrease food intake by enhancing adrenergic and dopaminergic neurotransmission, while antipsychotics are potent D_2 and α_1-adrenergic receptor antagonists (Peroutka et al. 1977; Svensson 2003), this outcome is consistent with their mutually antagonistic pharmacological properties.

Overall, where positive effects were reported with drug treatments, reductions in bodyweight have been relatively modest. In most instances when used as a preventative measure, the drugs did not abolish antipsychotic weight gain, and when used to treat the condition they failed to return weight to its starting-point. These data clearly reveal a significant unmet need especially when two of the clinically effective drugs, i.e. sibutramine and *d*-fenfluramine, have now been withdrawn.

5.2 Insights from Animal Models

Olanzapine-induced weight gain in rats has been used to predict the efficacy of various drugs to prevent antipsychotic-induced weight gain. The potential usefulness of sibutramine is consistent with reports that it is only moderately effective clinically (Henderson et al. 2005b; Maayan et al. 2010) as it only partially prevented olanzapine-induced weight gain in female rats on a high fat diet (Fig. 5a). Since increased noradrenergic neurotransmission via α_1-adrenoceptors plays a major role in sibutramine's action (Jackson et al. 1997) and antipsychotics are generally potent α_1-adrenergic antagonists (Peroutka et al. 1977; Svensson 2003), these conflicting pharmacological mechanisms explain its limited efficacy. We have shown that the 5-HT_6 partial agonist, E-6837, not only abolished olanzapine-induced weight gain in female rats, but also markedly reduced bodyweight below baseline (Heal et al. 2008; Fig. 5b).

Lyraglutide abolished olanzapine-induced weight gain in female rats but did not reduce bodyweight below baseline values (Lykkegaard et al. 2008). This glucagon-like peptide (GLP)-1 agonist also prevented olanzapine-induced increased insulin resistance (Lykkegaard et al. 2008). The anticonvulsant, zonisamide, and the SSRI, fluoxetine, prevented olanzapine-induced increases in both weight (Wallingford

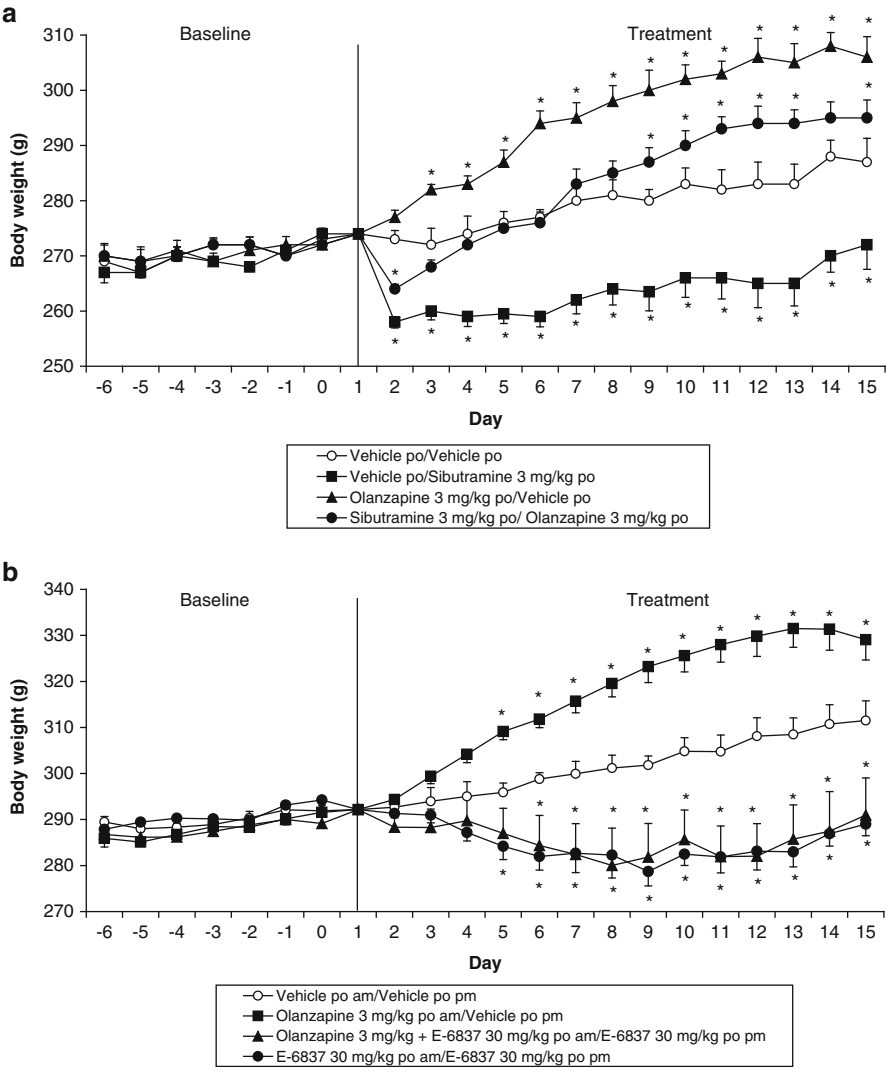

Fig. 5 Effect of repeated administration of (**a**) sibutramine or (**b**) the 5-HT_6 receptor partial agonist, E-6837, on olanzapine-induced weight gain in female rats maintained on a high fat diet. Female rats were maintained on reversed-phase lighting regime and a high fat diet. Drug treatment commenced Day 1. Results are adjusted means; $n = 10$. SEMs are calculated from residuals of the statistical model. Data analyzed by ANCOVA with bodyweight on Day 1 as covariate. Multiple comparisons versus the control group are by Dunnett's test. Significant differences versus control group, $*p < 0.05$. (**a**) Data on file RenaSci, (**b**) Heal et al. (2008)

et al. 2008; Perrone et al. 2004) and non-fasted plasma glucose in rats (Wallingford et al. 2008). Although compounds evaluated in rodents are relatively few, there is reasonable correlation between clinical and preclinical data. Therefore, olanzapine

may be a useful compound to employ in the preclinical profiling of potential new treatments for antipsychotic weight gain and metabolic dysregulation.

6 Summary and Future Directions

The reviewed evidence incontrovertibly demonstrates that many SGAs produce excessive weight gain and obesity. Furthermore, a significant number also have direct actions to impair glycemic control, thereby causing insulin resistance, impaired glucose tolerance, and type 2 diabetes (possibly leading to DKA). Schizophrenia is almost certainly causal in many endocrine and metabolic disturbances, making this population especially vulnerable to the adverse metabolic consequences of treatment with SGAs. Specific SGAs, e.g., aripiprazole and ziprasidone, may have a lower propensity for adverse metabolic effects, but they are not without risk. There is a widely held view that aripiprazole and ziprasidone are less clinically effective in treating schizophrenia than olanzapine or risperidone, and in addition, there are other safety factors to be taken into consideration. For example, ziprasidone causes QTc prolongation. Hence, there is an urgent need for a new generation of antipsychotic drugs that provide efficacy at least equal to olanzapine or risperidone, without their unwanted effects.

We have refrained from speculating on the pharmacological mechanisms responsible for the adverse effects of the SGAs on bodyweight and/or glycemic control as it is beyond the scope of this review. However, mechanisms such as 5-HT_{2C}, H_1, or M_3 receptor antagonism may contribute to their metabolic side effects. Clinical experience with both the FGAs and SGAs indicates that D_2 receptor antagonism, the therapeutic mechanism of almost all antipsychotics, may lead to the adverse effects of these drugs on bodyweight and glycemic control.

Pharmacological treatments for antipsychotic-induced weight gain are at best moderately effective, with metformin offering the dual benefits of weight reduction and improved insulin sensitivity. Clinical experience with antiobesity drugs and appetite suppressants is that they are generally poorly effective at managing weight gain caused by antipsychotics, unsurprising in view of the mutually antagonistic pharmacological mechanisms involved. In the absence of safe and effective alternatives to SGAs, there is substantial unmet clinical need for the introduction of new drugs to combat their adverse metabolic side effects. Preclinical experiments have mirrored the moderate efficacy of current antiobesity drugs in preventing antipsychotic-induced weight gain, but in the case of the GLP-1 agonist, lyraglutide, or the 5-HT_6 partial agonist, E-6837, have also revealed the existence of pharmacological mechanisms that are unlikely to be neutralised by the actions of the SGAs.

Predicting the liability of new antipsychotic drug–candidates to induce weight gain is still a major challenge for preclinical research. However, the situation is not as bleak as sometimes painted. First, there is evidence to demonstrate that all antipsychotic drugs are capable of causing substantial weight gain in patients; it

is only the percentage of subjects and magnitude of effect that varies across the SGAs. Hence, weight gain in rodent models induced by drugs like ziprasidone and aripiprazole is not the proof-of-concept failure that it is often stated to be. Second, predictive validity of the rodent models would be markedly improved if the effects of compounds are determined over a wide range of doses, and in addition to bodyweight, other metabolic endpoints, e.g., hyperphagia and visceral adiposity, are also measured.

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