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Antipsychotic drugs and obesity

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Abstract

Mechanisms underlying antipsychotic cardiometabolic adverse effects are incompletely understood. This hampers the identification of high-risk patients, low-risk antipsychotics and preventive/ameliorative treatments. Recent clinical, molecular, and genetic data suggest that i) antipsychotic-naïve samples provide the greatest power for mechanistic studies; ii) weight and metabolic effects can be discordant, pointing to overlapping and distinct mechanisms; iii) antipsychotics affect satiety and energy homeostasis signaling; iv) the specific peptides mediating these effects are unknown but likely overlap with those involved in idiopathic obesity; and v) single nucleotide polymorphisms in genes encoding known neurotransmitter receptors and metabolic proteins are promising pharmacogenomic targets for countering adverse affects. However, sophisticated molecular studies and genome-wide association studies, ideally in antipsychotic-naïve/first episode samples, are needed to further advance the field.

Keywords

Antipsychotics; Obesity; Weight Gain; Cardiometabolic; Risk Factors; Mechanisms; Satiety; Energy Homeostasis; Genetics

The problem of antipsychotic-related weight gain

Overweight and obesity have become a pandemic [1]. Patients with severe mental disorders are at even higher risk than the general population for obesity, cardiometabolic risk factors, and related morbidity and mortality [2,3]. In addition to medical consequences, obesity in the mentally ill can cause treatment nonadherence and decreased quality of life [4].

Although antipsychotic drugs are the cornerstone of treatment for many psychiatric disorders, these medications are significantly associated with weight gain, the development of obesity, and the accrual of cardiovascular risk factors [2–4]. These adverse effects of these medications are important factors in the reduced quality of life and premature death from cardiovascular disorders in patients with severe mental illnesses compared to the general population [3]. Moreover, treatments to prevent or ameliorate cardiometabolic side effects are scarce, only modestly more effective than placebo, and do not restore pretreatment body weight [5].

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Despite an increasing awareness of the clinical significance of antipsychotic-induced weight gain [3–6], recent data suggest that the magnitude of this side effect has been consistently underestimated by studies in chronically-treated adult populations. Such studies typically reveal an acute (≤12-week) body mass index (BMI) increase of less one unit (kg/m^2) for risperidone, one of the most commonly prescribed antipsychotics (Table 1 and Figure 1a). Conversely, the weight gain associated with early/first exposure to antipsychotics is far greater. The recently reported Comparison of Atypicals for First Episode (CAFE) trial in adults with first episode schizophrenia [8] (Figure 1a), demonstrated a nearly 1.5 kg/m^2 BMI increase after 12 weeks of treatment with risperidone, approximately three-times greater than in the first phase of the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) trial [7]. The CATIE trial is currently the largest randomized, double blind trial comparing four second-generation antipsychotics (SGAs, olanzapine, risperidone, quetiapine and ziprasidone, Table 1) with a first-generation antipsychotic (FGA, perphenazine, Table 1) in 1493 patients with chronic schizophrenia.

Moreover, studies of antipsychotic-induced weight gain in pediatric patients demonstrate consistently greater effect sizes than adult studies given similar methodologies (Figure 1a). Drug-naïve patients gain significantly more weight than patients exposed to antipsychotics in the past [11]. For example, drug-naïve pediatric patients were at far greater risk for risperidone–induced weight gain than pediatric patients as well as adult patients with substantial prior antipsychotic exposure [11, Figure 1a]. These data are taken from a recent study [11] reporting on the weight and metabolic effects of antipsychotics in a cohort of 272 antipsychotic drug-naïve (≤1 week prior treatment) pediatric patients beginning initial treatment with one of four SGAs (aripiprazole, olanzapine, quetiapine or risperidone, Table 1). The drug-induced weight gain was dramatic; patients gained significant weight on each of the SGAs with an overall mean weight gain of >10 pounds after only 12 weeks of treatment. The amount of weight gain was similar across the age range (adjusted for height), and was not affected by pubertal status, ethnicity or gender of the subjects. As shown in Figure 1a, the weight gain of risperidone was more than four-times greater than in the CATIE report that included pretreated adults.

In addition to weight gain and obesity, antipsychotics can also disturb glucose and lipid metabolism [3,4,7–11]. Metabolic abnormalities seems to be both mediated indirectly via weight gain, but also, at least with some antipsychotics (e.g., clozapine and olanzapine, Table 1), via direct molecular effects that do not require weight gain or that can even attenuate the effect of weight gain (e.g., aripiprazole, Table 1) [11].

Antipsychotic-induced cardiometabolic adverse effects have become a major issue in the treatment with SGAs. This is heightened by the fact that the broadened indications of SGAs (Table 1) have increased their use. The initially polarized view that cardiometabolic risks were associated with SGAs, but not FGAs has given way to the realization that both classes have heterogeneous cardiometabolic liabilities [3–5].

Despite the increased focus on cardiometabolic effects of antipsychotics, several questions require further clarification: i) What is the relative contribution of antipsychotic treatment, psychiatric illness, patient characteristics, and unhealthy lifestyle to the increased rates of obesity and cardiovascular morbidity in the severely mentally ill?; ii) are all (or most) antipsychotics associated with clinically relevant weight gain and/or glucose and lipid abnormalities?; iii) what are the mechanisms that link antipsychotics and cardiometabolic risk?; iv) what risk factors and mechanisms are modifiable and how can they best be targeted?; and v) what are the best approaches to answer these questions? In the following sections, we will address these questions.

Pathways to antipsychotic-related obesity

In general terms, antipsychotic-related weight gain and obesity result from a medication-induced or -aggravated imbalance between energy intake (type, amount and frequency of ingested calories) and energy expenditure (type, amount and frequency of activity/exercise) [12]. To date, data have been inconclusive whether antipsychotics increase weight via increased appetite and food intake, decreased activity or decreased metabolism. Owing to the importance of energy homeostasis, multiple and redundant pathways regulate behavior and metabolic processes related to food intake, satiety, resting metabolic rate, energy expenditure and, ultimately body weight [13]. Furthermore, in mentally ill patients receiving antipsychotics, illness effects, such as disorganization, agitation, apathy, anhedonia, depression, etc., and pharmacodynamic medication effects, including increased appetite, muscle stiffness, sedation, hypersomnia, etc., can add to these already complex interactions.

Moreover, despite the clinically significant weight gain observed in many studies with documented variability between specific antipsychotics (Table 1), there is consistent inter-individual variation even within treatment with the same antipsychotics. In the aforementioned, 12-week study of antipsychotic-naïve youth [11], for example, there were wide ranges of weight change, despite the fact that dosage ranges were relatively restricted and adherence to medication was monitored by plasma drug levels and parental interviews. For example, risperidone was associated with a mean weight gain of 5.3 kg in just 3 months, yet categorical weight gain outcomes varied considerably with some patients losing weight, whereas others gained 21% or more of baseline weight after 12 weeks of treatment (Figure 1b). The same heterogeneity was found for the other studied antipsychotics (i.e., aripiprazole olanzapine, and quetiapine, Table 1), albeit at different levels of severity [11].

This heterogeneity of the antipsychotic-induced weight gain results from poorly understood drug-gene-environment interactions, which result in a net change in the balance between peptides and hormones regulating food intake and energy homeostasis via orexigenic (anabolic) and anorexigenic (catabolic) processes [13]. Figure 2 summarizes moderators and mediators of antipsychotic-related weight gain. Moderators include patient demographics, treatment setting, illness characteristics, past and baseline antipsychotic and comedication treatments, and baseline diet, activity, and body composition. Mediators include antipsychotic dose, comedications, medication side effects and changes in diet and activity during antipsychotic exposure. Taken together, these factors interact and contribute to the observed antipsychotic-induced weight gain to varying degrees via incompletely understood mechanisms and pathways [12–14].

Moderators and mediators of antipsychotic-induced weight gain

Several moderators and mediators for weight gain during antipsychotic treatment have been reported, including patient factors (age, BMI, gender, etc.) illness-related factors (treatment naïve, extent of symptom reduction, etc.), and treatment variables (duration, dose and drug type) [4,14]. Moderator variables that have been replicated include young age and first episode illness status; these effects are likely related to minimal prior antipsychotic exposure and weight gain, rather than to developmental factors, as lower age *per se* does not correlate with weight gain in youth [11]. Although measures of antipsychotic intake, such as long treatment duration and strict medication adherence, consistently correlate with the degree of weight gain [4,14], dose-response relationship results have been mixed, with some studies finding a significant mediating effect of higher antipsychotic doses on weight gain, while others did not [16]. However, recent evidence in humans suggests a potential antipsychotic dose relationship with weight gain and metabolic abnormalities [11,15,16]. These data are supported by a six-month, fixed dose study of long-acting injectable olanzapine, which

assured full adherence; in this context, a clear dose response curve was observed [17]. Although associations with improvement in psychotic, depressive and manic symptoms have been observed [14], this relationship might be a secondary effect of greater treatment adherence and prolonged study participation in drug responders as compared to nonresponders [4].

Low baseline BMI and normal weight status (i.e., BMI< 25) have been frequently associated with greater antipsychotic-induced weight gain, but this might reflect regression to the mean [18] and not an underlying biological risk factor. In addition, a predisposition to overeating and lack of cognitive restraint [20] regarding food intake and appetite suppression might be coextensive with other mechanisms governing weight regulation more generally. Polypharmacotherapy has also been associated with greater weight gain than monotherapy [21,22]. However, this relationship is complicated by the range of medications that comprised polypharmacy, and interactions with illness severity, comorbidities and comedications, which might lead to weight gain.

Several moderating and mediating variables have been identified that modify antipsychotic-related cardiometabolic effects (Figure 2). However, available results are inconclusive, mostly due to methodological shortcomings, including small sample sizes; usually extensive prior antipsychotic treatment with unknown cardiometabolic effects; restricted number of assessed mediating and moderating variables; lack of antipsychotic blood levels; uncertain adherence levels, and the incomplete translation from animal models to human data.

Behavioral mechanisms

Although diet and exercise both moderate (as a baseline factor) and mediate (after change in response to treatment) antipsychotic-related weight gain (Figure 2) and they are amenable to direct study in humans, few clinical trials have comprehensively measured these components. It appears that patients exposed to most antipsychotics have greater appetites and eat more but the composition of their food is not necessarily altered on medication [14]. In addition to increased appetite, delayed or dampened satiety signaling has also been observed [14] and proposed as a mechanism for weight gain. However, owing to conflicting results, it remains unclear to what extent changes in energy resting metabolic rate or energy expenditure affect weight gain, whether these changes differ by drug, and whether these effects are mediated by sedation or extrapyramidal symptoms, such as parkinsonian side effects [23,24]. Some evidence from animal models addresses these questions. However, the data base is still slim and a comprehensive assessment of putative behavioral mechanisms concurrent with neurohormonal and neurotransmitter effects reviewed below is missing.

Neurohormonal mechanisms

Appetite, food intake and satiety signaling moderate and mediate antipsychotic-induced weight gain (Figure 2). Studies on animal models have produced important data regarding putative mechanisms of antipsychotic-induced weight gain [14], although results vary across species, strains, handling and housing conditions, and drug administration techniques. Results from animal studies have also been partly inconsistent with human clinical experience; examples of incongruence include the lack of weight gain of rats and mice with clozapine or in male rats with olanzapine, and weight loss of rats at high doses of antipsychotic drugs. The fact that relevant data in rodents did not match human data likely results from antipsychotic side effects in animals, such as sedation, and muscle stiffness that decrease activity and modify metabolism, thereby interacting with the antipsychotic effects on food intake, satiety and metabolism, especially in short-term trials [14].

Studies in humans have consistently shown that SGAs, especially those with strongest weight gain liabilities, increase levels of circulating leptin [25,26], a peptide hormone that regulates appetite and is produced by subcutaneous adipocytes. However, leptin increases that should decrease food intake occurred concurrent with weight gain, indicating that leptin increases are a consequence of rather than a cause of antipsychotic-induced weight gain, although the development of relative or absolute leptin resistance has also been reported [25]. Weight gain has been consistently associated with an increase in inflammatory markers [3,4,14], which are produced by both adipocytes and macrophages. Reports regarding the appetite-stimulating hormone, ghrelin have been mixed, likely resulting from the heterogeneity of patient populations, treatment types, and counterregulatory changes in appetite regulating peptides and hormones occurring in response to the antipsychotic-related weight gain. A careful review of the literature suggests that fasting morning ghrelin levels decrease early in the course of antipsychotic treatment and then increase after chronic exposure [26].

In addition to leptin and ghrelin, a host of peptides, hormones and receptors that have been associated with food intake and energy homeostasis are potentially involved in antipsychotic-induced weight gain [27,28]. Importantly, however, and in contrast to findings in rats [14], antipsychotics have not been demonstrated to bind receptors in the hypothalamus traditionally associated with weight regulation in humans. For example, binding of radiolabeled olanzapine or clozapine was not detected across 14 different hypothalamic receptors, including those with orexigenic (e.g. neuropeptide Y1 receptor), anorexigenic (e.g. neurotensin receptor 1), or fluid homeostatic (e.g. endothelin receptor) properties [29].

Because appetite and food intake increase with antipsychotics, antipsychotic effects on peptides and hormones involved in food intake and energy homeostasis have been suspected [14,27]. However, studies have been inconclusive, suffering from similar shortcomings as those focusing on moderators and mediators reviewed above. Additional factors include the selection of a limited number of examined peptides and hormones, lack of tight control of confounding variables, and reliance on peripheral markers that may or may not be a good proxy for levels of potentially etiologically important factors in the central nervous system or in peripheral tissues, such as intestine or liver.

Pharmacodynamic neurotransmitter receptor targets of antipsychotics

Strong binding (antagonism or partial agonism) at dopamine D2 receptors is the only mechanism common to all currently-approved antipsychotics and is (so far) a necessary component for antipsychotic efficacy [30]. However, the antipsychotics as a class are diverse in their targets, interacting with distinct receptor subtypes including the serotonin receptors, muscarinic acetylcholine receptors, histamine receptors, and noradrenaline receptors with varying degrees of affinity [31]. Consequently, much of the literature on antipsychotic-induced weight gain has compared neurotransmitter receptor profiles and the relative burden of each compound. In evaluating this literature, it is important to consider the probability that multiple, synergistic pharmacodynamic effects and interactions might produce weight gain phenotypes. Some of these effects could be common to many or all antipsychotics, whereas others could be specific to those with particular receptor affinities.

Dopamine

Despite the ubiquitous role of dopamine receptor blockade in antipsychotic action, this mechanism has been relatively understudied as a causal factor of weight gain. To some extent, this might derive from historical accident: prior to the reintroduction of clozapine and the subsequent development of SGAs, which were thought to be distinct from FGAs

because they interact with nondopamine receptors, antipsychotic-induced weight gain was not a major focus. However, weight gain is a feature of virtually all antipsychotics, including conventional antipsychotics (e.g. haloperidol) [32,33] that do not have the complex pharmacology of clozapine and olanzapine. A recent European study of first-episode patients with limited or no prior exposure to antipsychotics demonstrated clinically significant (≥7%) weight gain at the end of 12 months in more than half of subjects treated with haloperidol, and in 63% of patients treated with amisulpride (Table 1), which interacts exclusively with dopamine D2/D3 receptors [33]. Indeed, clinical studies in both first-episode and chronically treated patients have been notable for the relative similarities in mean weight gain observed across multiple SGAs (including risperidone and quetiapine) and FGAs [6,11,32,33,34]. This consistency, despite differences in the severity of weight gain [6,11,18], points to a potential common underlying mechanism, with D2 blockade as the most likely common factor.

Recent evidence supports a robust relationship between D2 activity and feeding behavior. For example, D2 agonists inhibit food intake in rodents [14], whereas risperidone and other antipsychotics increase food intake and core body temperature, while reducing locomotor activity in mice [14]. Moreover, food restriction increases D2 receptor levels in rodents [35], whereas obesity associates with lower D2 levels in the nucleus accumbens in humans [36]. A direct effect of leptin on dopamine neurons in the ventral tegmental area (VTA), which expresses the leptin receptor, has recently been established from two independent laboratories [37,38]. Direct administration of leptin to the VTA resulted in the activation of the intracellular JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway, reduced firing rate of VTA dopamine neurons compared to baseline or saline and decreased food intake compared to baseline [37]. Conversely, leptin-deficient mice showed reduced neuronal and behavioral (locomotor) responsivity to amphetamine compared to mice that had intact leptin signaling [38]. Taken together, these data suggest that D2 blockade might impact energy metabolism through alterations in reward signaling and decreased psychomotor activity.

Histamine

Several lines of evidence have implicated the histamine system in antipsychotic-induced weight gain. Histamine neurons are located in the posterior hypothalamus, project to many regions of the brain, and produce effects via several receptor subtypes, including the H1 receptor [39]. H1 receptor knockout animals demonstrate increased food intake, changes in feeding patterns, and obesity compared to wild-type controls [40]. Moreover, H1 receptor agonists might suppress food intake, whereas hypothalamic HI receptor antagonism increases food intake [41].

With respect to antipsychotics, Kim *et al.* [42] reported that SGAs activate hypothalamic AMP-kinase in mice, with clozapine and olanzapine having the greatest effects. Knockout of the H1 receptor, however, blocked these effects, suggesting that H1 receptor-linked activation of hypothalamic AMP-kinase could be critical in mediating antipsychotic-induced weight gain. Moreover, the affinity of antipsychotics for the H1 receptor correlated with the degree of weight gain associated with each drug. Similarly, Kroeze *et al.* [43] evaluated the binding of 17 FGAs and SGAs to multiple neurotransmitter receptors, including histamine H1, 5-HT_{2C} (5-hydroxytryptamine-2C) and dopamine D2, and found that binding to the histamine H1 receptor best predicted the reported weight gain liabilities of the antipsychotics in clinical studies.

Serotonin

Serotonin has been suggested to play a major role in regulating feeding behavior and satiety signaling. Serotonergic neurons project onto anorexigenic pro-opiomelanocortin (POMC) neurons in the hypothalamus, working in concert with leptin signaling to decrease food intake [44]. Because pharmacologic agonists of 5-HT_{2C} decrease feeding in animals [14], it is logical to conclude that 5-HT_{2C} antagonists, including most SGAs and low potency FGAs such as chlorpromazine [31], might increase food intake by impairing satiety. Several studies have demonstrated that rats treated with SGAs have increased food intake compared to untreated controls [14], and that olanzapine-induced weight gain can be abolished by the use of a pair-feeding paradigm, in which diet is yoked to the intake of a control animal [45]. Moreover, analysis of feeding patterns demonstrated increased meal size and duration rather than meal frequency in olanzapine-treated animals, suggesting delayed onset of satiety rather than decreased satiety signaling *per se* [14,45]. These results are consistent with the clinical observation that both clozapine and olanzapine can induce food craving and binge eating in human patients [46].

Notably, the two SGAs associated with the greatest weight gain, clozapine and olanzapine, are inverse agonists at 5-$HT_{2C.}$ The significance of this was demonstrated in a recent study by Kirk *et al.* [47], in which rats were exposed to a compound (SB 243213) that is a selective inverse agonist at the 5-HT_{2C} receptor. After five days, this agent produced significant weight gain compared to vehicle but less than that observed in olanzapine-treated animals. However, in combination with a potent dopamine D2-antagonist (haloperidol), the SB 243213 treated animals demonstrated a much larger weight gain, which was comparable to the effects of olanzapine. These results were not observed when mepyramine, a selective histamine H1 antagonist, was substituted. These data suggest that the histamine activity of olanzapine is neither necessary nor sufficient to produce weight gain, underscoring further the complex interactions underlying antipsychotic-induced weight gain.

Taken together, the available preclinical and human data indicate that no single one neurotransmitter system is responsible for antipsychotic-related weight gain. While rodent and indirect human evidence links the weight gain potential of antipsychotics to histamine H1 blockade [39–43], studies also implement other neurotransmitter systems [14,35–38,44–46]. These results are further supported by evidence of an interaction between histamine H1 and dopamine D2 blockade [47], genetic data [5,15,27,48–55], and by the fact that antipsychotics without relevant antihistaminergic activity, such as aripiprazole, amisulpride and haloperidol (Table 1), have clearly documented weight gain potential, especially in antipsychotic-naive and first episode patients [11,32,33]. Nonantihistaminergic candidates include dopamine D2 blockade [14,35–38], 5HT 2C blockade [44–47], and interactions with central or peripheral hormones and peptides involved in energy homeostasis [14,25–29].

Genetic mechanisms influencing antipsychotic-induced weight gain

The role of dopamine and serotonin modulation in antipsychotic-induced weight gain is further supported by pharmacogenetic data in humans [15,27,48–52]. In addition, genetic data have pointed towards a role of alpha-adrenergic transmission, G Protein, Leptin and leptin receptor activity, Promelanin-concentrating hormone (PMCH) and the cannabinoid receptor activity in antipsychotic-induced weight gain [5,48–50,53–55] (Table 3).

Surprisingly, dopamine-related genetic variation has not been widely studied with respect to the weight gain phenotype. Recently, however, two studies have implicated the dopamine D2 receptor (DRD2) in antipsychotic weight gain [15,51]. In one of these studies, a significant relationship was observed between a functional promoter polymorphism (*DRD2 -141C Ins/Del*), which affects transcription levels of the dopamine D2 receptor, and

antipsychotic weight gain [15]. Enhancing the power of this study, more than 75% of patients were antipsychotic-naïve, and all were first episode schizophrenia patients randomized to risperidone (n=32) or olanzapine (n=26). *DRD2 Del* carriers (i.e. individuals without any nucleotide at that position; n=29) were compared to *Ins/Ins* homozygotes (noncarriers, n=29) in a mixed model encompassing ten measurements over 16 weeks. *DRD2 Del* carriers gained substantially more weight compared to noncarriers after 6+ weeks of treatment, regardless of medication assignment. Mean weight gain in *Del* carriers at 6 weeks was ~six pounds greater than in noncarriers. At 16 weeks, genotype accounted for 15 pounds differential in weight gain. These data further support the notion that dopamine D2 blockade might be related to both antipsychotic effects and weight gain.

Perhaps the best studied genetic factor in antipsychotic–induced weight gain relates to the serotonin receptor, specifically at the promoter region single nucleotide polymorphism (SNP) 759T/C in the *HTR2C* gene. Initial findings of a significant interaction between antipsychotic-related weight gain and the 759T/C polymorphism in the *HTR2C gene* were obtained in antipsychotic-naïve Chinese patients, enhancing the power for the analyses. However, these findings have been replicated in several independent schizophrenia patient samples and across varying antipsychotic agents [52]. In a recent meta-analysis of eight studies, most of which were conducted with chronically ill patients, a greater than two-fold increase in risk for clinically significant (≥7%) weight gain was associated with the C allele at this SNP [52]. Since then, two large population-cohort studies have demonstrated that the C allele at this SNP is related to obesity in healthy individuals [56,57], indicating that acute antipsychotic administration might accelerate or accentuate behavioral and metabolic tendencies that could otherwise emerge.

Several pharmacogenetic studies have also tested the role of genes implicated in nonpsychiatric weight-related phenotypes. For example, the *GNB3* gene encodes a subunit of a heterotrimeric guanine nucleotide-binding protein (G protein), which integrates signals between receptors and effector proteins. The C825T SNP in the *GNB3* gene has been associated with essential hypertension and obesity, which is also associated with a high-activity splice variant of the *GNB3* gene. In a recent meta-analysis including five studies, the T allele of the C825T SNP was modestly (but significantly) associated with increased antipsychotic-induced weight gain [54].

Genome-wide association studies (GWAS) provide strong evidence for several genes, including *FTO*, *MC4R* and *TMEM18*, important in obesity and obesity-related phenotypes [58]. GWAS have the advantage of drawing on extremely large sample sizes (n>10,000) from the general population and examining >95% of the genome, so they provide fertile ground for developing testable hypotheses on the mechanisms of antipsychotic-induced weight gain. Only one GWAS has been published on antipsychotic-associated weight gain and related phenotypes [59]. Despite the heterogeneity of treatment conditions and patient history in this sample, several promising new leads for genes involved in the cardiometabolic adverse effect of antipsychotics were reported. This included genome-wide-significant results for a polymorphism in *MEIS2* for the increase in waist- and hip-circumference, a clinical proxy measure for intra-abdominal adiposity, in risperidone-treated patients. Intriguingly, this gene is involved in pancreatic development and function, providing a possible link between intra-abdominal adiposity and the development of diabetes [60]. Future GWAS in antipsychotic-naïve cohorts are needed to increase the power, which is necessary for signal detection and further hypothesis generation, as the testing of such a large numbers of SNPs requires a very high statistical threshold for significance.

Concluding remarks

Antipsychotics, which are frequently used for psychotic and nonpsychotic conditions, are associated with substantially increased appetite and weight gain, as well as increased risk for obesity and metabolic abnormalities. Taken together, the available data suggest that cardiometabolic pathology and risk factors in mentally ill patients result from several interactive factors, including i) the patient's genetic background; ii) the underlying illness; iii) unhealthy lifestyle behaviors; and iv) psychotropic medication effects.

Despite the importance of weight gain, obesity and metabolic abnormalities, the mechanisms underlying antipsychotic-related cardiometabolic adverse effect are still poorly characterized. This has interfered with the development of targeted and successful interventions for antipsychotic weight gain. In addition, because antipsychotics highly likely link to innate satiety, energy homeostasis and metabolic pathways, the lack of a detailed mechanistic understanding of antipsychotic-related cardiometabolic effects has also hampered a further unraveling of the mechanisms underlying the development and maintenance of idiopathic obesity. However, recent data support the view that antipsychotics affect key mechanisms that regulate appetite, satiety and energy homeostasis and involve hypothalamic serotonin $5HT_{2C}$, histamine H1 and cannabinoid receptors, dopamine and alpha-adrenergic transmission, as well as central and/or peripheral orexigenic and anorexigenic hormones and peptides and/or their receptors. Nevertheless, despite this body of work, many basic questions remain unresolved and should be addressed in future studies (Box 1).

Box 1

Outstanding questions

1. What are the relative contributions of illness, environmental and treatment related effects for weight gain and obesity associated with antipsychotics?
2. Can antipsychotic action be entirely separated from weight gain?
3. What are the reliable pretreatment and early intratreatment predictors of clinically relevant, antipsychotic-related weight gain?
4. What are the exact biological and environmental mechanisms of antipsychotic-related weight gain?
5. Can understanding mechanisms of antipsychotic-related weight gain lead to the development of novel antiobesity drugs for idiopathic obesity in nonmentally ill populations?
6. What are the most promising molecular and genetic targets for the development of preventive and ameliorative interventions for antipsychotic-induced weight gain?
7. To what degree are direct effects of antipsychotics that do not require weight gain responsible for metabolic complications?
8. What are the antipsychotic-related mechanisms that are uncoupled from weight gain that are responsible for glucose and lipid abnormalities?
9. Can understanding the mechanisms responsible for antipsychotic-related metabolic abnormalities that are unrelated to weight gain lead to the development of novel antidiabetic and/or lipid-lowering drugs for nonmedication-induced diabetes or dyslipidemia?

However, notwithstanding these unresolved questions, the potential for significant antipsychotic-related cardiometabolic effects has been established [3]; this risk differs across both FGAs and SGAs [3,6–11,32–34,61–63], and patients as well as behavioral factors are relevant [3–5]. Based on these findings, clinicians should: i) select antipsychotics with the least cardiometabolic liability whenever possible [3]; ii) council patients about, strongly encourage and proactively monitor healthy diet and exercise behaviors [4]; iii) monitor all patients treated with antipsychotics for the presence and emergence of cardiometabolic risk factors or disorders [3]; iv) be vigilant about the possibility of metabolic abnormalities in the absence of relevant weight gain or obesity; v) consider behavioral and pharmacologic interventions to mitigate antipsychotic cardiometabolic effects [4]; and vi) collaborate as part of an integrated care model with medical health care providers when cardiometabolic disorders emerge that require more complex medical interventions [3].

Future research is needed that takes advantage of the enhanced power obtained by studying antipsychotic-naïve individuals for proximal/early cardiometabolic effects. Likewise, for the study of distal/late effects, such as diabetes and cardiovascular events, sample enrichment strategies for the outcome under investigation should be used [64]. Although this strategy runs counter to the general procedures of excluding severely ill and metabolically compromised patients, focusing on such samples allows the focused and accelerated study of mechanisms of and risk factors for effects that take years to emerge. Furthermore, in addition to mechanistic proof of concept studies in highly selected samples, large pharmacoepidemiologic studies in generalizable samples are needed that have sufficient power to differentiate between different agents and to control for relevant confounding variables, such as prior treatment history, degree of weight gain, comedications, lifestyle, illness type and phase, comorbidities, cotreatments, etc.

Moreover, given the lack of conclusive evidence that current genetic candidates are actual susceptibility polymorphisms for antipsychotic-related cardiometabolic side effects, next generation, exploratory genomic approaches should be pursued. These hypothesis-generating studies will need to be followed by second-step hypothesis-testing of significant findings in enriched and in generalizable replication samples. Additionally, studies that go beyond the traditional weight gain approach need to be pursued. This includes the investigation of mechanisms involved in the reversal of antipsychotic-induced weight gain, focusing on peptide and hormonal changes as well as genetic factors affecting the variance in the observed weight loss after antipsychotic treatment discontinuation, after the switch to a lower risk medication, or after adding a weight loss intervention.

Finally, any novel leads from the study of antipsychotic-related cardiometabolic adverse effects should be translated into the field of idiopathic obesity research and vice versa. For example, medications tested in the idiopathic obesity field should prompt investigations of these agents in patients undergoing antipsychotic treatment [5]. Testing such agents in patients with antipsychotic-related obesity as well as in those with idiopathic obesity followed in the same study could further elucidate shared and unique pathways involved in the maintenance or reductions of abnormally elevated body weight and lipid and glucose metabolism. Given the importance of obesity and cardiometabolic risk factors, in general, and given the prevalence of antipsychotic use, in particular, the current lack of any decisive knowledge about mechanisms and best preventive treatment options should prompt an increase in the study of this important side effect cluster.

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Glossary box

Allele	one of several alternative forms of a gene at a given locus
Anorexigenic	causing a decrease in food intake (catabolic)
Cardiometabolic adverse effects	weight gain, development of overweight or obesity, hypertension, lipid and glucose abnormalities, metabolic syndrome and related cardiovascular disorders
Extrapyramidal side effects	side effects related to dopamine blockade in the nigro-striatal system, including acute dystonic reactions, parkinsonism (rigidity, akinesia, tremor), akathisia and tardive dysinesia
Genome-wide association study (GWAS)	research examining the relationship between a given phenotype and genetic variation at more than 95% of the entire genome
Genotype	an individual's allelic status at a given locus
Mediators	factors that interact with the primary causal factor and increase or reduce its influence
Moderators	factors that represent an intermediary step between distal cause and the ultimate effect
Orexigenic	causing an increase in food intake (anabolic)
Phenotype	any characteristic of the individual that can be observed, such as height, weight, or diagnosis
Polymorphism	genetic variation that occurs with a frequency of 1% or more in the population
Promoter	the region of a gene that controls the initiation of mRNA production
Single nucleotide polymorphism (SNP)	a genetic variation potentially altering a single "letter" or base pair in the DNA

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Figure 1a.

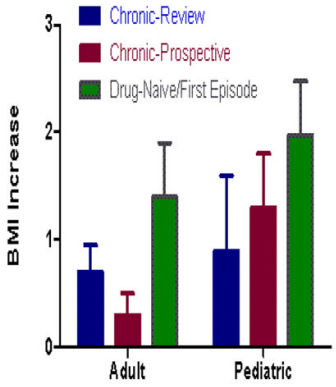

Figure 1b.

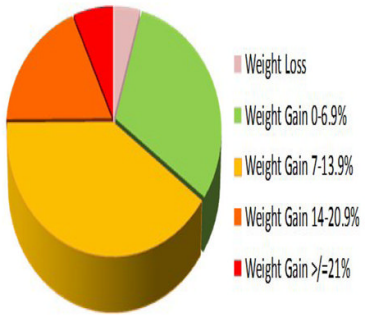

Figure 1.

Figure 1a. Effect of prior treatment exposure on BMI increase with risperidone in adults and youth [6–11]. The difference in the magnitude of weight gain associated with risperidone depends on patient age and treatment history. In adults and youth, the weight gain in antipsychotic-naïve and first-episode patients (green bar) is far greater than in patients with chronic illness and treatment exposure, either in pooled reviews (blue bars), or prospective studies (red bars). In comparison to adults, the weight gain in youth, and especially in those with no more than seven days of lifetime antipsychotic exposure (green bar on the right), was the greatest. The blue and red bars, respectively, at the left of Figure 1a display data summarized in a recent review [6], and data derived from the large-scale prospective CATIE trial [7].

Figure 1b. Heterogeneity of weight gain in antipsychotic-naïve youth treated with risperidone for three months [11]. The pie chart shows the heterogeneity of three-month weight gain in 135 children and adolescents receiving risperidone who were part of a cohort study of 272 antipsychotic-naïve youth. Despite a mean weight gain of 5.3 kg, weight gain outcomes varied considerably: weight loss occurred in 4.4%; weight gain of 0–6.9% of baseline body weight occurred in 31.1%; of 7–13.9% in 39.6%; of 14–20.9% in 18.5%; and of ≥21% in 6.7% of youth.

Figure 2.
Model of antipsychotic-induced weight gain. The heterogeneity of antipsychotic-induced weight gain results from still poorly understood drug-gene-environment interactions. Moderators of antipsychotic-induced weight gain include variables related to patient demographics, treatment setting, illness characteristics, past and baseline antipsychotic and comedication treatments, and baseline diet, activity, and body composition. Mediators include antipsychotic dose, comedications, medication side effects and changes in diet and activity. Taken together, these factors interact in specific ways leading to antipsychotic-induced weight gain via so far incompletely understood mechanisms and pathways.

Table 1

Neurotransmitter and cardiovascular risk characteristics of selected first- and second-generation antipsychotics [3–11,31–34,62,63]

Antipsychotic	Neurotransmitter targets	FDA indication	Risk level weight gain	Risk level lipid abnormalities	Risk level glucose abnormalities
FGAs (selection)					
CHLORPROMAZINE (Thorazine®)	Cholinergic M1 > serotonin 5HT2A > histamine H1 > > dopamine D2	Schizophrenia, bipolar mania (acute)	High	High	High
HALOPERIDOL (Haldol®)	Dopamine D2 > all other neurotransmitter receptors	Schizophrenia	Low	Low	Low
MOLINDONE (Moban®)	Dopamine D2 > all other neurotransmitter receptors	Schizophrenia	Low	Low	Low
PERPHENAZINE (Trilafon®)	Dopamine D2 > all other neurotransmitter receptors	Schizophrenia	Low	Low	Low
SGAs					
AMISULPRIDE (Solian®)	Dopamine D2 (putatively with regional selectivity)	Schizophrenia (not in the US)	Low	Low	Low
ARIPIPRAZOLE (Abilify®)	Partial dopamine D2 agonism (> serotonin 5HT 1a partial agonism >/= serotonin 5HT2A)	Schizophrenia (acute and maintenance, pediatric and adult), bipolar mania (acute (also as adjunct) and maintenance, pediatric and adult), unipolar depression (adjunct only)	Low	Low	Low
ASENAPINE (Saphrys®)	Serotonin 5HT2C > Serotonin 5HT2A > histamine H1 > alpha 1 >/= alpha 2 >/= dopamine D2	Schizophrenia (acute and maintenance); bipolar mania (acute)	Low	Low	Low
CLOZAPINE (Clozaril®)	Cholinergic M1 > serotonin 5HT2A> histamine H1 > serotonin 5HT2C > alpha 1 > alpha 2 ≫> dopamine D2	Schizophrenia (refractory)	High	High	High
ILOPERIDONE (Fanapt®)	Serotonin 5HT2A > alpha 1 ≫ alpha 2 >/= dopamine D2	Schizophrenia (acute)	Intermediate	Intermediate	Intermediate
OLANZAPINE (Zyprexa®)	Histamine H1 > serotonin 5HT2A> cholinergic M1 > serotonin 5HT2C > dopamine D2	Schizophrenia (acute and maintenance, pediatric and adult), bipolar mania (acute and maintenance, pediatric and adult), unipolar depression (only in combination with fluoxetine)	High	High	High
PALIPERIDONE (Invega®) [active metabolite of risperidone]	Serotonin 5HT2A >dopamine D2	Schizophrenia (acute and maintenance), schizo-affective disorder (acute)	Intermediate	Intermediate	Intermediate
QUETIAPINE (Seroquel®)	alpha 1 > histamine H1 > serotonin 5HT2A > alpha 2 > cholinergic H1≫ dopamine D2; serotonin reuptake inhibition	Schizophrenia (acute and maintenance, pediatric and adult), bipolar mania (acute and maintenance-as adjunct only, pediatric	Intermediate	High	Intermediate

Antipsychotic	Neurotransmitter targets	FDA indication	Risk level weight gain	Risk level lipid abnormalities	Risk level glucose abnormalities
		and adult), bipolar depression; unipolar depression (adjunct only)			
RISPERIDONE (Risperdal®)	Serotonin 5HT2A ≫ alpha 1 > dopamine D2	Schizophrenia (acute and maintenance, pediatric and adult), bipolar mania (acute - also as adjunct, pediatric and adult; maintenance-only as long acting injectable)	Intermediate	Intermediate	Intermediate
ZIPRASIDONE (Geodon®)	Serotonin 5HT2A ≫ dopamine D2; serotonin 5HT 1a partial agonism; noradrenaline reuptake inhibition	Schizophrenia (acute and maintenance), bipolar mania (acute and maintenance-adjunct only)	Low	Low	Low

Table 2

Appetite-regulating factors possibly involved in antipsychotic-related weight gain

Ligand	Receptor
Appetite-Stimulating (orexigenic)	
Hypothalamus-related signals	
Melanin-concentrating hormone (MCH)	MCH receptor
Orexin A/B = hypocretin I/II	Orexin A/B receptor
Neuropeptide Y (NPY)	Neuropeptide Y_1 and Neuropeptide Y_5
Agouti-related protein (AGRP)	Melanocortin 4 receptor (MC4R)
Galanin	Galanin receptor
Endocannabinoids (anandamine, 2-arachidonoyl glycerol)	Cannabinoid 1 receptor (CB1-R)
β-endorphin	μ-opiate receptor
Enkephalins, dynorphins	δ, κ-opiate receptors
Adiposity-Related Signals	
Ghrelin	Growth hormone secretagogue (GHS)
Appetite-Suppressing (anorexigenic)	
Hypothalamus-Related Signals	
Corticotropin releasing hormone	Corticotropin hormone I/II receptor
Growth hormone-releasing hormone (GRH)	GRH receptor
Thyreotropin-releasing hormone	Thyreotropin-releasing receptor
Melanocortin, melanocyte-stimulating hormone (α- MSH)	Melanocortin 4 receptor (MC4R)
Oxytocin	Oxytocin receptor
Galanin-like peptide	Galanin-like peptide receptor
Cocaine-amphetamine-regulated transcript (CART)	?
Prolactin-releasing neuropeptide	Prolactin-releasing neuropeptide receptor
Brain-derived neurotrophic factor (BDNF)	BDNF receptor
Ciliary neurotrophic factor	Ciliary neurotrophic factor receptor
Neurotensin	Neurotensin receptor
Urocortin I/II/III	Corticotropin-releasing factor receptor 1/2
Adiposity-Related Signals	
Leptin	Leptin receptor
Insulin	Insulin receptor
Tumor necrosis factor-alpha (TNF-α)	TNF receptor
Interleukin (IL) 1 and 2	IL-1 and IL-2 receptors
Meal-Related Signals*	
Cholecystokinin (CCK)	CCK A/B = I/II receptor
Bombesin	Bombesin receptor subtype 3 (BRS3)
Gastrin-releasing peptide	Gastrin-releasing peptide receptor
Glucagon	Glucagon receptor

Ligand	**Receptor**
Glucagon-like peptide-1 and 2 (GLP-1/2)	GLP-1/2 receptors
Oxyntomodulin	Oxyntomodulin receptor
Neuromedin B	Neuromedin B receptor
Enterostatin	Enterostatin receptor
Amylin	Amylin receptor
Apolipoprotein A-IV	Apolipoprotein A-I/AII receptors
Pancreatic polypeptide	Pancreatic polypeptide receptor
Somatostatin	Somatostatin receptor
Peptide YY3-36	Neuropeptide Y Y2 receptor

* Many "meal-related" signaling peptides and hormones are produced in the central nervous system and have nonmeal-related functions as well.

Table 3

Genetic polymorphisms associated with antipsychotic-related weight gain

Risk Gene (Chromosomal location)	Genetic mutation
Alpha-$_{2A}$Adrenergic receptor gene (10q24-26)	−1291C/G (rs1800544)
Cannabinoid receptor (CNR) 1 gene (6q14–q15)	rs806378 385C/A
Dopamine receptor D2 (DRD$_2$) gene (11q22–q23)	−141C Ins/Del rs4436578-C
G-Protein beta3 subunit (GNB3) gene (12p13)	C825T
Leptin gene (7q31.3)	−2548A/G (rs7799039)
Leptin receptor gene (1p31)	K109R (rs1137100) Q223R (rs12131454) K656N (rs8179183) 2548A/G
PMCH gene (12q23–q24)	rs7973796
Serotonin 2C (5HT$_{2C}$) receptor gene (Xq24)	−759C/T (rs3813929) c.1–142948(GT)n 13 repeat allele common allele rs3813929 C variant allele rs518147 C variant allele rs1414334 C