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Management of Antipsychotic-Related Weight Gain

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Abstract

Despite variations across individuals and agents, antipsychotics are associated with clearly documented weight gain and adverse metabolic effects. Although increased appetite/caloric intake and various receptors, hormones and peptides have been implicated, biological mechanisms contributing to the increase in weight and glucose and lipid abnormalities with antipsychotics are largely unknown. This has hampered the creation of antipsychotics that are free of cardiometabolic effects, even in antipsychotic-naïve/early-phase patients, as well as the development of strategies that can prevent or drastically diminish the adverse cardiometabolic effects. In general, three strategies can reduce the cardiometabolic risk of antipsychotics: 1) switching to a less orexigenenic/metabolically adverse antipsychotic, 2) adjunctive behavioral treatments and 3) adjunctive pharmacologic interventions. However each of these strategies has only been modestly effective. Among different behavioral interventions (N=14, n=746), group and individual treatment, dietary counseling and cognitive-behavioral therapy seem to be similarly effective. Among 15 different pharmacologic strategies (N=35 , n=1,629), only metformin, fenfluramine, sibutramine, topiramate and reboxetine were more effective than placebo, with the most evidence being available for metformin, yet without any head-to-head trials comparing individual pharmacologic interventions. Even in the most successful trials, however, the risk reduction was modest. Weight was not decreased to a pre-treatment level, and despite superiority compared to placebo, weight gain still often occurred, particularly in antipsychotic-naïve patients and when interventions were “preventively” co-initiated with antipsychotics. Future research should focus on combining treatment modalities or agents and on exploring novel mechanism-based interventions.

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Keywords

Antipsychotics; Obesity; Weight Gain; Cardiometabolic Risk; Mechanisms; Switching; Behavioral Intervention; Healthy Lifestyle; Pharmacologic Intervention; Metformin

Introduction

Weight gain and obesity have become a critical public health issue. In the US, medical spending on conditions associated with obesity has doubled in the past decade and could reach $147 billion a year [1]. For people with psychiatric illness, obesity is an additional health burden with problematic sequellae, adversely affecting compliance [2], arguably one of the most important facets of treatment [3], quality of life [4] , and cardiovascular morbidity and mortality [5].

While mental illness, unhealthy lifestyle behaviors and a variety of pharmacological treatments can worsen cardiometabolic status, it appears that a number of frequently used, second-generation antipsychotics (SGAs) are particularly likely to cause weight gain and metabolic abnormalities [5]. Since SGAs are the primary treatment for several psychiatric disorders in children and adults, their cardiometabolic side effects are of particular significance. In the following, we will examine current research delineating the extent of antipsychotic associated weight gain and metabolic abnormalities, underlying mechanisms and risk factors. We will then review data on strategies aimed at reducing the adverse cardiometabolic effects of antipsychotics, namely, antipsychotic switching, and adjunctive non-pharmacologic as well as pharmacologic interventions, and discuss future directions in research.

Cardiometabolic Effects of Antipsychotics

SGAs have become first line treatment for psychotic disorders, bipolar disorder and aggression/irritability associated with autism, and are also used adjunctively for other non-psychotic disorders. With the shift in usage from first-generation antipsychotics (FGA), the side effect concern has also changed from movement disorders to weight gain and metabolic abnormalities [5]. This is because, despite heterogeneity among individual agents, SGAs as a class are associated with a greater risk for weight gain and metabolic adverse effects than FGAs [5-7].

Based on the evidence from placebo controlled and active controlled trials, the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes [8]called for monitoring of all antipsychotic treated patients, grouping the SGAs regarding their weight gain potential, in that clozapine and olanzapine were most likely to cause weight gain, followed closely by risperidone and quetiapine, with aripiprazole and ziprasidone being least likely to lead to significant weight gain. A more recent meta-analysis comparing an FGA (haloperidol) with several SGAs, showed clozapine, olanzapine and sertindole to be associated with a greater than 3 kg weight gain compared to haloperidol [7]. Observational evidence for olanzapine suggests that this weight gain is most rapid in the first 6 weeks of treatment [9], being accelerated in those patients with the most early weight gain at the end of one year treatment.

However, weight gain is not only most pronounced early on in the administration of a given agent, but also early on in the disease. A one-year study of newly diagnosed individuals with schizophrenia (33% antipsychotic-naïve) followed in the European First Episode Schizophrenia Trial (EUFEST) showed dramatic weight gain: 13.9 kg on olanzapine, 10.5

kg on quetiapine, 4.8 kg on ziprasidone and 7.3 kg on the first-generation antipsychotic haloperidol [10]. Using at least 7% body weight gain as a benchmark of clinical significance showed that marked weight gain was quite pervasive with the most orexigenic agents, affecting 86% of those on olanzapine, 65% of those on quetiapine and 63% of those on amisulpride. Even with the less orexigenic haloperidol and ziprasidone, weight gain >7% still occurred in 53% and 37% respectively. Since between 33% of patients randomized to olanzapine and 72% of patient randomized to haloperidol discontinued treatment prematurely, these numbers are underestimations of the true weight gain potential. Similar rates of substantial weight gain were observed in another randomized trial of first episode schizophrenia patients (24% antipsychotic-naïve), the Comparison of Atypicals in First Episode of Psychosis (CAFÉ) [11] In this study, weight gain >7% occurred at 12 and 52 weeks with olanzapine in 58.9% and 80.0% of patients, compared to 29.2% and 50.0% with quetiapine and with 32.5% and 57.6% with risperidone.

Children and adolescents, another group that is often naïve to antipsychotic treatment or, at least, early on in their treatment course, generally demonstrate larger and more rapid patterns of weight gain than chronically ill adults. A 12-week, prospective study comparing adolescents with schizophrenia treated with olanzapine, risperidone and haloperidol showed 7.2 kg weight gain on olanzapine, with 90.5% gaining at least 7% of their baseline bodyweight, and 3.9 kg weight gain on risperidone, 42.9% gaining 7% or more of their baseline bodyweight, compared to 1.1 kg weight gain on haloperidol, with only 12.5% gaining 7% or more of their baseline bodyweight [12].

The Treatment of Early Onset Schizophrenia Spectrum disorders (TEOSS), a pediatric, double blind, randomized, comparative study found a similarly drastic weight increase during a shorter period of only 8 weeks of treatment, i.e., 6.1 kg for olanzapine and 3.6 kg for risperidone compared with a negligible 0.3 kg for the molindone/benztropine comparator [13]. In the TEOSS study, the findings for olanzapine were so dramatic that the data safety monitoring board reconsidered its risk-to-benefit ratio and recommended against enrolling additional participants in the olanzapine arm after an interim analysis [14].

Predictors of Cardiometabolic Effects of Antipsychotics

A systematic review published in 2004 examining young children, adolescents, adults and the elderly attempted to address whether there was a developmental trend to risperidone induced weight gain [15], finding an inverse relationship between age and the increase in percentage of baseline body weight. A more recent meta-analysis of all placebo controlled studies of risperidone examining therapeutic and adverse effects found a 5.7% increase in baseline body weight in children as opposed to 1.5% in adults [16], further supporting other studies that found a significant association between younger age and greater antipsychotic-related weight gain[17-21]. Of note, the weight gain seems to continue during long term risperidone treatment as well, with youth showing a developmentally inappropriate 0.5 standard deviation increase in BMI z-score over two years of treatment [22], and 40% of adults gaining 7% of their weight in a five-year study in adults. As expected, this weight gain was shifted towards the beginning of treatment with over 2/3 of the weight being gained in the first 2 years. [23]. Unfortunately, even when used as adjunctive agents along with stimulants [24] and mood stabilizers [25], SGAs still confer increased cardiometabolic risk, and coprescription of antidepressants (or comorbid depression) may possibly further increase this risk [26].

Findings of a higher rate and relative amount of weight gain in youth have led to two hypotheses. One hypothesis is that children and adolescents have a different metabolism and decreased cortical regulation of a generally upregulated hypothalamic drive from adults,

which results in an increased vulnerability to medication-associated weight gain. Another hypothesis explains these findings as an artifact caused by younger individuals having less prior exposure to medications than adults, with longer durations of prior weight gain in adults leading to an attenuated signal in the latter. Supporting this line of thought is the fact the increased weight gain seen in studies of youth is similar to that found in first episode adults, especially in samples with minimal prior antipsychotic exposure [27]. The acute, 12-week results of the Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) study, a naturalistic cohort study of children and adolescents aged 7-19 years old [27] shed some light on this issue. Data from the cohort of 272 antipsychotic-naïve youth demonstrated significant weight gain over the first 3 months of treatment with all SGAs, including aripiprazole: 4.4 kg, 58.4% gaining ≥7% weight; risperidone: 5.3 kg, 64.4% gaining ≥7% weight; quetiapine: 6.1 kg, 55.6% gaining ≥ 7% weight; and olanzapine: 8.5 kg, 84.4% gaining ≥ 7% weight during the 12 week period. The study also found increases in glucose, insulin and insulin resistance with olanzapine only, in cholesterol (total and non HDL) with olanzapine and quetiapine, and increases in triglycerides on olanzapine, quetiapine and risperidone. What made this uncontrolled sample particularly informative was that only youth with 7 days or less of antipsychotic exposure were included in the analyses and that a small control group of youth who refused or stopped antipsychotics was included and who did gain less than 0.5 kg of weight (0% gained ≥7% weight) over the same period of time. Comparing their results with adult samples with minimal past antipsychotic exposure, the authors posit that the size of these increases in youth are better accounted for by the lack of prior exposure to antipsychotic medication than to the relative age difference of the subjects. Nevertheless, since weight gain in previously exposed youth still appears to be quite high compared to previously treated adults [12,15] , it is possible that both the biological sensitivity and order effect hypotheses are relevant to explaining the greater weight gain in youth.

Aside from prior exposure to medication, there have been few other consistently identified predictors of antipsychotic associated weight gain. Some studies have shown low baseline BMI to be a risk factor [28]. However, this finding is easily confounded with stage in illness, as individuals earlier in treatment may have lower BMI. In adult clinical trials of aripiprazole [29] clozapine [30] olanzapine and risperidone [31], low BMI predicted greater weight gain. Since this finding was also replicated in a study of first episode, drug-naïve patients, randomized to olanzapine, risperidone or haloperidol, [32] this suggests that the vulnerability to weight gain in patients with lower BMI might be due to additional factors other than solely to less prior treatment exposure. Of note, another study found that lower baseline BMI was associated with more accelerated weight gain, but that higher baseline BMI as well as higher parental BMI were associated with greater ultimate endpoint weight gain [18]. Finally, in a post-hoc analysis of 7 placebo and active controlled trials of chronic patients with schizophrenia treated with ziprasidone, olanzapine and risperidone, Allison and colleagues [33] reported that the association between lower BMI and greater weight gain susceptibility was mostly due to the regression of outlying measurements to the mean rather than a robust clinical phenomenon.

Additional predictors and correlates of antipsychotic-induced weight gain include male sex [20], female sex [18], non-White ethnicity [17,34], higher levels of negative symptoms [26], lack of cognitive restraint in the presence of increased appetite[35], non-smoking status [18], early weight gain in the first 2-4 weeks [9,34,36] and, possibly, higher dose for risperidone[19,27,37]. Given the dearth of data and some conflicting results, further investigations of the relationship between baseline BMI as well as additional potential mediator variables and antipsychotic-related weight gain will require rigorously designed studies, ideally, in early phase or antipsychotic-naïve patients to be able to identify reliable trends that are relatively unaffected by prior treatment and resultant order effects.

In terms of risk factors for other metabolic abnormalities, like hyperglycemia, an analysis examining two 6-month studies of ziprasidone and olanzapine found that decreased HDL cholesterol (<28 mg/dL) or elevated age (>58 among adults) if HDL cholesterol was >28 mg/dL, post-treatment increase in triglycerides of >145 mg/dL or rapid weight gain >6.1 kg in 2 weeks if the increase in triglycerides was <145 mg/dL, predicted the development of diabetes (i.e., fasting glucose >126 mg/dL) [38]. Somewhat surprisingly, baseline fasting glucose >92 mg/dL was the only significant predictor of developing prediabetes (i.e., fasting glucose >100 mg/dL), accounting for 60% of cases. In another study, consistent with ethnic differences in diabetes susceptibility in the general population, antipsychotic-related glucoregulatory dysfunction was found to be greater in minority ethnicity subjects [39]. Moreover, in a study of antipsychotic youth, a higher olanzapine dose (>10 mg/day) was associated with greater insulin, glucose and insulin resistance increase in the first three months of treatment (22). Since weight gain was not dose dependent, the authors interpreted this as evidence for a direct metabolic effect of the molecule, which matches animal data [40].

Health Impact

Although this finding could also be confounded by shared environment and unhealthy lifestyle, early studies suggested a link between diabetes and schizophrenia, based on increased rates of diabetes in family members of patients suffering from schizophrenia [41]. In addition, more recent studies also suggested that, at least in part, schizophrenia may be related to diabetes and metabolic dysregulation independent of medication treatment. Although not consistently found across all samples, several small studies of medication-naïve patients with schizophrenia have shown impaired insulin resistance [42] and fasting glucose tolerance [43], a finding that was replicated by the same group using a larger sample [44]. Furthermore, a study of 160 patients enrolled in an early psychosis intervention program found that patients had a higher rate of diabetes than controls, despite the fact that controls had higher weight, LDL-cholesterol and BMI [45]. A larger Spanish sample of newly diagnosed, antipsychotic-naive people with schizophrenia and related disorders also exhibited a higher prevalence of abnormal glucose tolerance and diabetes than non-schizophrenic age and socioeconomically matched controls [46].

The health and metabolic impact of weight gain in the mentally ill, whether medication-related or disease-related, has been delineated in a number of studies [5,25,47]. In one of the largest studies of over 1400 schizophrenia patients that directly assessed cardiometabolic risk factors, McEvoy and colleagues [48] compared the relative risk of cardiovascular disease to that of the general population characterized in the National Health and Nutrition Examination Survey (NHANES). The proxy for increased cardiovascular risk was the prevalence of metabolic syndrome, a constellation of 5 risk factors: abdominal obesity, elevated triglycerides, blood pressure and fasting glucose, as well as decreased HDL cholesterol. Men were more than twice as likely as controls to have the metabolic syndrome when controlling for age, race and ethnicity, and women were more than three times as likely to have the metabolic syndrome. Of relevance for premature death, the most pronounced differences occurred between the ages of 20 and 40 [48], corresponding with data from Europe [49]. Metabolic syndrome is of great relevance, as it has been linked to an up to three times higher risk of cardiovascular disease over seven years of follow up [50].

Other data have directly related the higher prevalence of cardiometabolic risk factors to the increased mortality in the mentally ill compared to the general population. US epidemiologic data suggested that the majority of the 25-year shortened life expectancy in patients with severe mental disorders compared to the general population can be attributed to higher rates and/or earlier onset of cardiovascular and cerebrovascular diseases [51]. In addition, data

obtained by following 370 adults with schizophrenia from 1981 to 2006 in the UK demonstrated an increase in cardiovascular mortality relative to the general population in the past 15 years [52]. While recent epidemiologic data from Finland showed no increased risk for death from ischemic heart disease comparing treatment with antipsychotics with different weight gain potential in adults with schizophrenia [53] the analyses have been criticized for a number of methodological reasons [54]. In order to compare results obtained in different regions, a meta-analysis of studies describing mortality rates in schizophrenia from around the world was performed. The overall result was that patients with schizophrenia had a 2.5 times increased risk of mortality compared with age matched people from the respective general population. The authors noted a seeming increase over the past 25 years, commenting that individuals with schizophrenia do not seem to benefit from the general secular trend toward greater longevity. They speculate that this may be in part due to metabolic effects of medications, in addition to differences in health care availability, utilization and delivery for the mentally ill [55]. Importantly, these medical effects of antipsychotics, closely related to the metabolic syndrome and its individual components, are modifiable risk factors for premature death that occurs at higher rates in the severely mentally ill.

Mechanisms

While the phenomenology and impact of antipsychotic-associated weight gain has become fairly well defined (except for direct, long-term follow-up studies), its specific etiology and mechanism are still undetermined. Some data in rats implied that some antipsychotics may decrease physical activity [56]. A pilot study that used accelerometers to measure movement changes in male adolescent inpatients with schizophrenia treated with antipsychotics [57] demonstrated a trend toward decreased physical movement approaching significance. There is also evidence of changes in metabolism as a result of antipsychotic administration. Adults taking olanzapine displayed differential patterns of substrate utilization, a measure of the manner in which the body utilizes energy stores, presenting with a decrease in fat oxidation and increased carbohydrate oxidation[58]. Increased carbohydrate oxidation has been proposed as a putative mechanism for weight gain [59]. Moreover, in a study using double labeled water to measure caloric expenditure, individuals taking clozapine had a resting energy expenditure that was 20% lower than normative levels proposed by the World Health Organization [60].

Although alterations in resting metabolic rate, energy expenditure and activity levels have been proposed as potential mechanism for antipsychotic induced weight gain [61], the preponderance of evidence indicates increased caloric intake as a major cause of antipsychotic associated weight gain [62]. The most robust findings that match animal data [63] consist of adverse event reports documenting increased appetite and food intake in clinical trials [17,64,65]. These results match the more precise measurements conducted in the pilot study of adolescents cited above [57], in which food intake was weighed for 2 days at baseline and again after 4 weeks of olanzapine treatment. Mechanisms for the increased appetite and decreased satiety are likely complex, but serotonergic, dopaminergic, histaminergic receptors and hypothalamic peptides and hormones involved in energy homeostasis have all been implicated [61].

The relationship between antipsychotic use and the development of diabetes and metabolic syndrome is also poorly understood. Although the majority of data implies that the risk of diabetes is mediated indirectly via weight gain and adiposity [5], there is also evidence suggesting that patients taking antipsychotics may develop insulin resistance and diabetes mellitus even independent of weight gain or differences in BMI [66,67] The existence of an additional, weight-independent effect is further suggested by data suggesting that some

metabolic effects may be dose dependent [27]. Preliminary data suggest the potential involvement of muscarinic receptors in this phenomenon [68,69].

Additional data suggest that adiponectin, a circulating peptide released by adipose tissue that is a marker for relative protection from the metabolic syndrome in the general population, may be adversely affected, wither by antipsychotics themselves or by the related weight gain [70]. Leptin, a hormone secreted by adipose tissue that acts principally on the hypothalamus to inhibit appetite [71], has also been implicated to explain the increased caloric intake and disproportionate increase in adipose tissue accompanying antipsychotic use, with leptin resistance being an added potential mechanism. Pilot evidence in children gaining weight on risperidone suggest that there may also be a link between different compartments of adipose tissue and leptin levels [72]. However, a study published in 2005 [73] examining changes in leptin during antipsychotic induced weight gain by comparing patients with weight matched controls found little support for leptin's direct involvement, yet the findings suggested that leptin may have effects on the distribution of adipose tissue. The most robust support for the role of leptin comes from one of the few studies looking at SGA related weight gain, utilizing whole body MRI. In this study, leptin appeared to maintain its inhibitory effects on the accumulation of peripheral adipose tissue, but not on that of the more metabolically pernicious visceral adipose tissue, suggesting that antipsychotics may block the inhibitory action of leptin on visceral adipose accumulation [74]. The authors hypothesized that the serotonin 5HT2c receptor may be involved in this iatrogenic effect of leptin insensitivity.

Other receptors that have shown promise as an avenue of investigation for the etiology and treatment of antipsychotic associated weight gain are the hypothalamic histamine receptor, H1 and the functionally related H3 auto-receptor [75]. Both are involved in the regulation of appetite, and studies examining the correlation between receptor affinity and orexigenicity found affinity for the H1 receptor to be the highest in medications with the most potent weight gain potential [76]. Kim and colleagues [77] examined H1 as the central receptor mediating the orexigenic effects of SGAs through a second messenger; adenosine monophosphate activated kinase (AMPk). They demonstrated this connection in an elegant experiment utilizing mice bred without the hypothalamic H1 receptor gene (H1 knock out mice) exposed to clozapine. In H1 knockout mice, there was no change in AMPk levels or in appetite when these mice were exposed to clozapine. In wild type mice, however, AMPk levels dropped, and eating behavior increased when clozapine was administered. The authors [77] suggested that identifying therapeutic agents to reverse the histamine blockade produced by SGAs would be a fruitful avenue of investigation.

Further work has been conducted in the area of pharmacogenomics to uncover the biological underpinnings and mechanisms of antipsychotic induced weight gain [61]. A number of studies have suggested that polymorphisms of the 5HT2c receptor gene may predict, which patients are most vulnerable to weight gain on SGAs [78] For example, one study found antipsychotic related obesity to be three times as likely in individuals with a combined genotype of four genes in the 5HT2c promoter region. Specifically-the variant (less common polymorphism) HTR2C:c.1–142948(GT)n 13 repeat allele, the common allele rs3813929 C, the variant allele rs518147 C and the variant allele rs1414334 C – were significantly related to an increased risk of obesity (OR 3.71 (95% confidence interval: 1.24–11.12)) in adults on antipsychotic medications [79]. Other research looking at a haplotype of polymorphisms associated with those found in prior 5HT2c research did not find an increased risk of antipsychotic weight gain in a group of 139 adults with chronic schizophrenia [80]. However, relative long-term resistance to weight gain was conferred by another combination of polymorphisms involving the 5HT2c receptor and a leptin gene (2548a/g) [81]. A gene for intracellular signaling, GNB3, has also been implicated in antipsychotic weight gain with the single nucleotide polymorphism C825T conferring added risk [82]. However as C825T

is also associated with idiopathic weight gain [83] it is unclear how much vulnerability it adds with antipsychotics [84]. Additional receptor polymorphisms include the cannabinoid receptor CNR1 rs806378, which has been associated with resistance to weight gain. Patients of European ancestry with the protective allele gained 2.2kg less on clozapine or olanzapine than those without it [85]. Further, a single nucleotide polymorphism in an adrenaline receptor, ADRA1A, has been implicated in increasing vulnerability to antipsychotic associated weight gain, particularly in females [86].

Strategies to Reduce Antipsychotic Associated Weight Gain and Cardiometabolic Morbidity

Taken together, the accumulated data on the poor health outcomes in the severely mentally ill indicate that antipsychotic related weight gain is a major target to improve overall health, which is challenged by premature and increased rates of cardiovascular morbidity and mortality. Moreover, the reviewed, mostly still preliminary and evolving results from mechanistic studies suggest a number of potential behavioral and pharmacologic targets to reduce antipsychotic induced weight gain and adverse cardiometabolic effects.

Switching Agents

One of the most logical interventions to address antipsychotic associated weight gain is to switch to a less orexigenic agent, unless antipsychotics can be avoided altogether. Clinically, however this approach may have its complications[87]. Several studies have shown that rapid changes may worsen outcomes when switching to aripiprazole [88] or risperidone [89]. A preliminary review of data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that patients were more likely to discontinue treatment prematurely after switching medication than when they were blindly re-randomized to their pre-baseline antipsychotic [90]. However, in subsequent analyses no additional differences in any examined efficacy outcomes were observed in patients who were rerandomized to or switched off olanzapine, risperidone or quetiapine, with the only difference being that patients switched off olanzapine gained less weight than those who remained on olanzapine [91].

Likewise, a number of short-term [92-96] and long-term [97-99] studies have shown a significant decrease in weight and other cardiometabolic risk factors in patients switched to a lower weight and metabolic risk antipsychotic. For example, in a one-year study [99], patients switching from a first-generation antipsychotic to ziprasidone did not show any relevant change in weight or triglyceride levels. By contrast, patients switched off risperidone and olanzapine lost an average on 6.9 kg (=7.8%) and 9.8 kg (=10.3%), respectively. Of note, the predominant triglyceride decrease occurred in the first 6 weeks, although weight continued to decrease progressively after that early time period, suggesting weight independent lipid effects of these two SGAs that were reversed or reduced after discontinuation. Similarly, another 1-year study of schizophrenia patients with a BMI of >27 examining the effects of switching from one of five SGAs (olanzapine, quetiapine, zotepine, risperidone, ziprasidone) to amisulpride found a 7.8 kg weight loss in the amisulpride group versus 2.6 kg in the non-switch group [97]. The greater weight loss was accompanied by significant decreases in cholesterol, triglycerides, and HOMA insulin resistance and an increase in HDL cholesterol. Moreover, switching patients from olanzapine to amisulpride reduced the rate of metabolic syndrome in half, an outcome that was also observed in studies switching from olanzapine to aripiprazole [49] and to risperidone [94] where the metabolic syndrome rate decreased from 58% to 29% and 54% to 37%, respectively. Unfortunately, the study by Lin et al. [97] did not look at which medication individuals had been switching from. Instead, the authors grouped together, based on chemical structure, olanzapine with

quetiapine and zotepine, and ziprasidone with risperidone. Using this approach, they found the latter group to have less weight loss, likely because the pre-switch medications were less orexigenic [97]. This pattern matches the 1-year results by Weiden et al. [99] described above as well as differential short-term weight loss depending on the weight gain potential of baseline antipsychotic after an 8-week switch to aripiprazole [100] or ziprasidone [101]. While in general these studies help to define the potential benefits and advantages of switching antipsychotics, further studies are needed that utilize standardized switch procedures [87], and randomization by baseline metabolic and/or psychiatric characteristics to better determine the benefits and risks of switching or if clinically feasible, of stopping antipsychotic treatment altogether.

Adjunctive Non-Pharmacologic Treatments

Table 1 summarizes the randomized, controlled data base of behavioral interventions for antipsychotic related weight gain, consisting of 14 studies including 746 patients. In four of these studies (n=337) investigated the preventive effect of behavioral treatments, starting the intervention concurrently with the antipsychotic., A recent meta-analysis and systematic review of 10 of these studies (n=482) [102], included six studies of cognitive behavioral intervention, three of a nutritional intervention and one of a combined nutritional and exercise intervention, demonstrating a combined 2.56 kg (CI: 1.92, 3.20) greater reduction in weight compared to treatment as usual (Table 1). In a subanalysis of individual effect sizes, there was a trend in favor of nutritional counseling (−3.12 kg) and CBT (−2.14 kg), without reaching statistical significance. The authors also found, in contrast to data from pharmacologic approaches to reduce weight gain, that there were no significant differences between prevention and intervention trials. In addition, there was no significant difference between individual and group interventions. None of these studies, however, included children.

A subsequent systematic review included six additional controlled studies, two of which were randomized, finding that the three preventive studies had less weight gain in the treatment as opposed to the respective control groups [103]. Furthermore, the authors reported that across all studies, behavioral interventions started after weight gain had already taken place achieved 2.63 kg weight loss in 12-16 week studies, 4.24 kg over 6 month trials and 3.05 kg in 12-18 month studies. One of the more comprehensive programs involved 61 antipsychotic-naïve patients with psychotic disorders who were randomized to risperidone, clozapine or the FGA haloperidol. Patients were then also randomized to receive either routine clinical care or the addition of a comprehensive, 13-week behavioral intervention, comprised of education, nutritional counseling and exercise, which started approximately one month later [104] . Overall, subjects in the intervention group gained 2.8 kg less than those in the control group (i.e., +4.1 kg vs. +6.9 kg), and only 39.3% of patients in the intervention group gained >7% of baseline weight compared to 78.8 % in the control group. Considering individual antipsychotics, the reduction in weight, BMI, and proportion of patients gaining >7% baseline body weight were significant in the olanzapine and risperidone group, whereas changes were not significant compared to the control condition in patients randomized to the less orexigenic haloperidol.

While there are no studies of behavioral interventions to prevent or reduce weight gain in the particularly vulnerable pediatric population, recent guidelines from the American Academy of Pediatrics (American Medical Association) [201] have been issues that recommend 5 servings of fruits, 2 hours or less of screen time daily, greater than one hour of exercise and 0 soft drinks. Studies of idiopathic pediatric obesity management have shown the difficulty of achieving sustained weight loss [105]. Some studies of idiopathic weight gain in adults and children have employed the traffic light diet. In this specific diet, different food items are given different ratings (green = low calorie, yellow = moderate calorie, red = high

calorie, eat rarely) which had performed well in a 10-year follow up study of obese children [106] and which has demonstrated feasibility in a clinical setting [107]. A similar, behavioral, 12-step healthy lifestyle program has been proposed for youth (and adults) treated with antipsychotics, which includes the following: [108].

- Family involvement in meal planning
- Drink water instead of soft drinks
- Have 4-6 separate meals/day
- Eat breakfast every day
- Serve small portions
- Eat /Foods with low glycemic index slowly
- Reduce/avoid saturated fat intake
- At least 25-30 g of soluble fiber
- Avoid snacking while satiated
- Limit fast foods to less than 1 per week
- Limit sedentary behaviors to less than 2 hours/day
- Exercise at least 30-60 minutes daily

Adjunctive Pharmacologic Treatments

A number of pharmacologic agents have been studied to treat obesity and metabolic abnormalities in the general population. However trials of adjunctive medications for antipsychotic-associated weight gain and metabolic problems are still relatively few including generally small samples. Table 2 summarizes the data base of pharmacologic interventions to reduce antipsychotic weight gain, consisting of 35 studies and 1,629 patients. Eleven studies including 535 patients studied pharmacologic agents in the prevention of weight gain associated with antipsychotics, starting the adjunctive agent concurrently with the antipsychotic.

In an earlier study, Faulkner and colleagues [109] performed a systematic review and meta-analysis of randomized studies of behavioral interventions (N=5, n=233) and pharmacologic interventions (N=18, n=547) for antipsychotic weight gain, including studies up until April 2006. Comparing non-pharmacologic interventions and pharmacologic interventions against treatment as usual, they concluded that pharmacologic weight loss agents had insufficient evidence to back their usage for antipsychotic induced weight gain. Two years later Baptista and colleagues [110] performed a systematic review of 25 pharmacologic weight loss intervention studies (n=1,221). They considered results promising for amantadine, metformin, reboxetine, sibutramine, and topiramate noting, however, that the field was hindered by small sample sizes and heterogeneous populations. Indeed, the lack of head-to-head studies comparing different medications for the treatment or prevention of antipsychotic induced weight gain and the limited number and sample size of randomized, placebo controlled trials has made it difficult to evaluate the effectiveness of individual pharmacologic agents.

To address the dearth of data, a recently completed meta-analysis of 32 randomized placebo controlled studies (N=1,482) compared results of 15 pharmacological interventions for weight gain in patients with a psychiatric illness treated with antipsychotic medications [111] (Table 2). The result for all agents together was modest, with a pooled mean weight change of only −1.99 kg (CI:-2.77, −1.20) compared to placebo. However, the results were

highly heterogeneous, suggesting significant differences across individual studies and agents. Among individual medications, the results were significantly in favor of 5 of the 15 tested agents, including metformin, a biguanide indicated for type 2 diabetes mellitus, providing the greatest weight loss (−2.94 kg) compared to placebo, followed by fenfluramine (−2.60 kg) , sibutramine (−2.56 kg), topiramate (−2.52 kg) and reboxetine (−1.90 kg). Metformin, which had the largest data base, consisting of 7 randomized, placebo controlled trials [112-118], also demonstrated significant benefits for secondary outcomes, such as waist circumference, blood glucose and insulin levels. In terms of preventing >7% weight gain, a benchmark for clinical significance, metformin and reboxetine had clinically relevant, low NNTs of 2.5 and 3.0, respectively [111], with NNTs <10 generally being considered clinically meaningful [119].

However, these results for the individual medications, like those of the overall meta-analysis, were the product of studies with divergent outcomes. Sensitivity analyses performed in the meta-analysis showed the importance of early stage of illness or duration of prior antipsychotic treatment. This is suggested by the finding that even with the most effective agents substantial weight gain occurred during antipsychotic treatment, when they were started concomitantly with an antipsychotic aimed at preventing weight gain [111] .

For example, in the 2 of the 7 metformin trials that tested the preventive effects where individuals started metformin concomitantly with the antipsychotic, subjects gained weight in both treatment and placebo groups. In one study [115], subjects gained significantly less weight in the metformin augmentation group. In the other study [113] there was only a trend towards metformin ameliorating weight gain, but this did not reach statistical significance.

While metformin has been researched the most for the reduction of antipsychotic-induced weight gain, its efficacy may be limited in part by its narrow mechanism of action. Metformin decreases hepatic gluconeogenesis and increases peripheral glucose sensitivity [120], but it does not appear to act centrally where the orexigenic function of antipsychotic medications likely takes place. As mentioned above, other agents (Table 2), which outperformed placebo, included sibutramine (−2.56 kg), a centrally acting serotonin and norepinephrine reuptake inhibitor indicated for the treatment of obesity. Recently, however, its use has come into question among individuals with a predisposition for cardiac disease [202]. Topiramate, an anticonvulsant that may have peripheral and central activity to ameliorate weight gain, was found to decrease weight by 2.52 kg more than placebo when given in conjunction with antipsychotic. However, although its potential psychotomimetic effects are not an issue during concurrent antipsychotic treatment, it has cognitive side effects and in an open label pediatric study it was poorly tolerated [121]. Reboxetine, a norepinephrine-reuptake inhibitor and antidepressant also outperformed placebo demonstrating 1.90 kg less weight gain when given in addition to antipsychotic, but this agent is only available in Europe, not in the US.

Assuming that comparable populations were included in the different pharmacologic and non-pharmacologic trials, it would appear that behavioral interventions are slightly more effective than pharmacologic interventions. However, in the only randomized study in which these modalities were compared directly [116], the pharmacologic intervention – metformin – performed better than the non-pharmacological treatment (−3.2 kg (CI:-2.5, −3.9) vs. −1.4 kg (CI:- −0.7, −2.0; p<.05)). Of note, however, the most efficacious treatment in that study was the combined metformin and behavioral intervention (−4.7 kg (CI:-3.4, −5.7)), pointing to more need for research into combined behavioral and pharmacologic treatment options, especially those that could be applied to general clinical practice settings.

More recently, there have been proof of concept studies examining the efficacy of novel compounds for the amelioration of antipsychotic weight gain in non-psychiatrically ill patients (Table 3). One study utilized modafinil, a stimulant-like medication indicated for narcolepsy showing statistically significant superiority compared to placebo in a brief, three-week trial [122]. Two other studies examined mifeprestone, a glucocorticoid antagonist, to prevent olanzapine associated weight gain, in similarly designed, short-term proof of concept trial in healthy adults, showing a statistically significant 2 kg separation from placebo [123] and risperidone [124] . An unpublished trial also of similar design showed that betahisitine, a centrally acting H1 agonist used for Meniere's disease, was associated with 1.2 kg less weight gain than placebo in healthy adults during 3 weeks of olanzapine administration [203].

In terms of agents borrowed from the anti-obesity pharmacopeia, aside from the medications covered in the above mentioned meta-analysis [111], namely sibutramine and orlistat, there are several more at various stages of development (Table 3). A large trial of a cannabinoid CB1 receptor antagonist, rimonabant was successful in reducing weight compared to placebo in obese individuals [125], but it was not FDA approved in the US due to increased levels of depression and sucidality and subsequently removed from the European market. Trials of pramlintide, an amylin derivative used for the treatment of diabetes, have shown some success in idiopathic obesity [126]. Tesofensine, a serotonin, dopamine and norepinephrine reuptake inhibitor has shown success in a 24-week Phase 2 placebo controlled trial facilitating up to 10% weight loss with a step-wise dose response relationship among obese subjects [127]. A 12 week trial with Lorcaserin, a selective 5HT2c agonist, showed weight loss of 3.6 kg, with 31% of subjects in the high dose group losing at least 5% of body weight. Importantly, a clinical trial combining metreleptin, a leptin analogue, with pramlintide showed that the two agents combined yielded better results than either alone [128]. Indeed, much current research into pharmacological approaches to obesity examines a mechanistic combination of medications, such as nalterexone/buproprion, buproprion/zonisamide and phenteramine/topiramate [129]. This approach is based on understanding that weight regulation is multidetermined, an aspect of energy homeostasis and metabolic function that underscores the complications of combating antipsychotic-related weight gain. In this context, the absence of combination treatment trials, except for one small trial of metformin+sibutramine, that was inconclusive [130], highlights an important gap in the data for the reduction of weight and metabolic abnormalities in antipsychotic treated individuals.

Monitoring

The management of antipsychotic-related weight gain and metabolic abnormalities has to include appropriate identification of any problems and ongoing monitoring of the relevant parameters. As noted above, there are inter-individual differences regarding the speed and severity of cardiometabolic risk accumulation during antipsychotic treatment. However, severely mentally ill individuals treated with antipsychotics are considered at particular risk for cardiometabolic disorders and risk factors. This position generated by a review of the available evidence prompted the development of several monitoring guidelines (e.g., [8,131]. The most widely accepted guidelines for medical monitoring in patients receiving antipsychotics was issues in 2004 by the American Diabetes Association and American Psychiatric Association in conjunction with other medical associations [8] (Table 4). In 2006, a review on management and monitoring of adverse events in youth was also published suggesting even more frequent monitoring in this vulnerable age group [108] (Table 4).

Despite these clear recommendations, however, there appears to have been limited penetrance of these guidelines in clinical practice. Across various settings and populations,

metabolic monitoring rates in antipsychotic treated individuals have remained alarmingly low, were similar to non-antipsychotic treated controls receiving albuterol and appear to be virtually unaffected by the FDA warning about diabetes associated with antipsychotics in 2003 and the subsequent ADA/APA monitoring guidelines in 2004 [132-138]. For example a study of over 23,000 patients in a managed care database assessed pre and post ADA/APA guidelines demonstrated only a slight increase in rates of obtaining lipids at baseline from 8.4% to 10.5%, and at 12 weeks from 6.8% to 9.0% [135]. Similarly, baseline glucose testing rates also increased marginally at baseline from 17.3% to 21.8%, and at 12-weeks from 14.1% to 17.9%. Children, who are most vulnerable to metabolic dysregulation, were paradoxically least likely to be tested in this [135] and a subsequently examined sample [138].

However, even when metabolic data are obtained, it may not influence treatment decisions. A study examining data in 7904 patients from 2001-2004 showed that there was a small relationship between elevated glucose and medication selection, and no relationship with cholesterol, lipid levels or pre-existing diabetes [134]. Clearly the development of strategies that enhance adherence to monitoring metabolic parameters and implementing treatment based on this information is needed.

Expert Commentary

Antipsychotics frequently adversely affect appetite and satiety. This appears especially pronounced with the newer, second-generation antipsychotic medications. These medications are used commonly because of their utility in the treatment of a number of diverse, severe psychiatric illnesses, such as schizophrenia and related psychotic disorders, bipolar disorder, autistic disorder and disruptive behavior or aggressive spectrum disorder, also having a role as augmenting agents in major depressive disorder.

Although certain agents are more likely to cause weight gain than others, all antipsychotics can cause clinically significant weight gain. Unfortunately, mechanisms and predictors allowing individualized treatment selection are largely unknown. Antipsychotic-naïveté and early significant weight gain appear to be the most reliable predictors of antipsychotic-related weight gain, with pediatric patients also being among the most vulnerable populations. Regarding mechanisms of antipsychotic weight gain, the most robust findings implicate increased caloric intake, possibly mediated by histamine (H1) and serotonin (5HT2C) receptors. However, an influence of antipsychotics on peptides and hormones involved in food intake and energy balance via other central and, possibly, peripheral mechanisms is also likely. Work in pharmacogenetics has shown vulnerability conferred by certain polymorphisms in 5HT2c, leptin and cannabinoid receptors, but, clearly, more research is needed, and the search for antipsychotics without any cardiometabolic liability needs to continue.

Switching to lower weight gain producing agents has the chance of providing some benefit, and is usually most successful when a slow cross taper or, even, an overlapping, plateau cross-titration is performed. However research on changing or stopping antipsychotics is limited and where it exists, studies varied in their design and magnitude of outcomes.

The research conducted to date on interventions to attenuate weight gain has almost exclusively focused on adults. Behavioral treatment studies have shown possibly equal efficacy for prevention as for intervention, and for nutritional counseling and cognitive behavioral therapy. Results from pharmacologic augmentation studies have shown moderate beneficial effects for metformin, fenfluramine, sibutramine, topiramate and reboxetine, possibly with lower effects in weight gain prevention studies. The limited data from one

single study suggest that combined behavioral and pharmacologic interventions are most effective, but, clearly, more research is needed.

Current studies are underway to further delineate mechanisms of antipsychotic related weight gain in adults and children, and to examine novel treatment strategies. As interventions to treat obesity in the general population develop further, these can be applied to the treatment of antipsychotic related weight gain. In view of the magnitude of antipsychotic-related weight gain and the modest effects of the so far tested monotherapy options and based on theoretical considerations, pharmacologic and pharmacologic-behavioral combination treatments should be studied in far more detail. Finally, all patients receiving antipsychotics should be monitored carefully for the emergence of clinically relevant weight gain and related metabolic abnormalities, which should be targeted, either by the mental health care practitioner or after referral to a medical specialist in order to optimize physical and mental health outcomes.

Five Year View

The work of managing antipsychotic weight gain during the next five years will likely be informed and enhanced by outcomes of ongoing research in the antipsychotic field and the general obesity arena. There are several current initiatives to explore the phenomenology and treatment of antipsychotic associated weight gain. In order to further investigate underlying mechanisms, one group is utilizing double labeled water as a technique to compare energy usage in individuals on olanzapine with those on the less orexigenic ziprasidone [204]. Another NIMH trial examines hepatic gluconeogenesis and liponeogenesis in adults on aripiprazole, olanzapine and placebo [139]. In youth, there is also an NIMH funded study examining the efficacy of antipsychotic medication in controlling aggression as well as metabolic effects of antipsychotic medications in youth using assessments of resting metabolic rate, total body fat, and insulin action in skeletal muscle, liver and adipose tissue [205].

In terms of clinical interventions, several trials are underway that test behavioral methodologies to treat antipsychotic associated weight gain. There are also multiple adult trials of metformin, both with and without lifestyle components. Novel agents under investigation as adjuvants to antipsychotic medication that are hoped to help attenuate antipsychotic related weight gain include exenatide [206], an agent FDA indicated for type 2 diabetes, and ramelteon, a melatonin MT 1 and MT 2 receptor agonist indicated for sleep disturbance [207]. In terms of research in youth, a multi-site, NIMH funded study was recently launched to examine the effects of switching to a possibly less orexigenic antipsychotic (aripiprazole) versus adding metformin versus a control group receiving healthy lifestyle guidance that is provided to all three groups [208]. This will be the first study to compare directly a switch to a lower cardiometabolic-risk antipsychotic with adjunctive weight loss medication treatment [208]. However, we were unable to find a registered trial of combination treatment approaches, either combining two pharmacologic treatments or combining a pharmacologic plus behavioral intervention compared to the individual treatments and a control condition. Therefore, the next five years should bring a refinement in the use of pharmacological and behavioral adjunctive treatments to help attenuate antipsychotic related weight gain, with possibly the emergence of a standard agent (as benztropine has been used for extra pyramidal symptoms) that would be widely used clinically and as a comparator in further head to head trials.

Finally, obviously, there also needs to be an ongoing search for the discovery of antipsychotic agents that are free of any cardiometabolic adverse effects in all or most patients.

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* of interest

** of considerable interest

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207. Ramelteon as an Adjunct Therapy in Non-Diabetic Patients With Schizophrenia. National Library of Medicine (US); Bethesda (MD: 2000. http://clinicaltrials.gov/ct2/show/NCT00595504

208. Reducing Weight Gain and Improving Metabolic Function in Children Being Treated With Antipsychotics. national Library of Medicine (US); Bethesda (MD: 2000. http://clinicaltrials.gov/show/NCT00806234

Key Points

1. Despite heterogeneity among individuals and specific agents, antipsychotics are associated with significant weight gain and adverse metabolic affects that can decrease patient's life expectancy and quality of life
2. While some of the likely related endpoints, including diabetes, metabolic syndrome and ischemic cardiac events, take more time to develop, antipsychotics seem to contribute to premature death rates due to the accelerated cardiometabolic risk accumulation
3. Antipsychotic related weight gain and development of dyslipidemia are most pronounced in youth and during the early phase of treatment, whereas other predictors, such as low BMI, gender, ethnicity, etc, have been less reliably associated with the magnitude of these adverse events
4. Mechanisms underlying antipsychotic-related cardiometabolic adverse effect are still unknown, impeding the development of truly targeted and successful interventions, but effects on food intake and energy homeostasis, such as ehypothalamic 5HT2c and H1 receptors, central or peripheral hormones and peptides, are likely involved.
5. Monitoring of cardiometabolic side effects is still insufficient in clinical practice, reducing the identification of targets for the improvement of cardiometabolic health in patients receiving antipsychotics.
6. In general, three strategies that have been modestly successful in limiting antipsychotic weight gain compared to a control condition include:1) the switch to an antipsychotic with lower cardiometabolic risk; 2) adjunctive behavioral interventions; and 3) adjunctive psychopharmacological interventions.
7. Among behavioral interventions, group and individual treatment, dietary counseling and cognitive-behavioral therapy seem similarly effective.
8. Among 15 pharmacologic strategies, five were more successful than placebo, including metformin, which has the largest data base, fenfluramine, sibutramine, topiramate and reboxetine.
9. However, the weight reduction was only modest compared to the control condition and did not always include true weight loss compared to baseline. Moreover, weight gain was still considerable/occurred frequently, especially in antipsychotic-naïve patients and when using strategies "preventively".
10. Future research is needed that compares head-to-head different treatment modalities and pharmacologic agents
11. Novel adjunctive medications acting at canabinoid and melatonin receptors, among others, might hold promise for the future, but interventions utilizing multiple modalities and/or combining agents with different and complementary mechanisms are most likely to be successful.

Table 1

Study, Patient and Treatment Characteristics in 14 Randomized Non-Pharmacologic Intervention and Prevention Trials for Antipsychotic Induced Weight Gain.

Study	Design	Duration (weeks)	Group	N[2]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][3]	Anti-psychotic Dose (daily dose)	Weight Δ (kg) [n][4]
NON-PHARMACOLOGICAL INTERVENTIONS										
Intervention Trials										
Brar et al., 2005 [140]	Cognitive Behavioral Therapy	14	Behavioral treatment Control	34 37	40.0±10.1 40.5±10.6	47.1 35.1	52.9 45.9	Schizophrenia and schizoaffective disorders [34/37]	Switched from olanzapine to risperidone	−2.0±3.79 [34] −1.1±3.11 [37]
Khazaal et al., 2007 [141]	Cognitive Behavioral Therapy	24	CBT Control	31 30	43.0±9.8 38.3±10.4	42 50	— —	Schizophrenia and schizoaffective [25/20], bipolar [1/4], schizotypal [2/2], depression and personality disorders [3/4]	Olanzapine, risperidone , clozapine, quetiapine, amisulpride	Baseline: 90.9±16.6 Endpoint: 87.4±14.8 Baseline: 84.3±17.2 Endpoint: 83.5±17.4
Kwon et al., 2006 [142]	Cognitive Behavioral Therapy	12	Weight management Control	33 15	32.00±9.22 29.80±6.07	30.3 33.3	— —	Schizophrenia and schizoaffective disorders [33/15]	Olanzapine 5-20 mg/day	−3.94±3.63 * [33] −1.48±1.88 [15]
McKibbin et al., 2006 [143]	Cognitive Behavioral Therapy	24	Diabetes Awareness Rehabilitation Training Control	29 28	53.1±10.4 54.8±8.2	67.9 62.1	50 72.4	Schizophrenia and schizoaffective disorder and type-2 diabetes mellitus [29/28]	Typical or atypical with low weight gain liability (aripiprazole, ziprasidone) [7/6] Atypical with moderate weight gain liability (risperidone, quetiapine) [13/14] Atypical with high weight gain liability (clozapine, olanzapine) [8/9]	−2.30±5.70 * : 3.10±4.60

Study	Design	Duration (weeks)	Group	N[2]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][3]	Anti-psychotic Dose (daily dose)	Weight Δ (kg) [n][4]
Weber & Wyne, 2006 [144]	Cognitive Behavioral Therapy	16	Cognitive/behavioral Control	8 9	- -	37.5 22.2	25.0 33.3	Schizophrenia and schizoaffective disorders [8/9]	Olanzapine, Risperidone, Ziprasidone, Quetiapine	−2.45±2.97 [8] −0.62±3.34 [9]
Poulin et al., 2007 [145]	Nutritional & Exercise Intervention	72	Diet and exercise Control	59 51	36.1±6.1 35.3±5.2	53 51	100 100	Schizophrenia [19/15], Schizoaffective [19/17], Bipolar [21/19]	Clozapine, Olanzapine, Risperidone, Quetiapine	−3.1 * [59] 3.6 [51]
Milano et al., 2007 [146]	Nutritional & Exercise Intervention	8	Diet and exercise Control	22 14	46 45	45.45 42.86	__ __	Schizophrenia, Bipolar	Olanzapine Mean: 16.8 mg/day Mean: 15.7 mg/day	1.47 * 3.5
Wu et al., 2007 [147]	Nutritional & Exercise Intervention	24	Diet and exercise intervention Control	28 25	42.2±7.5 39.0±6.7	39 44	0 0	Schizophrenia [28/25]	Clozapine [28/25] ≥ 300 mg/day	−4.2±4.4 * 1.0±3.4
Mauri et al., 2008 [148]	Psychoeducational Program	12	Psychoeducational Control	15 18	Overall: Mean: 38.9 Range: 19-60	46.7 38.9	__ __	Bipolar I [41], Bipolar II [2], Schizoaffective [5], Depression [1]	Olanzapine 5-20 mg/day	−3.6±2.6 * 0.2±2.9
Scocco et al., 2006 [149]	Psychoeducational & Nutritional Counseling	8	Psychoeducational intervention/ nutritional counseling Control	9 8	51.7±12.4 39.2±9.9	33.3 87.5	__ __	Schizophrenia and schizoaffective disorders [9/8]	Olanzapine	0.99±3.34 9 2.96±3.08 [8]
Prevention Trials										
Álvarez-Jiménez et al., 2006 [104]	Cognitive Behavioral Therapy	13	Early behavioral intervention Control	28 33	26.0±15.5 27.5±8.5	71.4 78.8	__ __	Psychotic disorder [28/33]	Olanzapine 13.1±3.3 mg/day, Risperidone 4.2±0.9 mg/day, Haloperidol 4.9±1.4 mg/day	4.10±3.99 * [28] 6.98±4.50 [33]
Álvarez-Jiménez et al., 2010 [150]	Cognitive Behavioral Therapy	12	Early behavioral intervention Control	28 33	Overall: 26.8±7.7	Overall: 76.4	__ __	Psychotic disorder	Olanzapine 5-20 mg/day, Risperidone 3-6 mg/day, Haloperidol 3-9 mg/day	4.1±3.99 * 6.9±4.5
Evans et al., 2005 [151]	Nutritional Counseling	24	Nutritional Counseling Control	29 22	34.6±9.6 33.6±11.6	38 50	__ __	Schizophrenia [9/3], schizoaffective disorder [4/6], schizophrenoform psychosis [4/6], bipolar disorder [4/4], depression [2/3]	Olanzapine 13.9±3.3 mg/day 10.6±4.8 mg/day	2.0±5.0 * [29] 0.8±1.8 [22]

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Study	Design	Duration (weeks)	Group	N[2]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][3]	Anti-psychotic Dose (daily dose)	Weight Δ (kg) [n][4]
Littrell et al., 2003 [152]	Nutritional Counseling	24	Nutritional Counseling Control	35 35	33.66±9.23 34.51±9.99	62.9 60.0	74.3 74.3	Schizophrenia and schizoaffective disorders [35/35]	Olanzapine [35/35] 5-20 mg/day	−0.06±9.43 * [35] 9.57±12.98

[1] All values represent mean ± standard deviation, unless otherwise stated or it was not reported.

[2] N= total number of subjects randomized in the study.

[3] [n_t/n_p]= number of subjects in the treatment group/number of subjects in the placebo group with the diagnosis.

[4] [n]= number of subjects included in analysis.

[5] "—" indicates data was not provided.

[6] Summary data is presented as total number of participants in treatment and placebo groups for the above intervention.

[7] The overall percentage in % Male and % White categories is calculated using studies with available data only. If the data was not reported for that trial, the trial was not utilized in the summary statistic and its population was not included in the overall calculation.

* Indicates significant difference from placebo at $p < 0.05$

Table 2

Study, Patient and Treatment Characteristics in 32 Randomized Pharmacologic Intervention and Prevention Trials for Antipsychotic Induced Weight Gain

Study	Design	Duration (weeks)	Group	N[2]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][3]	Antipsychotic Dose (daily dose)	Weight Δ (kg) [n][4]
										PHARMACOLOGIC INTERVENTIONS
Intervention Trials										
Deberdt et al., 2005 [153]	Double-Blind Placebo-Controlled	16	Amantadine 100-300mg Placebo	60 65	40±12 41±12	52 45	77 86	Schizophrenia and related disorders [36/33] Bipolar I [24/32]	Olanzapine 5-20 mg/day	−0.19±4.58 [59] 1.28±4.26 [64]
Graham et al., 2005 [154]	Double-Blind Placebo-Controlled	12	Amantadine 300mg/day Placebo	12 9	Adult	—*5*	—	Schizophrenia and related disorders or Bipolar disorder [12/9]	Olanzapine 5-30 mg/day	−0.36±3.54 * [12] 3.95±5.31 [9]
Modell et al., 1965 [155]	Double-Blind Placebo-Controlled	16	Dextroamphetamine 20 mg/day Placebo	10 10	44.1±6.5 41.1±5.8	100 100	—	Schizophrenia [10/10]	Chlorpromazine 125±11 mg/day Thioridazine 242.8±181 mg/day Chlorpromazine 566.7±251.7 mg/day Thioridazine 189.3±202 mg/day	0.91±4.8 [10] 0.09±2.35 [10]
Goodall et al., 1988 [156]	Double-Blind Placebo-Controlled	12	D-Fenfluramine 30 mg/day Placebo	16 13	38.93±8.53 37.07±7.93	50 61.5	—	Schizophrenia [16] Schizophrenia [13]	Fluphenazine Flupenthixol Clopenthixol	−5.4±3.4 * [9] −2.8±1.65 [7]
Bustillo et al., 2003 [157]	Double-Blind Placebo-Controlled	16	Fluoxetine 20-60 mg/day Placebo	15 15	33±12 36±11	80 80	46.7 53.3	Schizophrenia and related disorder [15/15]	Olanzapine 5-20 mg/day	3±3.12 [15] 1.7±3.12 [15]
Arman et al., 2008 [117]	Double-Blind Placebo-Controlled	12	Metformin 500 mg/day Placebo	16 16	11.25±2.46 8.93±4.28	68.8 62.5	—	Schizophrenia and related disorders [16/16]	Risperidone 6 mg/day	0.81±0.33 [16] 2.2±2.54 [16]

Study	Design	Duration (weeks)	Group	N[2]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][3]	Antipsychotic Dose (daily dose)	Weight Δ (kg) [n][4]
Baptista et al., 2007 [113]	Double-Blind Placebo-Controlled	12	Metformin 850-2550 mg/day Placebo	40 40	44.3 44.6	63.9 52.8	—	Schizophrenia Bipolar disorder [40/40]	Olanzapine 5-20 mg/day	−1.4±3.2 [36] −0.18±2.8 [36]
Baptista et al., 2008 [130]	Double-Blind Placebo-Controlled	12	Metformin 850-2250 mg/day + Sibutramine 20 mg/day Placebo	13 15	45.5 49.3	—	—	Schizophrenia [13/15]	Olanzapine 10-20 mg/day	−2.8±3.2 [13] −1.4±2.6 [15]
Carrizo et al., 2009 [114]	Double-Blind Placebo-Controlled	14	Metformin 1000 mg/day Placebo	31 30	39.6±9.7 38.3±8.7	—	—	Schizophrenia and related disorders Bipolar I disorder [31/30]	Clozapine 25-500 mg/day	−1.87±2.9 * [24] −0.16±2.9 [30]
Klein et al., 2006 [118]	Double-Blind Placebo-Controlled	16	Metformin 500-850 mg Placebo	18 20	12.9±2.4 13.3±2.4	50 60	77.8 60	Multiple diagnoses: Schizophrenia and related disorders Bipolar disorder Attentional disorders Oppositional defiant disorder Autism and Asperger's syndrome [18/20]	Olanzapine mean: 10±4.1 mg/day Risperidone mean: 1.33±0.98 mg/day Quetiapine mean: 400±255 mg/day Olanzapine mean: 8.5±3.4 mg/day Risperidone mean: 1.25±0.42 mg/day Quetiapine mean: 387±218.4 mg/day	−0.13±2.88 * [18] 4.01±6.23 [20]
Assuncao et al., 2006 [158]	Double-Blind Placebo-Controlled	12	Nizatidine 300 mg bid Placebo	27 27	35.5±12.4 34.9±12.2	66.7 51.9	74.1 59.3	Schizophrenia and related disorders [27/27]	Olanzapine 5-20 mg/day	1.1±3.25 [27] 0.7±2.47 [27]
Atmaca et al., 2003 [159]	Double-Blind Placebo-Controlled	8	Nizatidine 150 mg bid Placebo	18 17	27.1±7.3 28.7±8.8	22.2 17.6	—	Schizophrenia [18/17]	Olanzapine 5-25 mg/day	−4.5±2.2 * [17] 2.3±0.9 [17]
Atmaca et al., 2004 [160]	Double-Blind Placebo-Controlled	8	Nizatidine 150 mg bid Placebo	14 14	31.2±7.9 29.1±8.1	53.8 50	—	Schizophrenia [14/14]	Quetiapine 300-750 mg/day	−1.0±0.6 * [13] 1.2±1.2 [12]
Joffe et al., 2008 [161]	Double-Blind Placebo-Controlled	16	Orlistat 120 mg tid Placebo	35 36	38.3±9.4 37.1±9.7	—	—	—	Olanzapine Clozapine	−1.25±4.33 [31] 0.44±3.73 [32]

Study	Design	Duration (weeks)	Group	N[2]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][3]	Antipsychotic Dose (daily dose)	Weight Δ (kg) [n][4]
Borovicka et al., 2002 [162]	Double-Blind Placebo-Controlled	12	Phenylpropanolamine 75 mg/day Placebo	8 8	42 46.5	100 75	—	Schizophrenia [8/8]	Clozapine mean: 506±115 mg/day Clozapine mean: 431±187 mg/day	Baseline: 104.78±16.1[8] Endpoint: 106.14±3.5 [8] Baseline: 99.79±18.7 [8] Endpoint: 101.15±2.4 [8]
Baptista et al., 2009 [163]	Double-Blind Placebo-Controlled	12	Rosiglitazone 8 mg/day Placebo	15 15	44.8 52.1	57.1 40	—	Schizophrenia [15/15]	Olanzapine 10-20 mg/day	3.2±4.5 [14] 2.2±2.3 [15]
Henderson et al., 2009 [164]	Double-Blind Placebo-Controlled	8	Rosiglitazone 4 mg/day Placebo	8 10	39.2±9.2 39.7±7.4	75 70	100 80	Schizophrenia and related disorders [8/10]	Clozapine mean: 338±162 mg/day Clozapine mean: 363±133 mg/day	Baseline: 89.81±16.32 [8] Endpoint: 89.35±16.32 [8] Baseline: 85.73±22.22 [10] Endpoint: 86.18±21.77 [10]
Henderson et al., 2005 [165]	Double-Blind Placebo-Controlled	12	Sibutramine 5 mg tid Placebo	19 18	43.2±10.6 40.7±9.9	63.1 61.1	68.4 66.6	Schizophrenia and related disorders [19]	Olanzapine	−3.76±1.09 * [19] −0.82±0.73 [18]
Henderson et al., 2007 [166]	Double-Blind Placebo-Controlled	12	Sibutramine 5 mg tid Placebo	11 10	41±10 39±10	73 80	64 80	Schizophrenia and related disorders [11/10]	Clozapine mean: 400±310 mg/day Clozapine mean: 363±277 mg/day	−1.86±3.0 [10] −0.54±2.17 [8]
Afshar et al., 2009 [167]	Double-Blind Placebo-Controlled	8	Topiramate up to 300 mg/day Placebo	16 16	37.5±5.7 38.1±4.6	56 68	—*6*	Schizophrenia [16/16]	Clozapine (≥100 mg) Clozapine (≥100 mg)	37.5% lost weight 6.2% lost weight
Chengappa et al., 2007[168]	Double-Blind Placebo-Controlled	8	Topiramate 276±108 mg/day Placebo	32 16	42.6±8.9 42.8±6.7	44 50	63 44	Schizoaffective, Bipolar Type [32/16]	Valproate (61±7mg/mL) Lithium (0.70±0.15 mEq/L) Valproate (69.4±15 mg/mL) Lithium (0.69±0.13 mEq/L)	−1.49±3.85 [32] 2.72±6.44 [14]

Study	Design	Duration (weeks)	Group	N[2]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][3]	Antipsychotic Dose (daily dose)	Weight Δ (kg) [n][4]
Ko et al., 2005 [169]	Double-Blind Placebo-Controlled	12	Topiramate 100 mg/day Topiramate 200 mg/day Placebo	22 22 22	34.2±7.62 35.3±9.75 37.6±7.98	37.5 41.2 60	0	Schizophrenia [66/6]	Risperidone mean: 5.7±2.6 mg/day Risperidone mean: 5.4±2.5 mg/day Risperidone mean: 5.1±1.7 mg/day	−1.68±5.3 [16] −5.35±4.35 * [17] −0.3±2.59 [20]
Narula et al., 2010 [170]	Double-Blind Placebo-Controlled	12	Topiramate 200 mg/day Placebo	33 34	31.21±9.70 31±10.09	66.7 64.7	—	Schizophrenia [33/34]	Olanzapine mean: 11.52±0.41 mg/day Olanzapine mean: 11.47±0.4 mg/day	−1.27±2.28 [33] —
Nickel et al., 2005 [171]	Double-Blind Placebo-Controlled	10	Topiramate 250 mg/day Placebo	25 18	35.2±8.2 34.5±9.2	0	—	Psychosis [13/7] Unipolar and Bipolar disorders [12/11]	Olanzapine mean: 7.8±3.6 mg/day Olanzapine mean: 7.2±3.1 mg/day	Mean Difference between groups: 5.6 kg [−8.5, −3.0]
Prevention Trials										
Poyurovsky et al., 2004 [172]	Double-Blind Placebo-Controlled	6	Famotidine 40 mg/day Placebo	7 7	23±1.4 22.1±1.9	57.1 71.4	—	Schizophrenia and related disorders [7/7]	Switched from olanzapine to risperidone	−2.0±3.79 [34] −1.1±3.11 [37]
Poyurovsky et al., 2002 [173]	Double-Blind Placebo-Controlled	8	Fluoxetine 20 mg/day Placebo	15 15	24.3±4.4 26.1±7.9	81.8 69.2	—	Schizophrenia [15/15]	Olanzapine, risperidone , clozapine, quetiapine, amisulpride	Baseline: 90.9±16.6 Endpoint: 87.4±14.8 Baseline: 84.3±17.2 Endpoint:
HinzeSelch et al., 2000 [174]	Randomized Open Label	6	Fluvoxamine 50-75 mg/day Placebo	11 12	32±15 39±15	45.5 50	—	Schizophrenia and related disorders [11/12]	Olanzapine 5-20 mg/day	−3.94±3.63 [33] −1.48±1.88 [15]
Lu et al., 2004 [175]	Randomized Open Label	12	Fluvoxamine 50 mg/day Placebo	34 34	32.9±8.5 35.1±9.4	0	—	Schizophrenia [34/34]	Typical or atypical with low weight gain liability (aripiprazole, ziprasidone) [7/6] Atypical with moderate	Baseline: 101.05±22.55 Endpoint: 98.73±21.27 Baseline: 96.41±16.73 Endpoint: 99.5±16.95

Study	Design	Duration (weeks)	Group	N[2]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][3]	Antipsychotic Dose (daily dose)	Weight Δ (kg) [n][4]
									weight gain liability (risperidone, quetiapine) [13/14] Atypical with high weight gain liability (clozapine, olanzapine) [8/9]	
Baptista et al., 2006 [112]	Double-Blind Placebo-Controlled	14	Metformin 850-1700 mg/day Placebo	20 20	~47.7	52.6 66.7	—	Schizophrenia and related disorders [20/20]	Olanzapine, Risperidone, Ziprasidone, Quetiapine	−2.45±2.97 [8] −0.62±3.34 [9]
Wu et al., 2008 (AJP) [115]	Double-Blind Placebo-Controlled	12	Metformin 750 mg Placebo	20 20	25.4±3.9 24.8±3.5	—	0	Schizophrenia [20/20]	Clozapine, Olanzapine, Risperidone, Quetiapine	−3.1 [59]* 3.6 [51]
Cavazzoni et al., 2003 [176]	Double-Blind Placebo-Controlled	16	Nizatidine 150 mg bid Nizatidine 300 mg bid Placebo	57 58 60	18-65 (range)	—	—	Schizophrenia and related disorders [57/60]	Olanzapine Mean: 16.8	1.47 3.5
Poyurovsky et al., 2003 [177]	Double-Blind Placebo-Controlled	6	Reboxetine 2 mg bid Placebo	13 13	34.6±13.0 26.5±6.7	60	—	Schizophrenia [13/13]	Clozapine [28/25] ≥ 300 mg/day	−4.2±4.4* 1.0±3.4
Poyurovsky et al., 2007 [178]	Double-Blind Placebo-Controlled	6	Reboxetine 2 mg bid Placebo	31 28	30.3±8.5 29.5±7.2	74.2 53.6	—	Schizophrenia [31/28]	Olanzapine 5-20 mg/day	−3.6±2.6* 0.2±2.9
Kim et al., 2006 [179]	Randomized Open Label	12	Topiramate 50 mg bid No adjunctive treatment	30 30	Adult	—	—	Schizophrenia [30/30]	Olanzapine	0.99±3.34 [9] 2.96±3.08 [8]
Combined Treatments										
Wu et al., 2008 (JAMA) [116]	Lifestyle Intervention Double-Blind Placebo-Controlled	12	Psychoeducational, dietary, and exercise programs Metformin 750 mg Control	32 32 32	26.4 26.8 25.8	53.1 50.0 50.0	— — —	Schizophrenia [32/32]	Clozapine mean: 106.8 [98.9-114.7] Olanzapine mean: 5.6 [4.6-6.6] Risperidone mean: 2.7 [2.3-3.2] Sulpiride mean: 566.7 [512.5-620.9] Clozapine mean: 112.5 [99.8-	−1.4±1.87*[32] −3.2±2.0*[32] 3.1±1.87 [32]

Study	Design	Duration (weeks)	Group	N[2]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][3]	Antipsychotic Dose (daily dose)	Weight Δ (kg) [n][4]
									125] Olanzapine mean: 5.7 [4.6-6.8] Risperidone mean: 2.5 [2.1-2.9] Sulpiride mean: 557.1 [507.7-606.5]	

[1] All values represent mean ± standard deviation, unless otherwise stated or it was not reported.

[2] N= total number of subjects randomized in the study.

[3] [n_t/n_p]= number of subjects in the treatment group/number of subjects in the placebo group with the diagnosis.

[4] [n]= number of subjects included in analysis.

[5] "—" indicates data was not provided.

[6] Summary data is presented as total number of participants in treatment and placebo groups for the above intervention.

[7] The overall percentage in % Male and % White categories is calculated using studies with available data only. If the data was not reported for that trial, the trial was not utilized in the summary statistic and its population was not included in the overall calculation.

[*] Indicates significant difference from placebo at $p < 0.05$

Table 3

Selected pharmacological agents with research data or in development for the treatment of SGA weight gain

Drug	Mechanism/Treatment Target	Comments/Side Effects
Amantadine	Dopamine receptor	Limited efficacy in DBPCT for SGA weight gain.
Atomoxetine	Noradrenaline-reuptake inhibitor	Has adult and pediatric ADHD indication. Suicidality warning.
Betahistine	H_1 receptor agonist/H_3 receptor antagonist	DBPCT data in SGA weight gain in control adults. Indicated for Meniere's disease in Europe, but not in US.
Bupropion	Dopamine-noradrenaline-reuptake inhibitor	Limited data for weight loss. Suicidality warning.
Exenatide (exendin-4)	GLP-1	Currently IM. Has adult indication for Type 2 Diabetes.
Fluoxetine	5-HT-reuptake inhibitor	Limited efficacy in DBPCT for SGA weight gain. Suicidality warning.
Fluvoxamine	5-HT-reuptake inhibitor	Limited efficacy in DBPCT for SGA weight gain. Suicidality warning.
Intranasal PYY	PYY_{3-36}	Limited efficacy in DBPCT for obesity.
Lorcaserin	5-HT2C agonist	Has DBPCT data for obesity; in development.
Metformin	Activates AMP-activated protein kinase	Has preponderance of DBPCT data in SGA weight gain. Indicated in children and adults for T2DM.
Metreleptin	Leptin	Has DBPCT data for obesity; in development as monotherapy and in combination with other mechanisms drugs.
Mifeprestone	antiprogestrogen, antiglucocorticoid, weak antiandrogen.	Has DBPCT data in antipsychotic associated weight gain in healthy controls only.
Nizatidine	H_2 receptor antagonist	Limited efficacy in DBPCT for SGA weight gain. Orlistat Gastric lipase inhibitor Limited data in DBPCT for SGA weight gain. Diarrhea, especially if not combined with fat reduced diet.
Phenylpropanolamine	Sympathomimetic	DBPCT data in SGA weight gain. Cardiovascular risk.
Pramlintide	Amylin	IM formulation. Has indication for adult T2DM.
Reboxetine	Norepinephrine reuptake inhibitor	Some DBPCT data in SGA weight gain showing efficacy. Not available in US.
Rimonabant	Cannabinoid CB_1 Receptor antagonist	Not available in US or Europe. Psychiatric side effects.
Rosiglitazone	Binds peroxisome proliferator-activated receptors	Limited efficacy in SGA weight gain in DBPCT.
Sibutramine	5-HT-noradrenaline-reuptake inhibitor	DBPCT data in SGA weight gain. Tachycardia, hypertension, warning for cardiovascular events. Has pediatric and adult indication for obesity.
Tesofensine	Dopamine, norepinephrine and serotonin reuptake inhibitor	Convincing results in Phase II obesity DBPCT. Dry mouth, insomnia, tachycardia, hypertension.
Topiramate	Antiepileptic drug targeting multiple proteins	Has pediatric and adult epilepsy indications and DBPCT data in SGA weight gain. Memory impairment can be a limiting side effect
Zonisamide	Antiepileptic drug targeting multiple proteins	Has pediatric and adult epilepsy indications. No DBPCT data in antipsychotic induced weight gain.

DBPCT - Double Blind Placebo Controlled Trial, SGA - Second Generation Antipsychotic, T2DM - Type 2 (non-insulin dependent) Diabetes Mellitus

Table 4

Monitoring protocol for adult and pediatric patients receiving antipsychotic medications.

	Baseline	Each Visit	12 Weeks	Quarterly	Bi-annually	Annually	Every 5 years	Only if symptomatic
Adult patients[1]								
Personal/family medical history	X					X		
Weight, BMI	X	X						
Waist circumference	X					X		
Blood pressure	X		X			X		
Fasting plasma glucose	X		X		X			
Fasting lipid profile	X		X			X[2]	[X][2]	
Pediatric patients[3]								
Personal/family medical history	X					X		
Lifestyle behaviors	X	X						
Weight, height, BMI%ile, BMI z-score	X	X						
Blood pressure/pulse	X		X		X			
Fasting plasma glucose & lipids	X		X		X			
Sexual/reproductive dysfunction	X			X				
Prolactin								X
TSH	X					X		

[1] Adapted from American Diabetes Association (2004)[8].

[2] Originally, fasting lipid testing was proposed every five years if normal and at three months if not. In view of the frequency of antipsychotic related lipid abnormalities, annual lipid testing is now generally recommended

[3] Adapted from Correll (2008)[180].