Strategies to counter antipsychotic-associated weight gain in patients with schizophrenia

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**Strategies to counter antipsychotic-associated weight gain
in patients with schizophrenia**

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Abstract

Introduction

Patients living with schizophrenia have a marked risk of clinically significant weight gain and obesity compared to the general population. The risks have been highlighted following the introduction of second-generation antipsychotics. In turn, obesity is associated with a higher prevalence of cardiovascular disease, the most common cause of premature mortality in patients with schizophrenia.

Areas Covered

In this review we outline possible mechanisms that induce obesity in patients with schizophrenia taking antipsychotics. We discuss the safety and effectiveness of three main approaches for attenuating antipsychotic-associated weight gain (AAWG), including lifestyle interventions, switching antipsychotics, and augmentation with other medications.

Expert Opinion

When selecting antipsychotics, effective treatment of psychotic symptoms should be highest priority but obesity, and related metabolic comorbidities associated with antipsychotics, should not be neglected. Further research into mechanisms of weight gain associated with antipsychotics will guide future treatments for AAWG and development of antipsychotics that produce minimal metabolic adverse effects. With current strategies only producing modest weight loss in already overweight and obese individuals, clinicians should transition to an approach where they aim to prevent weight gain when initiating antipsychotic treatment.

Keywords: antipsychotic, lifestyle, mechanisms, obesity, pharmacological, schizophrenia, weight gain, switching

Article Highlights

- The introduction of second-generation antipsychotics has resulted in higher incidences of metabolic risk factors, specifically obesity.
- The mechanisms responsible for antipsychotic-induced weight gain are believed to be changes in hormones and peptides involved in energy homeostasis, antagonism of receptors in appetite and satiety centres, and pharmacogenetic differences between patients. Additionally, recent research has demonstrated a possible role of the gut microbiome.
- Lifestyle interventions including exercise, nutritional advice, and cognitive-behavioural therapy have shown modest reductions in weight gain. However, to be effective such interventions must be adequately designed and resourced in order to promote adherence and lifestyle changes in this population.
- Switching to antipsychotics with a lower risk of inducing weight gain such as aripiprazole, ziprasidone and amisulpride may show promise but applicability is limited by poorly designed studies with high discontinuation rates (largely due to symptom exacerbation).
- Augmentation with other medications is an effective strategy. Metformin and GLP-1RAs have the most robust data demonstrating favourable reductions in weight and minimal reports of serious side effects.

1.0 Introduction

Cardiovascular disease (CVD), is the largest contributor to the 2-3-fold increased mortality rate and disparity in life expectancy of 10-20 years in patients with schizophrenia compared to the general population.[1-3] The prevalence of CVD in patients with schizophrenia is estimated to be 11.8% with an incidence of 3.6% per year.[1] It is therefore imperative that clinicians manage CVD-modifiable risk factors including obesity, dyslipidaemia, hypertension, diabetes, and smoking.[4] Obesity is highly prevalent with studies suggesting up to 60% of patients with schizophrenia are obese (BMI ≥30), and is a significant contributor to increased CVD risk.[1] Patients with schizophrenia have double the risk of developing obesity than the general population.[5]

The causes of weight gain are complex and multifactorial. Identified genetic, environmental, and disease-specific factors contribute to increased susceptibility.[6] These include high caloric diets combined with a sedentary lifestyle, stigma and discrimination due to mental illness, social isolation, and poor psychotic symptom management.[7] The introduction of second-generation antipsychotics (SGA) such as clozapine, olanzapine, and quetiapine in the 1990s has highlighted the significant impact of metabolic adverse effects (including weight gain) associated with antipsychotic treatment.[8-10] A well-defined hierarchy of weight gain risk associated with both first-generation antipsychotic (FGA) and SGA agents has been established in the literature. However, this is often limited to populations with chronic illness; with young and antipsychotic-naïve patients gaining 3-4-fold more weight irrespective of the antipsychotic initiated.[11]

Obesity, type 2 diabetes mellitus, dyslipidaemia, and metabolic syndrome are associated with an increased risk of cardiovascular events.[12] Obesity also affects other lifestyle behaviours, such as increasing social withdrawal[13] and sedentary behaviour[14], both of which are themselves risk factors for worsening cardiometabolic health[15]. Alongside cardiovascular risk, obesity is a modifiable risk factor for other non-communicable diseases which disproportionately reduce life expectancy in people with severe mental illness including multiple types of cancer, liver disease, and respiratory illnesses[16]. Furthermore, if obesity is not appropriately addressed it can negatively influence the patient's view of treatment and reduce medication adherence leading to a deterioration in psychosocial function, an increase in hospital readmissions, and reduced quality of life.[17,18]

Additionally, evidence from the general population has provided compelling evidence for casual links for obesity with depression, inflammation, cognitive dysfunction, and neural atrophy[19-21] – all of which are often observed but untreated in patients with schizophrenia despite been associated with worse prognosis and higher burden of illness[22-24]. Importantly, cognitive deficits represent a core symptom domain for schizophrenia with the possibility that the well-recognized metabolic adverse effects of antipsychotics could contribute to cognitive impairments over the course of treatment[25]. Given all of the above, it is clear that the heightened rates of obesity which arise in those taking antipsychotic medications cannot be accepted as a necessary part of treatment and must be addressed in order to improve both physical and functional outcomes of psychotic disorders.

This situation has created challenges for clinicians trying to balance antipsychotic-associated weight gain (AAWG) whilst still ensuring effective treatment of schizophrenia with minimal extra-pyramidal side effects (EPS). We aimed to review the mechanisms for weight gain in schizophrenia and strategies to manage AAWG with an emphasis on maintaining treatment effectiveness in order to guide clinical practice and identify current gaps in research.

2.0 Methods

In this narrative review we examined relevant publications on the mechanisms responsible for inducing obesity in patients with schizophrenia who are taking antipsychotics. We explored the three common therapeutic options employed by clinicians for dealing with this issue: 1) lifestyle intervention and advice; 2) switching to another antipsychotic with a reduced propensity to induce metabolic adverse effects; or 3) augmentation with another medication. Other interventions such as bariatric surgery and smoking cessation were beyond the scope of the review. We concentrated on recent studies describing the efficacy and safety of the therapeutic strategy and the its impact on mental health outcomes. We followed the Joanna Briggs Institute (JBI) guidelines for narrative reviews.[26] We searched PubMed and Google Scholar (advanced search) databases from database inception until 29 April 2019 with papers restricted to English. Search terms included (antipsychotic* OR neuroleptic*) AND (“weight gain” OR obesity OR “body mass index” OR “waist circumference”).

3.0 Mechanisms of antipsychotic-induced weight gain

Obesity is a result of an caloric imbalance where energy intake greatly outweighs energy expenditure, resulting in excessive fat accumulation.[27] Energy homeostasis is a complex interplay of peripheral and central signals, integrated by the hypothalamus and caudal brainstem.[28] Antipsychotics appear to influence and interfere with aspects of this homeostatic control, through the mechanisms described below, resulting in hyperphagia, hyperglycaemia, and reduced energy expenditure.[29]

3.1 Hormones and peptides

Central control of satiety and appetite largely occurs in the arcuate nucleus (ARC) of the hypothalamus.[28] The ARC contains an abundance of orexigenic, neuropeptide Y (NPY) and agouti-related peptide (AgRP), and anorexigenic, pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), neurons that are influenced directly or indirectly by peripheral signals of satiety.[30]

Peripheral hormones such as glucagon-like peptide 1 (GLP-1) and leptin elicit anorexigenic effects.[28,29,31] Changes in circulating levels of these hormones have been observed in patients experiencing AAWG. By reducing GLP-1 secretion, SGAs such as olanzapine, clozapine, and quetiapine impair glucose homeostasis and increase diabetogenic risk in mice.[32,33] Additionally, reduction in GLP-1 alters gustation thereby impairing sweet-taste sensitivity.[34] This is consistent with findings showing olanzapine and clozapine induce cravings for higher-caloric carbohydrate foods.[33,35]

Circulating leptin levels increase in parallel with increases in adiposity.[36] Leptin receptors are present throughout the ARC and ventral tegmental area, allowing leptin to mediate its anorexigenic effects through multiple neuronal pathways.[28,37] High levels of leptin are observed in obese patients with schizophrenia suggesting a resistance to endogenous leptin similar to that of obese patients in the general population.[38] This indicates hyperleptinemia is resultant of AAWG rather than a pathophysiological cause.[38,39] Ghrelin is an orexigenic hormone that elicits a response opposite to that of leptin.[36] It plays a large role within satiety homeostasis but conflicting results have been observed with regards to AAWG. [40-43]

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Insulin in the periphery represents an anabolic hormone, while in the central nervous system it has opposing catabolic and anorexigenic effects; through modulation of the reward system and homeostatic signals in the hypothalamus insulin reduces feeding, impacts food preferences, and lowers glucose production at the liver.[44] In turn, weight gain and adiposity associated with antipsychotic medications can indirectly result in insulin resistance. Moreover, in rodents, antipsychotics can directly, and acutely inhibit whole body insulin action[45,46], as well as central insulin action, leading to disruptions glucose and feeding homeostasis[47,48].

Melatonin, a hormone largely secreted by the pineal gland, is involved in various physiological processes including circadian rhythm, immune modulation, and energy metabolism.[49] Olanzapine-treated subjects demonstrate an increase in weight and visceral adiposity with a corresponding decrease in nocturnal circulating melatonin.[50] Daily supplementation of melatonin restores circulating levels and reduces secondary increases in weight and adiposity.[50,51] Further, seasonal changes in leptin sensitivity are linked to melatonin’s regulation of the circadian rhythm.[36]

The role of hormones and peptides is summarised in Table 1.

[Table 1 here]

3.2 Neurotransmission

SGAs exhibit mixed receptor antagonism with varying effects on dopaminergic, serotonergic, histaminergic, cholinergic, and adrenergic receptors.[10] This variation is considered a mechanism by which SGAs induce fewer extrapyramidal and prolactin-related adverse effects than FGAs but increase weight and alter metabolic parameters.[6,10] Literature largely revolves around the effects of SGAs on central neurotransmission, with the role of peripheral receptors less clear and understood.[36]

The importance of the dopaminergic system as a mechanism of weight gain was originally neglected in favour of other targets but associations between dopamine and feeding behaviour have become apparent.[6,52,53] Dopaminergic neurons located in the mesolimbic pathway, from the ventral tegmental area to the striatum, regulate reward-associated behaviour and have a significant influence on appetite.[52,53] D2 receptor deficiency in this pathway increases reward-seeking behaviour e.g. increased food intake and appetite in obese individuals.[52,54]

Antagonism of the serotonin receptors, particularly the 5-HT2A and 5-HT2C receptor subtypes, is a characteristic of many SGAs and is widely implicated as a pathway involved in weight gain.[36] Serotonin is a key component of the homeostatic control of satiety and appetite, with expression of the 5-HT2C receptor on POMC and NPY neurons in the ARC.[36,55] Mice treated with olanzapine have shown greater appetite and corresponding weight gain but locaserin – a 5-HT2C agonist – diminished this.[56] This suggests that antagonism of 5-HT2C induces weight gain.[56] Further substantiating the significance of the 5-HT2C receptor in terms of weight gain, olanzapine and clozapine are inverse agonists and induce more weight gain than ziprasidone and aripiprazole, which are partial agonists.[6,53,57] Limited data is available concerning the involvement of the 5-HT2A receptor. However, a study in fifteen antipsychotic-naïve patients experiencing their first-episode of schizophrenia has shown a possible link.[58] In this study neocortical binding of 5-HT2A by quetiapine positively correlated with an increase in BMI.[58]

Additionally, histamine 1 (H1) receptors further coordinate energy homeostasis.[29] Stimulation of H1 receptors result in anorexigenic actions.[29,36] However mice administered with clozapine and

olanzapine, potent H1 receptor antagonists, demonstrate greater activation of hypothalamic AMP-related kinase (AMPK), which is associated with appetite stimulation.[59,60] Ziprasidone, haloperidol and aripiprazole – antipsychotics less likely to induce weight gain – did not increase AMPK activity.[59] Additionally, leptin’s anorexigenic actions are partly mediated by this histaminergic pathway and increased AMPK activity disrupts and nullifies these actions.[29]

The role of neuroreceptors is summarised in Table 2.

[Table 2 here]

3.3 Pharmacogenetics

An array of genes and single nucleotide polymorphisms (SNP) are potential contributors to AAWG. The HTR2C gene, which encodes the 5-HT_{2C} receptor, is the most researched factor with the SNP rs3813929 the most consistently reported.[61,62] The T allele has increased transcriptional activity, resulting in higher numbers of 5-HT_{2C} receptors, which appears to protect against AAWG in contrast to the more frequent wildtype C allele.[61] Among people on clozapine, the SNP rs381328 in HTR2C with a T allele was associated with a lower BMI compared to the C allele.[63] Other treatment-related genes with robust association with AAWG include DRD2 and ADRA2A, which are the precursors for the dopamine D2 receptor and alpha 2A receptor, respectively.[61]

The genes associated with obesity in the general population are also implicated in AAWG. The GNB3 and MC4R genes have been extensively covered in gene-wide association studies and significant links with obesity reported.[61] This link appears to work via impacts on the endogenous hormone and neuronal systems regulating energy homeostasis.[61] Other genes like FTO, LEPR, BDNF, INSIG2, and SNAP25 are also associated with obesity by similarly affecting energy homeostasis.[61,62]

Table 3 summarises frequently identified genes, which contribute to AAWG.

[Table 3 here]

3.4 Gut microbiome

More recently, the microbiome-gut-brain axis has been explored as a possible mechanism for weight gain.[53] The gut microbiome interacts directly and indirectly with the central nervous system (CNS) through interactions on the gut surface and the production of neurotransmitters and short-chained fatty acids.[64] It is postulated that this influences the pathophysiology of neuropsychiatric conditions like schizophrenia but, additionally, is implicated as a contributing factor for obesity in patients treated with SGAs.[64]

Mice administered either olanzapine or risperidone demonstrate changes in the composition of the gut microbiota, with increases in the bacterial phylum Firmicutes and decreases in Proteobacteria, Actinobacteria, and particularly Bacteroidetes. The above changes are associated with an increase in body fat.[65,66] These preliminary findings were further supported in a study which attenuated weight gain in olanzapine-treated mice through the co-administration of antibiotics to prevent these microbiota changes.[67] The increase in Firmicutes and decrease in Bacteroidetes following SGA use has been replicated in a small study of 28 male children and adolescents taking regular risperidone compared to controls.[68] Overall, the effects of SGAs on the gut microbiome and the corresponding changes in weight are poorly understood and further research in humans is required and is ongoing.

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4.0 Treatment for antipsychotic-associated weight gain

Clinician’s strategies to ameliorate AAWG are vital to limit further CVD morbidity and mortality. With an array of pharmacological and non-pharmacological options available the challenge is to employ an effective and feasible approach.

4.1 Lifestyle interventions

Reductions in rigorous physical activity and a corresponding increase in sedentary behaviour within the general population is a general trend.[69] Patients with schizophrenia have high levels of sedentary behaviour (an average of 9-10 hours per day), and less physical activity and poorer fitness than the general population.[70,71] Furthermore, individuals with schizophrenia have substantially higher calorie intake than the general population[72] including higher daily intakes of obesogenic foods containing refined carbohydrates and saturated fats.[73] Interventions aimed at optimising exercise and diet appear to be beneficial in attenuating and preventing AAWG but are limited by poor adherence in many patients.

Physical activity interventions are heterogenous in nature with variations in the type and intensity of exercise.[74,75] Significantly increased physical fitness and improved cardiometabolic parameters following exercise is observed in some patients with schizophrenia.[74,75] A recent meta-review reported a significant reduction in body weight (standardised mean difference = -0.96) with a large effect size after exercise initiation.[76] Further, moderate-to-vigorous exercise has shown a positive effect on psychiatric symptoms and functioning.[74,77] However, the effects of exercise are inconsistent; other studies show no difference in weight, BMI, and psychiatric symptoms compared to usual care.[78,79] Nutritional and dietary interventions have moderate effects on reducing body weight, BMI and waist circumference, and improving blood glucose levels.[76,80] The best results were from interventions led by dieticians.[80]

Exercise and nutrition interventions are frequently used together with other non-pharmacological interventions like cognitive-behavioural therapy (CBT). CBT has shown moderate weight-reducing effects but better results and adherence is observed when CBT is provided alongside structured diet and exercise interventions.[80,81] A high attrition rate is frequently observed in these studies (most following a per protocol analysis), particularly in those involving physical activity.[74,82] Barriers to uptake of these strategies include negative symptoms of schizophrenia, somnolence (possibly induced by treatment), and a lack of supervision and support.[82] This is echoed throughout studies which show individualised interventions outperform group-based interventions but the former are more resource-intensive and initial cost-effectiveness analyses are not promising.[76,78,82] The principles of evidence-based lifestyle interventions, such as the Diabetes Prevention Program, are recommended when designing lifestyle interventions which are effective and engaging for individuals with schizophrenia and other mental illness [4]. Furthermore, using lifestyle interventions from the initiation of antipsychotic treatment – as a preventative strategy – may confer greater benefits for reducing the onset of obesity in patients with schizophrenia [4].

4.2 Switching antipsychotics

Switching antipsychotics is a common approach considered for AAWG. SGAs have different weight gain properties and a hierarchy of weight gain potential has been widely reported (Table 4).[6,57,83]

Patients experiencing AAWG after treatment with high risk of weight gain medications like olanzapine are often switched to SGAs such as aripiprazole, ziprasidone, or amisulpride.[84]

Aripiprazole has a unique mechanism compared to other antipsychotics with partial D2 and 5-HT1A receptor agonism and antagonism of 5-HT2A receptors.[6] A reduced affinity to H1 and 5-HT2C receptors contributes to the lower risk of weight gain.[85] A multi-site randomised trial including 311, predominantly male, outpatients switched from other antipsychotics (mostly olanzapine or risperidone) to 30mg aripiprazole daily reported a mean weight loss of 1.3-1.7kg (depending on how quickly antipsychotics were switched) after eight weeks.[86] The study was open-label with an overall discontinuation rate of 28%, largely due to adverse effects (7%), worsening of schizophrenia (9%), and withdrawal of consent (6%).[86]

A more recent 24-week multi-site, randomised study included 215 patients at risk of CVD who had previously been taking olanzapine, risperidone, or quetiapine.[87] Following a four-week cross-titration to aripiprazole (mean dose of 16.9mg daily), those who switched had a reduction in weight of 2.9kg and BMI of 1.07 kg/m² compared to those who remained on their initial antipsychotic.[87] The study was open-label and included a behavioural intervention aimed at improving diet and exercise.[87] Two in five (43.9%) switchers and one in four (24.5%) stayers discontinued their designated antipsychotic before the end of the 24 weeks.[87] One in 12 (8%) patients dropped out of the aripiprazole arm due to a lack of efficacy. Of the remaining patients there was no difference in treatment efficacy between the groups.[87]

Ziprasidone shows an even lower risk of producing weight gain than aripiprazole.[57,83] It has a relatively high affinity for H1 and 5-HT2C receptors but its 5-HT2A/D2 receptor affinity ratio is much greater than other SGAs. [6,88] A year-long multi-centre open-label study recruited 185 patients experiencing ineffective treatment or adverse effects with risperidone, olanzapine, or FGAs.[89] All were switched to ziprasidone (mean dose of 120mg daily) and randomised to one of three cross-titration strategies.[89] Switching from either risperidone or olanzapine resulted in a mean reduction in weight of 6.9kg and 9.8kg at 58 weeks, respectively.[89] There was no change in weight after switching from a FGA.[89] Importantly the reduction in weight gain was incremental over the 12 month period.[89] Like aripiprazole, switching to ziprasidone showed no deterioration in symptoms of schizophrenia in patients continuing therapy for the entire study but this was confounded by a high drop-out rate (61% of patients at trial conclusion).[89]

A year-long prospective open-label comparison study comprised 52 patients who were switched to either ziprasidone (mean dose 126.5mg daily) or aripiprazole (mean dose 14.5mg daily).[90] Significant differences between the ziprasidone and aripiprazole groups for BMI and body weight were only found after 52 weeks of treatment.[90] The ziprasidone group had a mean reduction of 2.3kg/m² in BMI and 6.30kg in body weight whereas the aripiprazole group had a 0.2kg/m² and 0.6kg reduction at 52 weeks, respectively.[90] Weight loss was greatest for ziprasidone at 52 weeks (6.30kg) whereas for aripiprazole weight loss was greatest at 12 weeks (2.81kg) suggesting greater long-term incremental weight loss with ziprasidone.[90] These results are limited by a drop-out rate of nearly half (48.1%) at 12 months, and the open label nature of the study meant patients were able to initiate other drugs such as mood stabilisers.[90] The primary reasons for discontinuation were poor treatment adherence (28%), patient decision, (24%) and lack of treatment efficacy (16%).

Amisulpride is a SGA which demonstrates relatively selective antagonism of D2 and D3 receptors with minimal effects on H1 and serotonergic receptors.[91] Amisulpride exhibits a moderate potential for weight gain.[6,91] A year-long open-label study of 46 Chinese inpatients switched from SGAs (mostly olanzapine and risperidone) to amisulpride (doses between 600mg-1000mg daily) were

compared to 46 inpatients who remained on their original SGA.[92] Compared to their baseline weight, patients switched to amisulpride lost 7.8kg on average compared to patients who remained on their SGA, who lost 2.6kg on average.[92] Within patients switched to amisulpride, 13 did not complete the study, largely due to psychotic symptom exacerbation (69.2%).[92]

Lurasidone has no significant affinity for 5-HT_{2C} and H₁ receptors and may induce less weight increase.[93] A recent 6-month open-label extension study showed a mean weight reduction of up to 1kg.[94] Interestingly, this was observed in the subgroup switched from ziprasidone whereas the subgroup switched from risperidone gained 0.7kg.[94]

Brexipiprazole and cariprazine – newer SGAs with a very similar mechanism of action to aripiprazole – may be a promising alternatives in the future.[95] Reviews suggest cariprazine is associated with fewer incidences of weight gain compared to aripiprazole and brexipiprazole (the agent that appears to cause the most weight gain of the three).[96,97] However, these results are preliminary; there is a paucity of data from randomised controlled trials comparing the agents and reporting on outcomes related to metabolic parameters (including weight gain).

Although switching to ziprasidone or aripiprazole to attenuate AAWG may be effective to reduce weight, clinicians must carefully consider their treatment approach. It is important to select an appropriate switching strategy (e.g. abrupt discontinuation vs cross-tapering) to minimise the risk of relapse and withdrawal symptoms.[98,99] One study compared these strategies when switching to aripiprazole; long-term safety and efficacy outcomes were comparable but abrupt discontinuation induced a higher risk of worsening symptoms within the first two weeks than cross-tapering.[100] In selecting the right strategy, the clinician should consider the severity and duration of illness, presence and quality of surrounding support, and previous experiences with treatment and switching.[98] A robust systematic review and meta-analysis examining the effect of switching on metabolic parameters like weight gain is lacking. Furthermore, confidence in maintaining the efficacy of schizophrenia treatment following switching is hampered by open-label design, varying doses, and high drop-out rates in studies.

As an alternative to switching antipsychotics, dose-lowering strategies have been discussed following evidence of a dose relationship with metabolic adverse effects like weight gain. This has only been observed for olanzapine and clozapine, with other SGAs showing mixed results[101]. However, studies examining this relationship are very limited and the strategy should be avoided until more data is available. Further, greater relapse rates are associated with dose reduction with a significantly higher risk of all-cause and schizophrenia hospital admission and emergency room visits.[102]

[Table 4 here]

4.3 Augmentation with other medications

Although several adjunctive pharmacological treatments have been studied, only a few are successful in treating AAWG. Metformin is a first line treatment for type 2 diabetes mellitus in conjunction with lifestyle modification; it decreases intestinal absorption of glucose, increases insulin sensitivity, reduces hepatic gluconeogenesis, and suppresses appetite.[103,104] Metformin induces weight loss in diabetic and non-diabetic obese patients with a medium effect size.[76,105] Specific meta-analyses of studies of metformin in patients on clozapine and olanzapine treatment – SGAs with the highest liabilities for weight gain – reported mean reductions of 3.12kg and 5.02kg,

respectively, compared to placebo.[106,107] Interestingly, metformin-associated attenuation of AAWG may be greater in first episode patients compared to chronically ill populations, thereby supporting early intervention approaches.[108]

GLP-1RAs, including exenatide and liraglutide, mimic endogenous GLP-1; enhancing its role in energy and glucose homeostasis.[31] A recent meta-analysis found a mean reduction in body weight of 3.71kg with GLP-1RA than controls.[109] Currently both exenatide and liraglutide are subcutaneous injections which presents a potential barrier for treatment; a recent pilot study found fewer than half felt comfortable self-administering the injections.[110] An oral formulation of another recently approved GLP-1RA, semaglutide, is currently being investigated in a phase 3 trial.[111]

Topiramate, an antiepileptic agent, reduces appetite and increases energy expenditure through actions on NPY neurons and leptin mRNA.[112] A recent meta-analysis reported significant reductions in anthropometric measures in patients with schizophrenia, namely a mean weight loss of 3.76kg.[113] However, side effects – including paresthesia and dose-dependent psychomotor slowing and memory disturbance – limit the acceptability of topiramate as a weight-loss augmentation agent.[113,114]

Lorcaserin is a 5-HT_{2C} receptor agonist with FDA approval for weight management alongside diet and exercise interventions.[115] Binding of the 5-HT_{2C} receptor in the hypothalamus elicits anorexigenic effects, reducing appetite and food intake.[56,115] Placebo-controlled trials in the general population have showcased encouraging results with the BLOSSOM trial finding significantly more participants achieved greater than 5% weight loss compared to placebo (47.2% on 10mg twice daily, 40% on 10mg daily and 25.0% on placebo).[116] Case studies reporting weight loss and reduced food cravings in patients experiencing olanzapine-induced weight gain have demonstrated potential benefit for patients with schizophrenia.[117] A randomised-controlled study comparing a combination of metformin and lorcaserin to an active-control of lorcaserin and a control of placebo is currently underway and will provide greater insight for benefit in this population. [118]

Orlistat, a lipase inhibitor, prevents the absorption of dietary fat, allowing it to pass through the body undigested. Benefits within the general population have been reported[119], however a study of 63 patients with schizophrenia treated with olanzapine and clozapine found no difference between orlistat and placebo over 16 weeks regarding weight change, except solely in the male cohort.[76,120] Although discontinuation rates were similar at study conclusion, high drop-out rates have been observed in other studies.[119,120] This is largely due to an unfavourable adverse effect profile including oily spotting on underwear and around the perianal area, increased defecation of oily and fatty stools, faecal urgency/incontinence, and abdominal pain.[121]

Naltrexone (an opioid antagonist) and bupropion (a norepinephrine-dopamine reuptake inhibitor and a nicotinic acetylcholine receptor antagonist) have recently been used in combination to induce weight loss. These agents are believed to synergistically increase activity of hypothalamic POMC neurons thereby reducing appetite.[115] In phase 3 randomised placebo-controlled trials, combinations of sustained-release formulations of naltrexone and bupropion in the general population reduced baseline body weight by 6.4%.[122,123] Additionally, simultaneous benefit for patients with alcohol, drug and nicotine dependence has been observed.[124] No trials to date examine the combination in patients with schizophrenia.

More recently betahistidine has shown promising results. This is a centrally-acting histamine H₁ receptor agonist and H₃ receptor antagonist that reverses olanzapine-induced weight gain in mice.[125] It is relatively well tolerated and is used to treat vestibular disorders.[126] A study in 48

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healthy female patients demonstrated that pre-treatment with betahistine as monotherapy for one week prior to coadministration of betahistine and olanzapine for two weeks reduced weight gain compared to placebo and olanzapine (1.24kg gain vs 1.93kg gain).[127]

The discovery of new mechanisms for AAWG have seen the emergence of further potential treatments. For instance, the role of melatonin in energy metabolism has already been described with a systematic review exploring the efficacy of melatonin agonists in AAWG.[49] Conflicting results were found in patients depending on the liability of the antipsychotic to induce weight gain.[49] Coadministration of melatonin appears more effective with risperidone and quetiapine - agents with an intermediate risk to induce AAWG – compared to olanzapine and clozapine – agents that are high risk.[49] Another option is targeting the microbiome-gut-brain axis.[64] A two-week study in female rats reported that olanzapine-induced weight gain was reduced with the coadministration of a prebiotic galacto-oligosaccharide.[128]

5.0 Expert Opinion

AAWG must be considered in clinical decisions to reduce morbidity and mortality within patients with schizophrenia. Several mechanisms of AAWG are proposed but the phenomenon is still not fully understood. The effects of different neurotransmission systems and genetic factors have the most convincing data. Conflicting results and lack of human data limits the applicability of some evidence involving hormonal systems of energy metabolism and the evolving role of the microbiome-gut-brain axis. Growing knowledge of these mechanisms has been vital in guiding management strategies including new pharmacological treatments and the most appropriate antipsychotic switching regimens. Furthermore, they can form the basis of new antipsychotic agent discovery similarly to that seen with the development of brexpiprazole and cariprazine.

Patients newly diagnosed with schizophrenia and psychosis experience significantly more weight gain and this is reported regardless of the antipsychotic prescribed. AAWG and metabolic abnormalities should be at the forefront of clinician’s minds when initiating antipsychotic treatment in newly diagnosed patients. Clinicians should consider an agent that has smaller impact on weight, such as aripiprazole and ziprasidone, with the intention of limiting future morbidity and mortality. Further, prevention plans should be discussed and implemented alongside the commencement of antipsychotic treatment to attenuate weight gain.

When reviewing approaches to ameliorate AAWG in already obese patients, antipsychotic effectiveness is essential to minimise any risk of relapse and hospitalisation. However, management of the associated obesity should not be neglected. Individualised strategies and goals should be implemented considering the patient’s severity of weight gain, the history of their condition, and their opinion of treatment. Frequent monitoring of weight and adverse effects (if a pharmacological treatment chosen) should accompany regular symptom control monitoring. This allows clinicians to decide if the approach is effective in reducing weight for the patient and is not having a detrimental effect on schizophrenia treatment.

Although not consistent, lifestyle interventions show some evidence of reducing weight particularly when addressing multiple lifestyle risk factors and making use of specialised health professionals (such as qualified nutrition and physical-activity staff). Such interventions, beyond weight reduction, can also have a positive impact on cardiovascular disease and symptoms of schizophrenia with particularly strong evidence for exercise. Employing these interventions is a challenge, however, with many barriers preventing uptake and long-term effectiveness of the approach. Intensive and

individual support is often required to promote and maintain adherence to regimens. This is often resource-intensive and preliminary cost effectiveness trials demonstrate poor value for money. Further, lifestyle regimens studied in this population have been substantially heterogeneous thereby creating difficulties for clinicians when identifying approaches to employ. Recent guidelines suggest that adhering to principles of evidence-based lifestyle interventions developed in the general population, while using these to protect physical health from the very initiation of treatment (before weight gain has occurred), may provide the optimal approach for preventing AAWG.[4] However, if lifestyle interventions are deemed inappropriate or unsuccessful, pharmacological strategies should then be considered.

With an abundance of data showcasing the propensities of different antipsychotics to induce weight gain, switching antipsychotics is a theoretically sound approach. Evidence suggests patients experience the most weight loss following a switch to aripiprazole, ziprasidone or amisulpride. High discontinuation and drop-out rates, largely due to symptom exacerbation, confound these trials and limit their applicability to the real-world. A lack of homogeneous objective outcomes and large focus on treatment efficacy instead of metabolic outcomes in the literature has contributed to a paucity of meta-analysable data. Research in the future should aim to critically appraise current literature through a systematic review and re-enforce the current gaps in knowledge including which agents are most effective and whether the risks of relapse outweigh the benefits in reducing weight.

Additionally, augmentation with other medications has proven effective in ameliorating AAWG. Metformin and GLP-1RAs are the most promising agents, with an abundance of data demonstrating effectiveness and few incidences of side effects. GLP-1RAs are currently limited by a subcutaneous formulation but the recent development of an oral agent could create a larger role for the medication class in the future. Novel developments into the use of lorcaserin and a combination of naltrexone and bupropion have shown great benefit in the general population and preliminary results in patients with schizophrenia have so far supported these previous results. More experimental treatments including betahistine, melatonin agonists, and prebiotics, evolving from new research into mechanisms of AAWG require larger, well-designed long-term randomised controlled data in human populations.

Overall, the importance of improving cardiometabolic health in patients with schizophrenia has been recognised yet neglected for decades. Ameliorating obesity once it has occurred is challenging and often not achieved by clinicians. A standardised strategy for reversing weight gain is unlikely to be able to be recommended. Lifestyle intervention and augmentation with other medications are the most feasible but only showcase modest effects. Switching antipsychotics presents a higher risk of symptom exacerbation in patients in remission and similarly exhibit modest reduction in weight. Preventing AAWG and related complications with carefully considered initiation of antipsychotics is widely accepted and should aim to be the focus of guidelines and treatments in the coming years.

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Table 1: Summary of hormone/peptides role in energy homeostasis and the impact of antipsychotics

Hormone or Peptide	Role in normal energy metabolism and homeostasis	Antipsychotics impact on hormone/peptide
Glucagon-like peptide-1 (GLP-1)	Enhances insulin secretion Decreased glucagon secretion Reduces hepatic gluconeogenesis Delays gastric emptying Satiety regulation	Shown to reduce GLP-1 secretion and modulate sweet taste sensitivity in mice
Leptin	Controls adiposity Regulates energy intake by up- and down-regulating neurons in the ARC Modulates mesolimbic dopaminergic pathway involved in reward-seeking behaviour of appetite	Correlation between antipsychotic use and high levels of leptin. Believed to be due to weight gain, rather than a cause of weight gain
Ghrelin	Effects on glucose and lipid metabolism Role in acid secretion and gastric emptying Induces hunger and increases food intake	Conflicting results – some studies have shown reductions, and some have shown increases in circulating levels
Insulin	Largely involved in regulating glucose homeostasis Additionally, acts centrally in the hypothalamus and modulates dopaminergic reward associated neurons to reduce appetite and alter food preferences	Antipsychotic associated weight gain can result in insulin resistance. Further, antipsychotics have been shown to inhibit peripheral and central insulin action
Melatonin	Regulates circadian rhythm Regulates body weight, glucose and lipid metabolism Synchronizes metabolism with rest and activity	Associated with reduction in melatonin

Table 2: Summary of role of neuroreceptors in AIWG

	Neuroreceptor			
	D2	5-HT2C	5-HT2A	H1
Receptor role in metabolic homeostasis	D2 receptor deficiency increases reward-seeking behaviour e.g. increased food intake and appetite in obese individuals	Expression of the 5-HT2C receptor on POMC and NPY neurons in the ARC. Inverse agonism may induce more weight gain	Neocortical binding of 5-HT2A has shown a positive correlation with increased BMI	H1 receptor antagonism leads to, greater activation of hypothalamic AMP-related kinase (AMPK), which is associated with appetite stimulation

Table 3: Summary of genes frequently identified as contributors to AIWG

Genes involved in AIWG	Responsible for encoding	SNPs reported in literature
HTR2C	Serotonin 2c receptor (5HT-2c)	rs3813929 rs6318 rs518147 rs381328
DRD2	Dopamine 2 receptor	rs1799978 rs7131056 rs6275 rs2242591 rs1079598
ADRA2A	Alpha 2a receptor	rs1800544
GNB3	Guanine nucleotide-binding protein beta subunit	rs5443
MC4R	Melancortin 4 receptor	rs17782313 rs489693
FTO	Fat mass and obesity-associated protein	rs9939609
LEPR	Leptin receptor	rs1137101
BDNF	Brain-derived neurotrophic factor	rs6265
INSIG2	Insulin induced gene 2	rs10490624 rs17047764 rs17587100 rs7566605
SNAP25	Synaptosomal nerve-associated protein 25	rs1051312 rs3746544 rs8636

*Table adapted from Malhotra (2016)

Table 4: Associated risk of weight gain with commonly prescribed SGAs

Antipsychotic	Risk to induce weight gain
Amisulpride	Intermediate
Aripiprazole	Low
Brexipiprazole	Low
Cariprazine	Low
Clozapine	High
Lurasidone	Low
Olanzapine	High
Quetiapine	Intermediate
Risperidone	Intermediate
Ziprasidone	Low