Therapeutic management of obesity induced by antipsychotic drugs

Postępowanie terapeutyczne w otyłości indukowanej stosowaniem leków przeciwpsychotycznych

Wojciech Merk[*1], Michał Lew-Starowicz[1]*

[1] *Department of Psychiatry, Centre of Postgraduate Medical Education, Warsaw, Poland*

KEYWORDS:

- antipsychotics
- obesity
- schizophrenia
- non-pharmacological interventions
- weight-reducing medications

ABSTRACT

The introduction of second-generation antipsychotic drugs (SGAs) has contributed to a more effective treatment of mental diseases and patients' improved quality of life. Their particular superiority to first-generation antipsychotics (FGAs) includes better outcomes in treating "negative" symptoms, impact on mood and lower risk of motor side effects (1). Their increasing use, going beyond psychotic disorders, has highlighted the problem of medication-induced weight gain and obesity in patients. Obesity leads to increased cardiovascular morbidity and mortality, decreased quality of life, and poor adherence. This narrative review discusses the impact of various SGA on weight gain and related adherence to medication, as well as available pharmacological and non-pharmacological interventions to counteract these effects. Most SGA commonly cause weight gain but the risk appears to be highest with olanzapine and clozapine. The best preventative strategies are tailored antipsychotic drugs and close monitoring of body weight and other metabolic parameters. Switching from one SGA to another less likely to cause metabolic disturbances is an option but carries a risk of relapse. Non-pharmacological interventions in the form of dietary counseling, exercise programs, cognitive and behavioral strategies appear to be equally effective in both individual and group forms. Both non-pharmacological prophylaxis and intervention strategies showed little effect on weight. Of the additional weight loss medications, metformin appears to be the compound with the best documented efficacy. There is no evidence of benefit from the routine prescription of additional weight loss medications. Drawing conclusions is hampered by the high heterogeneity of research methodology, as well as the participation of other factors such as lifestyle, genetic and disease-related factors.

SŁOWA KLUCZOWE:

- leki przeciwpsychotyczne
- otyłość
- schizofrenia
- interwencje niefarmakologiczne
- leki zmniejszające masę ciała

STRESZCZENIE

Wprowadzenie leków przeciwpsychotycznych drugiej generacji (SGA) przyczyniło się do skuteczniejszego leczenia chorób psychicznych oraz poprawy jakości życia pacjentów. Ich przewaga nad lekami przeciwpsychotycznymi pierwszej generacji (FGA) obejmuje lepsze rezultaty leczenia objawów negatywnych, wpływ na nastrój i mniejsze ryzyko pozapiramidowych działań ubocznych (1). Coraz szersze ich stosowanie, wykraczające poza obszar zaburzeń psychotycznych, uwypuklił problem przyrostu masy ciała i otyłości u leczonych nimi pacjentów. Przyrost masy ciała i otyłość prowadzą do zwiększonej chorobowości i śmiertelności z przyczyn sercowo-naczyniowych, obniżonej jakości życia i słabego przestrzegania zaleceń lekarskich. W niniejszym przeglądzie narracyjnym omówiono tendencję różnych leków przeciwpsychotycznych do powodowania przyrostu masy ciała, dostępne interwencje farmakologiczne i niefarmakologiczne przeciwdziałające temu zjawisku. Większość SGA powoduje przyrost masy ciała, jednak ryzyko wydaje się być największe w przypadku olanzapiny i klozapiny. Dostosowanie leków przeciwpsychotycznych do indywidualnych potrzeb oraz ścisłe monitorowanie masy ciała i innych parametrów metabolicznych stanowią najlepsze strategie zapobiegawcze. Zmiana leku przeciwpsychotycznego na inny, o mniejszych skłonnościach do powodowania zaburzeń metabolicznych jest opcją, ale niesie ze sobą ryzyko nawrotu choroby i nie zawsze jest możliwe. Niefarmakologiczne interwencje w postaci poradnictwa dietetycznego, programów ćwiczeń oraz strategii poznawczych i behawioralnych wydają się być równie skuteczne zarówno w formie indywidualnej, jak i grupowej. Spośród interwencji

*Address for correspondence: *Wojciech Merk, Department of Psychiatry, Center of Postgraduate Medical Education, Bielański Hospital, Cegłowska 80 Street, 01-809 Warsaw, Poland, e-mail: wojciech.merk@cmkp.edu.pl.*
ISSN 2657-9669/
Published and financed by Centre of Postgraduate Medical Education; https://doi.org/10.36553/wm.70

farmakologicznych stosowanych w celu redukcji masy ciała u pacjentów przyjmujących SGA metformina jest związkiem o najlepiej udokumentowanej skuteczności. Brak jest szeroko zakrojonych badań dokumentujących korzyści płynące z rutynowego przepisywania dodatkowych leków zmniejszających wagę ciała. Wysuwanie wniosków utrudnia dodatkowo duża heterogeniczność metodologii badań, jak również udział innych czynników takich jak styl życia, czynniki genetyczne i chorobowe.

Introduction

For several years now, attention has been paid to the problem of premature mortality among people suffering from schizophrenia. In this group, the occurrence of such metabolic disorders as obesity, metabolic syndrome and diabetes related cardiovascular morbidity, is more frequent than in the general population (2). Metabolic disorders are associated not only with a lower life expectancy, but also a poorer quality of life. The more frequent occurrence of the above-mentioned metabolic abnormalities in the group of mentally ill people is related not only to the loss of physical activity, but also to addictions (especially smoking) and unhealthy eating habits (3, 4), which in turn leads to an increase in body weight. Adult patients with schizophrenia have a 3.5 times higher risk of death compared to the general population, with cardiovascular disease being the most common cause of death (5). Lahti et al. (6) showed a higher risk of death among women than men suffering from schizophrenia, which is evidence of gender differences in response to treatment (7). Second-generation antipsychotics (SGA) are used not only in the treatment of schizophrenia and bipolar disorder but also in depressive disorder, dementia, obsessive-compulsive disorder, autism spectrum disorders, and in other diseases (1, 8, 9). The present study does not address the significant increase in the use of antipsychotic drugs in the pediatric population. Clinical observations indicate a faster weight gain in children than in adults, which predisposes this group to the consequences of weight gain for many years. Overweight children and adolescents may have problems with body image and self-esteem.

The use of SGA is associated with weight gain, referred in the literature as antipsychotic-induced weight-gain (AIWG). Research results support previous findings that weight gain occurs rapidly (10). It has also been suggested that women gain more weight than men under SGA treatment (7). It has been estimated that women are 5.0 times more likely to increase body mass index (BMI) compared to men after 2 years or more (11). In the group of patients receiving SGA, with particular emphasis on patients diagnosed with schizophrenia, the above-mentioned dietary choices, lack of physical activity and social deprivation, which are important etiological factors in the development of obesity, should not be forgotten. Weight gain is one of the reasons why people are not compliant with antipsychotic treatment and results in increased risk of relapse and hospitalization. The study by Weiden et al. indicated that obese patients are 13 times more likely to discontinue treatment due to weight gain than patients without obesity (12). Similarly, in the CATIE study, more patients discontinued olanzapine because of weight gain compared to other agents (13). Fighting obesity and overweight is commonly a long and difficult process.

The benefits of the introduction of SGAs and their widespread use in psychiatry on the one hand, and their cardiometabolic burden on the other, substantiates the need for an increased awareness of the risk of treatment-related obesity, the ability to stratify the individual risk as well as develop tailored treatment strategies for patients among clinicians.

The aim of this narrative review is to collect most recent data on mechanisms, risk factors and SGAs-related risk of weight gain and obesity, as well as on medical interventions that may be helpful to counteract metabolic complications while antipsychotic treatment is mandatory.

Methods

We searched Pubmed, Google Scholar and Cochrane database. We used the key words: weight gain, weight change, obesity AND antipsychotics, SGAs, FGAs. We retrieved relevant reviews and RCTs published between 2015 and 2020. The number of articles retrieved was not recorded and the quality of articles was not assessed in a systematic way as this is not a systematic review.

Effect on body weight – differences among particular antipsychotics

The first meta-analysis of weight gain in patients taking FGA and SGA was conducted by Allison et al. (14). Its results indicated that most antipsychotics caused weight gain, with clozapine, olanzapine, thioridazine, sertindole, chlorpromazine, and risperidone causing significant weight gain ranging from 2.10 to 4.45 kg. A significant limitation of this study, as well as of the others cited in this paper, is the short period of observation, usually not exceeding 12 weeks. In clinical practice, weight gain is much higher with some FGAs and SGAs. However, rapid weight gain observed in studies in a short period of time may be an unfavorable predictor of further weight gain over the course of treatment. Leucht et al. (15) showed in another meta-analysis that all antipsychotics except haloperidol, lurasidone and ziprasidone induced weight gain. Olanzapine and zotepine caused significantly higher weight gain than other drugs (15). De Hert et al. (16) indicated that newer antipsychotic drugs, such as asenapine, iloperidone, paliperidone caused clinically significant (over 7%) increase in body weight. Only lurasidone did not cause significant weight gain in patients and was metabolically safe (16). The above observations were confirmed by a meta-analysis of the effect of antipsychotics on body weight in patients with first episode of schizophrenia: weight gain was recorded by 3.22 kg in the short-term follow-up and 5.3 kg in the long-term compared to placebo (17). A study conducted among people with first episode of schizophrenia (33% of people were drug-naïve), conducted in the European First Episode Schizophrenia Trial (EUFEST), showed weight gain: 13.9 kg on olanzapine, 10.5 kg on quetiapine, 4.8 kg on ziprasidone and 7.3 kg on haloperidol (18). Significant weight gain was experienced by 86% of olanzapine users, 65% of quetiapine and 63% of amisulpride, and 53% and 37% of haloperidol and ziprasidone, respectively. In another randomized trial of patients with first episode of schizophrenia (24% drug-naïve), weight gain >7% was achieved in 58.9% and 80.0% of patients receiving olanzapine at weeks 12 and 52, compared

with 29.2% and 50.0% of patients receiving quetiapine, and 32.5% and 57.6% in the risperidone group (19). A recent network meta-analysis of 116 studies found that 12 of the 26 antipsychotics contributed to significant weight gain compared to placebo, with olanzapine, zotepine and sertindole having the greatest increases. The risk of clinically significant weight gain from baseline compared to placebo was reported for olanzapine, quetiapine, iloperidone and also for the newer drug brexpiprazole, while cariprazine was metabolically safe (20). In another network meta-analysis of 100 randomized controlled trials (n = 25.952 patients), mean differences for weight gain versus placebo ranged from -0.23 kg for haloperidol to 3.01 kg for clozapine; for BMI from -0.25 kg/m² for haloperidol to 1.07 kg/m² for olanzapine. The antipsychotic medications differed significantly in their effects on body weight, BMI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glucose levels. The use of olanzapine and clozapine is associated with the greatest degree of metabolic dysregulation. It was also shown that, compared with placebo, lurasidone led to a reduction in glucose levels, cariprazine to a reduction in LDL cholesterol, and aripiprazole and brexpiprazole to an increase in HDL cholesterol. This meta-analysis also investigated the prognostic factors of antipsychotic-induced metabolic changes. The authors concluded that increased baseline body weight, male gender, and non-white ethnicity predict greater susceptibility to antipsychotic drug-induced metabolic disturbances, suggesting an overlapping risk factor for metabolic disease in the general population and in those with antipsychotic drug-induced metabolic disease. The relationship between the baseline body weight and the rate of weight gain induced by antipsychotics has not been confirmed (21), which has been observed in some previous studies. In a retrospective cohort study of patients diagnosed with psychotic disorder (22,306 women and 16,559 men) treated with olanzapine, quetiapine or risperidone, the change in body weight was assessed 4 years before and 4 years after the initiation of antipsychotic treatment by gender and dose size. The authors concluded that treatment with olanzapine was associated with the largest change in body weight, with dose-dependent increase (>5 mg: weight gain for women 6.1 kg on average; dose 5 mg: weight gain 4.4 kg on average). Similar trends were observed in men. Less weight gain was observed in patients taking risperidone and quetiapine both in the short and long term of follow-up (22). Domecq et al. (23) conducted a systematic review and meta-analysis of 257 randomized trials (54 different drugs, SGAs included; 84 696 patients enrolled) to summarize the evidence about commonly prescribed drugs and their association with weight change. In their meta-analysis weight gain was associated with the use of i.a., olanzapine (2.4 kg), quetiapine (1.1 kg) and risperidone (0.8 kg). The overall results of the meta-analysis of 27 randomized trials were that compared to placebo, antipsychotics led to significantly more weight-gain ($p < 0.001$) and to a significantly higher risk of gaining ≥7% of the baseline weight (RR = 2.04) after 3 to 12 weeks of treatment (10). Although the potential to induce weight gain varies considerably in SGA, it has been established that haloperidol, ziprasidone, lurasidone, aripiprazole, cariprazine, and amisulpride are agents associated with low weight gain, at least in long-term patients who often are already overweight. Paliperidone, risperidone and quetiapine induce moderate weight gain, while sertindole, chlorpromazine, and iloperidone strongly increase body weight with extreme BMI increases in BMI in case of clozapine, zotepine and olanzapine (15, 16). Most of the weight gain was caused by olanzapine, followed by asenapine, risperidone, aripiprazole, quetiapine XR, brexpiprazole, cariprazine, and lurasidone. Thus, also relatively new compounds such as cariprazine and brexpiprazole showed greater weight gain compared to placebo. Only aripiprazole, lurasidone and quetiapine XR did not result in clinically significant weight gain of ≥7% (10).

Mechanism underlying weight gain and other metabolic abnormalities caused by antipsychotics

Peripheral hormones and insulin resistance

Peripheral hormones such as glucagon-like peptide 1 (GLP-1) and leptin are anorexigenic. In animal studies, SGA such as olanzapine, clozapine and quetiapine by decreasing GLP-1 secretion, weaken glucose homeostasis and increase the risk of diabetes (24, 25). Additionally, decrease of GLP-1 reduces the sensitivity to sweet taste, which explains the increased appetite after olanzapine and clozapine for high-calorie carbohydrate foods (25). Circulating leptin levels increase with obesity, high leptin levels are seen in obese patients with schizophrenia, suggesting endogenous leptin resistance similar to obese patients in the general population (26). This suggests that hyperleptinaemia is a result of antipsychotic-induced weight gain rather than a pathophysiological cause (26). Increased leptin and decreased adiponectin levels were observed in olanzapine-treated patients in short and long term follow-up (27, 28). The effect of antipsychotics on glucose and fat metabolism was associated with their effect on weight gain and obesity, which indirectly contributed to insulin resistance (29). A recent meta-analysis showed that impaired appetite regulation in form of elevated insulin and lowered leptin levels occurs in early psychosis before antipsychotic treatment. Additionally, hyperinsulinemia may be associated with negative symptoms (30).

Neurotransmitters and receptors

SGAs show mixed receptors antagonism with various effects on dopaminergic, serotonergic, histaminergic, cholinergic and adrenergic receptors. The literature largely concerns the effects of SGA on central neurotransmission, with the role of peripheral receptors being less clear and understood (31). Dopaminergic neurons located in the mesolimbic pathway regulate reward behavior and have a significant effect on appetite (32, 33). It is postulated that the deficiency of the D2 receptor in this pathway exacerbates reward-seeking behaviors, e.g., increased food consumption and appetite in obese people (32, 34). Antagonism on 5-HT2A and 5-HT2C receptors, characteristic for many SGA, is widely recognized as a pathway associated with weight gain (31). Serotonin is a key ingredient in homeostatic satiety and appetite control. 5-HT2C antagonism induces weight gain (35): olanzapine and clozapine are inverse agonists and cause greater weight gain than ziprasidone and aripiprazole, which are partial 5-HT2C agonists (33). Less data concerns the potential involvement of the 5-HT2A receptor. A study of drug-naïve patients with first episode of schizophrenia showed a possible positive correlation between quetiapine use and an increase in BMI, and the postulated mechanism was the binding of quetiapine with 5-HT2A receptor in the cerebral cortex (36). The stimulation of H1 receptors results in an anorexigenic effect (31). However, in animal models clozapine and olanzapine, potent

H1 receptor antagonists, showed greater activation of the hypothalamic AMP-related kinase (AMPK), which is associated with appetite stimulation (37). Ziprasidone, haloperidol, and aripiprazole – antipsychotics that are less likely to cause weight gain – did not increase AMPK activity (37).

Genetic factors

A variety of genes and single nucleotide polymorphisms (SNPs) are potential factors of AIWG. The most studied gene is *HTR2C*, which encodes the 5-HT2C receptor, the SNP rs3813929 being the most commonly described (38, 39). The T allele increased transcriptional activity, resulting in more 5-HT2C receptors, that appears to protect against AIWG as opposed to the more common wild-type C allele (38). Among people treated with clozapine, SNP rs381328 in *HTR2C* with the T allele was associated with a lower BMI compared to the C allele (40). Other treatment-related genes strongly related to AIWG includes *DRD2* and *ADRA2A*, which are precursors of the dopamine D2 receptor and the alpha 2A receptor, respectively (38). The *GNB3* and *MC4R* genes have been extensively discussed in whole-genome association studies and have been reported to have significant associations with obesity (38). This link seems to work by influencing endogenous hormonal and neuronal systems that regulate energy homeostasis (38). There is also an effect of gender on the expression of obesity-related genes after initiating antipsychotic treatment (altered expression of 240 genes in the male group and 37 in the female group), which could explain the observed differences between women and men in relation to weight gain (36).

Microbiome

Interesting data is provided by studies assessing the microbiome-gut-brain axis as a possible mechanism of weight gain. The microbiome acts directly and indirectly on the CNS through interactions on the gut surface and the production of neurotransmitters and short-chain fatty acids (41). Olanzapine or risperidone in animal models caused changes in the composition of the intestinal microflora, such as an increase in the Firmicutes bacterial cluster and a decrease in the number of Proteobacteria, Actinobacteria, and especially Bacteroidetes, and these changes are associated with an increase in adipose tissue (42, 43). The administration of olanzapine to mice and an antibiotic to prevent changes in the bacterial flora reduced the weight gain of the animals (44). The increase in Firmicutes and the decrease in Bacteroidetes after the use of SGA was replicated in a study of 28 children and adolescents taking risperidone regularly (45). This is only the beginning of research on the effect of SGA on the gut microbiome and the corresponding changes in body weight, therefore it is impossible to draw far-reaching conclusions.

Management of antipsychotic-induced weight gain

Non-pharmacological strategies

Until today, there is a feeling of helplessness among caregivers of people with mental illnesses in relation to lifestyle interventions in this group of patients. Despite this pessimism, a considerable amount of effort was made to design appropriate interventions in this population. It was initially suggested that, contrary to expectations, lifestyle interventions might be effective. Non-pharmacological strategies include: cognitive and behavioral interventions, dietary consultation, and physical exercise. Cognitive interventions include analysis of eating behavior and physical well-being, while behavioral means the training of effective problem-solving, goal setting, social support, monitoring exercise and eating habits. Dietary consulting includes a reduction of 500-1000 kcal of daily consumption and reduction of daily fat intake up to 30%. The remaining interventions will involve approximately 150 minutes of moderate (55-69% maximum heart rate) exercise per week (46). A systematic review of non-pharmacological interventions to prevent weight gain in young, newly diagnosed patients with schizophrenia or bipolar disorder, identified physical activity and practical dietary interventions as more effective than lifestyle counseling. Research indicated that a significant decrease in waist circumference was achieved after 10-14 weeks of aerobic exercise (47). In an earlier meta-analysis, Alvarer-Jimenez et al. showed that the use of non-pharmacological interventions (cognitive-behavioral, nutritional counseling, and combined nutritional and exercise interventions) resulted in a weight loss of 2.56 kg on average (CI: 1.92-3.92) compared to standard treatment. No significant differences have been found between trials designed to prevent weight gain and trials investigating treatments for weight loss (48). Similar conclusions were reached by Bonfioli et al. (49), who found a significant impact of non-pharmacological interactions on the experimental groups, with a decrease in mean BMI by -0.98 kg/m² compared to the control groups (49). Another meta-analysis by Bruins et al. (50) indicated that lifestyle interventions (including supervised exercise, dietary counseling, motivational interviewing, and cognitive behavioral therapy) were effective for both weight loss (effect size = -0,52; p <0.0001) and prevention of weight gain (effect size = -0.84; p = 0.0002). Regardless of the method, these interventions had significant beneficial effects on weight loss, waist circumference, triglycerides level, fasting glucose and insulin, without affecting blood pressure and cholesterol levels. It was also noted that changes in BMI would be a more appropriate parameter than mean change in body weight (50). The results of another meta-analysis indicate that lifestyle modifications (LM) had a significantly higher effectiveness in weight reduction (-0.64, 95% CI -0.89, -0.39, Z = 5.03, overall effect p <0.00001), BMI (-0.68, 95% CI -1.01, -0.35, Z = 4.05, overall effect p <0.0001) and waist circumference (-0.60, 95% CI -1.17, -0.03, Z = 2.06; overall effect p = 0.04) compared with standard care. LM was significantly more effective than standard treatment even in a short time (p = 0.0001) and regardless of the place of treatment (developed and developing countries), therefore, according to the authors, it should be routinely recommended to all patients, preferably at the beginning of SGA treatment. It was also considered that 4 months is the optimal time needed for the intervention group to achieve any change in weight or BMI (32). A systematic review of 20 studies of non-pharmacological interventions (physical activity, diet modification, psychoeducation) that addressed various aspects of physical health (exercise capacity and metabolism) showed that programs longer than 12 weeks and also shorter can be equally effective and lead to a slight but significant weight loss or improvement in cardiovascular fitness in patients with schizophrenia. It is also important to notice that non-pharmacological interventions can be performed in schizophrenia patients both on an outpatient basis and during hospitalization (51). In contrast: one meta-analysis of 41 randomized

controlled trials (n = 4267 patients) showed that interventions reduced the mean BMI by 0.63 kg/m², which corresponds to a weight loss of 2.2 kg combined with a reduction in waist circumference. Participants in the intervention group were 50% more likely to lose weight than participants in the control group. This effect is less than previously reported, and since a 5% weight loss is generally recommended for improving health, it is unlikely to be of clinical relevance. Experimental diet and/or exercise were found to have only limited clinical significance at the group level, the effects considered too small to be clinically relevant. Experimental interventions reduced the mean difference in BMI by -0.63 kg/m² (compared to the control groups). During the post-intervention follow-up period (17 RCTs), the effect remained similar, but was no longer significant. According to the authors, there is a statistically significant, but clinically insignificant, average effect of personalized lifestyle interventions on weight loss in people with severe mental disorders, at least in Western countries, and in the subgroup of people diagnosed with schizophrenia. The authors also suggest that future research could evaluate the impact of the intervention on other causes of unhealthy lifestyle, such as loneliness or low socioeconomic or structural status facilitating access to healthy food and making physical activity more attractive (52). Exercise and dietary change interventions are often used together with cognitive behavioral therapy to promote better outcomes and adherence (53). At the same time, studies show a high dropout rate, especially in those with physical activity (54). One of the reasons could be negative symptoms of schizophrenia, somnolence (caused by treatment), and a lack of supervision and support. It was also shown that individualized interventions outweigh group interventions, but they are definitely more resource-demanding (55).

Pharmacological strategies

Analysis of randomized clinical trials, meta-analyzes and systematic reviews assessing the effectiveness of pharmacological interventions in the treatment of AIWG provides evidence of moderate impact of such strategies. One of the most cited meta-analysis of 40 trials showed that metformin was the most used drug; in 13 studies any treatment to support weight loss/prevent weight gain was started concurrently with antipsychotic treatment, especially when non-pharmacological interventions were not effective and the antipsychotic medication could not be changed (55).

Possible strategies include:

1. Changing antipsychotic medication

Changing one SGA for another with a safer metabolic profile seems to be the best option, unless this class of drugs can be completely avoided. Switching medications should be done after careful consideration of the risk of relapse and discussion with the patient, as this approach may have complications. Data from meta-analyzes show that FGA haloperidol and SGAs lurasidone, ziprasidone, aripiprazole, and amisulpride are considered to be the best options when deciding to switch the antipsychotic treatment (15). One study showed an average weight loss of 1.94 kg after switching from olanzapine to aripiprazole or quetiapine (56). In another, weight loss after switching to aripiprazole was on average 2.55 kg ± 1.5 kg (57). One randomized trial reported that switching from olanzapine, quetiapine, or risperidone to aripiprazole was associated with weight loss and an improvement in metabolic parameters but increased the rate of treatment discontinuation (58). Similarly, switching to ziprasidone from olanzapine and risperidone resulted in a significant reduction in body weight in treated patients (12). Another strategy may be to reduce the dose of the drug. Such relationship has been observed with olanzapine and clozapine (59). A meta-analysis of 3 randomized trials also showed that adding aripiprazole to either clozapine or olanzapine resulted in a modest weight reduction of approximately 2.13 kg compared to placebo (55).

2. Metformin

Metformin is a hypoglycaemic drug which acts by inhibiting gluconeogenesis in the liver and improving insulin sensitivity in skeletal muscles with the participation of adenosine monophosphate kinase. It also lowers LDL cholesterol and triglycerides. The mechanisms behind weight loss may be a reduction in insulin resistance and suppression of appetite (elevated GLP-1 levels may contribute to this). In the meta-analysis by Mizuno et al. in the group of patients using metformin, weight loss compared to placebo was on average -3.17 kg (54). de Silva et al. in a recent meta-analysis of 12 studies found a mean change in body weight between the metformin group and the placebo group of -3.27 kg (60). Metformin compared to placebo caused a significant reduction in BMI and insulin resistance (60). The dose used in the studies ranged from 750 to 1500 mg/day. Zheng et al. conducted a meta-analysis that investigated the efficacy and tolerability of combined metformin use and lifestyle change in SGA-induced weight gain in schizophrenia. The combined intervention is effective and safe in reducing body weight and BMI compared to only lifestyle change, metformin intake or placebo. The results also showed a significantly lower weight gain of ≥7% in the combined group (metformin and non-pharmacological interventions) (61).

3. Topiramate

Topiramate is an antiepileptic drug that may reduce body weight by stimulating lipoprotein lipase, inhibiting carbonic anhydrase and lipogenesis. It also suppresses appetite and increases the feeling of fullness (62). Topiramate was effective in reducing weight gain in the olanzapine group with a mean weight loss of 4.4 kg in the topiramate group vs placebo (+1.2 kg) – patients who gained the most during antipsychotic treatment also had the greatest weight loss when topiramate was added (63). A recent meta-analysis showed a significant mean weight loss of 3.76 kg in patients diagnosed with schizophrenia (64). However, side effects – including paraesthesia and dose-dependent psychomotor retardation and memory impairment – limit the tolerability of topiramate as a widely used weight loss agent (64).

4. Norepinephrine reuptake inhibitors

In two randomized clinical trials addition of reboxetine in patients taking olanzapine resulted in significantly less weight gain in the group receiving the drug compared to placebo (65, 66). However, the side effects of this class of drugs, including changes in blood pressure and heart rate, can

nullify the weight loss benefits. Ghanizadeh et al. in one randomized trial of zonisamide showed a moderate but significant reduction in body weight caused by antipsychotics in a group of patients with schizophrenia (67). Betahistine, an H1 receptor agonist and an H3 receptor antagonist, has also been shown to be effective in reducing weight gain by 37% while using olanzapine. The potential for weight loss by betahistine is seen in its action on the hypothalamus and the liver to induce thermogenesis and reduce food consumption. Other studies have shown that betahistine, alone or in combination with reboxetine, is significantly effective in reducing weight gain during olanzapine treatment (68, 69).

5. GLP-1 analogs

The most promising new class of drugs are GLP-1 receptor agonists (GLP-1RA), including eskenatide and liraglutide. These drugs are used to treat diabetes and cause weight loss as well as better glucose control. Liraglutide is also approved for obesity treatment in higher doses (3 mg once-daily vs the antidiabetic dose up to 1.8 mg once-daily) (70). Three studies of GLP-1 receptor agonists in people taking antipsychotics have been completed, two of which have shown a weight loss of more than 5 kg (71, 72). Currently, both exenatide and liraglutide are in form of subcutaneous injections which can be a potential barrier for many patients; a pilot study found that less than half of the treated patients felt comfortable with self-injection (71). The oral form of another GLP-1RA, semaglutide, is a promising alternative to subcutaneous injection. One recent meta-analysis of 3 studies (exenatide once-weekly = 2; liraglutide once-daily = 1) suggests that GLP-1RAs may cause clinically significant weight loss in overweight or obese patients with schizophrenia taking antipsychotic drugs. Treatment with GLP-1RAs was associated not only with a 3.71 kg reduction in body weight compared to the control group, but also with greater decreases in BMI, fasting glucose, HbA1c levels, and visceral fat. Weight loss was greatest in those taking clozapine and/or olanzapine compared to other antipsychotics. Age, gender, severity of psychotic symptoms, nausea, any adverse drug reaction and GLP-1RAs did not affect weight or other metabolic variables (73).

Other medications used to reduce body weight in patients taking antipsychotic drugs include: sibutramine, d-fenfluramine. These drugs were withdrawn from the market due to severe side effects. Clinical trials with atomoxetine, dextroamphetamine, famotidine, fluoxetine, fluvoxamine, and nizatidine have shown no benefit in treating obese patients taking antipsychotics.

Metformin is the most studied adjuvant and has the best evidence. Evidence from meta-analysis suggests a mean difference of 3 kg over placebo in trials which lasted up to 24 weeks. Metformin may be also more effective in preventing AIWG in drug-naïve first episode patients. Effects of metformin beyond weight reduction, such as glycemic control, are also an advantage. Topiramate has less evidence but may also result in weight loss. Although orlistat is approved by the Food and Drug Administration as a weight-reducing agent, there is no evidence that it is effective in AIWG. In a systematic review and meta-analysis of 257 randomized trials (23) weight loss was associated with the use of i.a., metformin (1.1 kg), liraglutide (1.7 kg), zonisamide (7.7 kg), topiramate (3.8 kg), bupropion (1.3 kg), and fluoxetine (1.3 kg). The evidence regarding other adjuvant medications is inadequate to recommend their use in clinical practice.

Conclusion

AIWG is a very common but often overlooked side effect of antipsychotic medications. The most important consequence of AIWG is the increased risk of developing metabolic syndrome, diabetes and cardiovascular diseases and odds to premature mortality of people with severe mental illness. The available studies focus on patients diagnosed with schizophrenia and bipolar disorder, despite the increasing use of FGAs and SGAs in other diseases (depression, autism, dementia, anxiety disorders). To effectively counter the AIWG problem in clinical practice and research, high-risk individuals should be identified to offer tailored supportive therapies (pharmacological and lifestyle interventions). Recommendations of the Polish Psychiatric Association on metabolic risk reduction in patients with schizophrenia treated with antipsychotics were created as useful guidelines for implementation by professionals in the management of persons suffering from schizophrenia in Poland. It includes a thorough assessment of metabolic risk in each patient who is treated with SGA, appropriate selection of the agent, possible switch to another antipsychotic drug with a lower potential to cause metabolic disorders and constantly encouraging patients to change unhealthy habits or lifestyle (74). There is a need for prevention and early monitoring of weight gain after antipsychotic drug treatment is initiated. Monitoring of body weight should be consistently implemented as a clinical routine in the treatment of any patient taking antipsychotic drugs. Non-pharmacologic interventions which were effective in patients with AIWG include dietary counseling, exercise interventions, cognitive and behavioral strategies. With regard to pharmacological strategies, the best-studied drug with proven efficacy is metformin. It is also recommended to add metformin in clinical situations where changing to an antipsychotic with less metabolic risk may be difficult or even impossible. Further research is needed to increase the use of new GLP-1RA drugs.

References

(1) Hasan A, Falkai P, Wobrock T et al. WFSBP Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia – a short version for primary care. Int J Psychiatry Clin Pract 2017; 21(2):82-90.
(2) de Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 2011; 10(1):52-77.
(3) Strassnig M, Brar JS, Ganguli R. Dietary intake in patients with schizophrenia. Psychiatry 2005; 31-35.
(4) Pearsall R, Praveen KT, Pelosi A, et al. Dietary advice for people with schizophrenia. Cochrane Database of Syst Rev 2016; 3:CD009547. DOI:10.1002/14651858.CD009547.pub2.
(5) Olfson M, Gerhard T, Huang C, et al. Premature mortality among adults with schizophrenia in the United States. JAMA Psychiatry 2015; 72(12):1172-1181.
(6) Lahti M, Tiihonen J, Wildgust H, et al. Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia. Psychol Med 2012; 42:2275-2285.
(7) Seeman M. Men and women respond differently to antipsychotic drugs. Neuropharmacology 2020; 163:107631. DOI: 10.1016/j.neuropharm.2019.05.008.
(8) Jauhar S, Young AH. Controversies in bipolar disorder; role of second-generation antipsychotic for maintenance therapy. Int J Bipolar Disord 2019; 7(1):10. DOI:10.1186/s40345-019-0145-0.

(9) Calsolaro V, Antognoli R, Okoye Ch, et al. The Use of Antipsychotic Drugs for Treating Behavioral Symptoms in Alzheimer's Disease. Front Pharmacol 2019; 10:1465. DOI: 10.3389/fphar.2019.01465.
(10) Barton B, Segger F, Fischer K, et al. Update on weight-gain caused by antipsychotics: a systematic review and meta-analysis. Expert Opin Drug Saf 2020; 19(3):295-314. DOI:10.1080/14740338.2020.1713091.
(11) Koga M. Clinical factors related to gains in body mass index (BMI) among patients under long-term antipsychotic treatment. Seishin Shinkeigaku Zasshi 2003; 105(4):473-88.
(12) Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. Schizophr Res 2004; 66(1):51-57.
(13) Manschreck TC, Boshes RA. The CATIE schizophrenia trial: results, impact, controversy. Harv Rev Psychiatry 2007; 15(5):245-258.
(14) Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156(11):1686-1696.
(15) Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013; 382(9896):951-962.
(16) De Hert M, Yu W, Detraux J, et al. Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis. CNS Drugs 2012; 26(9):733-759.
(17) Tek C, Kucukgoncu S, Guloksuz S, et al. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. Early Interv Psychiatry 2016; 10(3):193-202.
(18) Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 2008; 371(9618):1085-1097.
(19) McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry 2007; 164(7):1050-1060.
(20) Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 2019; 394(10202):939-951.
(21) Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 2020; 7(1):64-77. DOI:10.1016/S2215-0366(19)30416-X.
(22) Bazo-Alvarez J, Morris T, Carpenter J, et al. Effects of long-term antipsychotics treatment on body weight: A population-based cohort study. J Psychopharmacol 2020; 34(1):79-85. DOI: 10.1177/0269881119885918.
(23) Domecq JP, Prutsky G, Leppin A, et al. Clinical review: Drugs commonly associated with weight change: a systematic review and meta-analysis. J Clin Endocrinol Metab 2015; 100(2): 363-370. DOI: 10.1210/jc.2014-3421.
(24) Smith GC, Vickers MH, Cognard E, et al. Clozapine and quetiapine acutely reduce glucagon-like peptide-1 production and increase glucagon release in obese rats: implications for glucose metabolism and food choice behaviour. Schizophr Res 2009; 115(1):30-40.
(25) Smith GC, Vickers MH, Shepherd PR. Olanzapine effects on body composition, food preference, glucose metabolism and insulin sensitivity in the rat. Arch Physiol Biochem 2011; 117(4):241-249.
(26) Potvin S, Zhornitsky S, Stip E. Antipsychotic-induced changes in blood levels of leptin in schizophrenia: a meta-analysis. Can J Psychiatry 2015; 60(3):26-34.
(27) Ak M, Sezlev D, Sutcigil L, et al. The investigation of leptin and hypothalamic neuropeptides role in first attack psychotic male patients: olanzapine monotherapy. Psychoneuroendocrinology 2013; 38(3):341-347.
(28) Hosojima H, Togo T, Odawara T, et al. Early effects of olanzapine on serum levels of ghrelin, adiponectin and leptin in patients with schizophrenia. J Psychopharmacol 2006; 20(1):75-79.
(29) Goncalves P, Araujo JR, Martel F. Antipsychotics-induced metabolic alterations: focus on adipose tissue and molecular mechanisms. Eur Neuropsychopharmacol 2015; 25(1):1-16.
(30) Misiak B, Bartoli F, Stramecki F. Appetite regulating hormones in first-episode psychosis: a systematic review and meta-analysis. Neurosci Biobehav Rev 2019; 102:362-370. DOI:10.1016/j.neubiorev.2019.05.018.
(31) Shin YK, Martin B, Golden E, et al. Modulation of taste sensitivity by GLP-1 signaling. J Neurochem 2008; 106(1):455-463.
(32) van Galen KA, Ter Horst KW, Booij J, et al. The role of central dopamine and serotonin in human obesity: lessons learned from molecular neuroimaging studies. Metabolism 2018; 85:325-339.
(33) Singh R, Bansal Y, Medhi B, et al. Antipsychotics-induced metabolic alterations: Recounting the mechanistic insights, therapeutic targets and pharmacological alternatives. Eur J Pharmacol 2019; 844:231-240.
(34) Nielsen MO, Rostrup E, Wulff S, et al. Striatal Reward Activity and Antipsychotic-Associated Weight Change in Patients With Schizophrenia Undergoing Initial Treatment. JAMA Psychiatry 2016; 73(2):121-128.
(35) Lord CC, Wyler SC, Wan R, et al. The atypical antipsychotic olanzapine causes weight gain by targeting serotonin receptor 2C. J Clin Invest 2017; 127(9):3402-3406.
(36) Rasmussen H, Ebdrup BH, Oranje B, et al. Neocortical serotonin2A receptor binding predicts quetiapine associated weight gain in antipsychotic-naïve first-episode schizophrenia patients. Int J Neuropsychopharmacol 2014; 17(11):1729-1736.
(37) Kim SF, Huang AS, Snowman AM, et al. From the Cover: Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. Proc Natl Acad Sci USA 2007; 104(9):3456-3459.
(38) Malhotra AK, Robinson DG, Lencz T, et al. Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis. Schizophrenia Bulletin 2016; 42(6):1418-1437.
(39) Zhang JP, Malhotra AK. Recent Progress in Pharmacogenomics of Antipsychotic Drug Response. Curr Psychiatry Rep 2018; 20(4):24.
(40) Suetani RJ, Siskind D, Reichhold H, et al. Genetic variants impacting metabolic outcomes among people on clozapine: a systematic review and meta-analysis. Psychopharmacology 2017; 234(20):2989-3008.
(41) Kanji S, Fonseka TM, Marshe VS, et al. The microbiome-gut-brain axis: implications for schizophrenia and antipsychotic induced weight gain. Eur Arch Psychiatry Clin Neurosci 2018; 268(1):3-15.
(42) Davey KJ, O'Mahony SM, Schellekens H, et al. Gender-dependent consequences of chronic olanzapine in the rat: effects on body weight, inflammatory, metabolic and microbiota parameters. Psychopharmacology 2012; 221(1):155-169.
(43) Bahra SM, Weidemann BJ, Castro AN, et al. Risperidone-induced weight gain is mediated through shifts in the gut

microbiome and suppression of energy expenditure. EBioMedicine 2015; 2(11):1725-1734.
(44) Davey KJ, Cotter PD, O'Sullivan O, et al. Antipsychotics and the gut microbiome: olanzapine-induced metabolic dysfunction is attenuated by antibiotic administration in the rat. Transl Psychiatry 2013; 3(10):e309.
(45) Bahr SM, Tyler BC, Wooldridge N, et al. Use of the second-generation antipsychotic, risperidone, and secondary weight gain are associated with an altered gut microbiota in children. Transl Psychiatry 2015; 5(10):e652.
(46) Faulkner G, Cohn T, Remington G. Interventions to reduce weight gain in schizophrenia. Schizophr Bull 2007; 33(3): 654-656.
(47) Nyboe L, Lemcke S, Møller AV, Stubbs B. Non-pharmacological interventions for preventing weight gain in patients with first episode schizophrenia or bipolar disorder: A systematic review. Psychiatry Res 2019; 281:112556. DOI:10.1016/j.psychres.2019.112556.
(48) Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, et al. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry 2008; 193(2):101-107.
(49) Bonfioli E, Berti L, Goss C, et al. Health promotion lifestyle interventions for weight management in psychosis: a systematic review and meta-analysis of randomised controlled trials. BMC Psychiatry 2012; 12(1):78-89.
(50) Bruins J, Jorg F, Bruggeman R, et al. The effects of lifestyle interventions on (long-term) weight management, cardiometabolic risk and depressive symptoms in people with psychotic disorders: a meta-analysis. PLoS One 2014; 9(12):e112276.
(51) Tumiel E, Wichniak A, Jarema M, Lew-Starowicz M. Nonpharmacological Interventions for the Treatment of Cardiometabolic Risk Factors in People With Schizophrenia – A Systematic Review Front Psychiatry 2019; 10:566. DOI:10.3389/fpsyt.2019.00566.
(52) Speyer H, Storch Jakobsen A, Westergaard C, et al. Lifestyle Interventions for Weight Management in People with Serious Mental Illness: A Systematic Review with Meta-Analysis, Trial Sequential Analysis, and Meta-Regression Analysis Exploring the Mediators and Moderators of Treatment Effects. Psychother Psychosom 2019; 88(6):350-362. DOI: 10.1159/000502293.
(53) Caemmerer J, Correll CU, Maayan L. Acute and maintenance effects of non-pharmacologic interventions for antipsychotic associated weight gain and metabolic abnormalities: A meta-analytic comparison of randomized controlled trials. Schizophr Res 2012; 140(1):159-168.
(54) Firth J, Rosenbaum S, Stubbs B, et al. Motivating factors and barriers towards exercise in severe mental illness: a systematic review and meta-analysis. Psychol Med 2016; 46(14):2869-2881.
(55) Mizuno Y, Suzuki T, Nakagawa A, et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. Schizophr Bull 2014; 40(6):1385-1403.
(56) Mukundan A, Faulkner G, Cohn T, Remington G. Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. Cochrane Database Syst Rev 2010; (12):CD006629. DOI:10.1002/14651858.CD006629.pub2.
(57) Barak Y, Aizenberg D. Switching to aripiprazole as a strategy for weight reduction: a meta-analysis in patients suffering from schizophrenia. J Obes 2011; 2011:898013. DOI: 10.1155/2011/898013.
(58) Stroup TS, McEvoy JP, Ring KD, et al. Schizophrenia Trials Network. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). Am J Psychiatry 2011; 168(9):947-956.
(59) Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. J Clin Psychiatry 2009; 70(7):1041-1050.
(60) de Silva VA, Dayabandara M, Wijesundara H, et al. Metformin for treatment of antipsychotic-induced weight gain in a South Asian population with schizophrenia or schizoaffective disorder: a double blind, randomized, placebo controlled study. J Psychopharmacol 2015; 29(12):1255-1261.
(61) Zheng W, Yang XH, Cai DB, et al. Adjunctive metformin for antipsychotic-related hyperprolactinemia: A meta-analysis of randomized controlled trials J Psychopharmacol 2017; 31(5):625-631. DOI:10.1177/0269881117699630.
(62) Generali JA, Cada DJ. Topiramate: antipsychotic-induced weight gain. Hosp Pharm 2014; 49(4):345-347.
(63) Nickel MK, Nickel C, Muehlbacher M, et al. Influence of topiramate on olanzapine-related adiposity in women: a random, double-blind, placebo-controlled study. J Clin Psychopharmacol 2005; 25(3):211-217.
(64) Goh KK, Chen CH, Lu ML. Topiramate mitigates weight gain in antipsychotic-treated patients with schizophrenia: meta-analysis of randomised controlled trials. Int J Psychiatry Clin Pract 2019; 23(1):14-32.
(65) Poyurovsky M, Isaacs I, Fuchs C, et al. Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: a double-blind, placebo-controlled study. Am J Psychiatry 2003; 160(2):297-302.
(66) Poyurovsky M, Fuchs C, Pashinian A, et al. Attenuating effect of reboxetine on appetite and weight gain in olanzapine-treated schizophrenia patients: a double-blind placebo-controlled study. Psychopharmacology 2007; 192(3):441-444.
(67) Ghanizadeh A, Nikseresht MS, Sahraian A. The effect of zonisamide on antipsychotic-associated weight gain in patients with schizophrenia: a randomized, double-blind, placebo-controlled clinical trial. Schizophr Res 2013; 147(1):110-115.
(68) Lian J, Huang XF, Pai N, Deng C. Ameliorating antipsychotic-induced weight gain by betahistine: Mechanisms and clinical implications. Pharmacol Res 2016; 106:51-63.
(69) Barak N, Beck Y, Albeck JH. Betahistine decreases olanzapine-induced weight gain and somnolence in humans. J Psychopharmacol 2016; 30(3):237-241.
(70) Ishøy PL, Knop FK, Broberg BV, et al. Effect of GLP-1 receptor agonist treatment on body weight in obese antipsychotic-treated patients with schizophrenia: a randomized, placebo-controlled trial. Diabetes Obes Metab 2017; 19(2):162-171.
(71) Siskind DJ, Russell AW, Gamble C, et al. Treatment of clozapine-associated obesity and diabetes with exenatide in adults with schizophrenia: A randomized controlled trial (CO-DEX). Diabetes Obes Metab 2018; 20(4):1050-1055.
(72) Larsen JR, Vedtofte L, Jakobsen MS, et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine – or olanzapine – treated patients with schizophrenia spectrum disorder: a randomized clinical trial. JAMA Psychiatry 2017; 74(7):719-728.
(73) Siskind D, Hahn M, Correll CU, et al. Glucagon-like peptide-1 receptor agonists for antipsychotic-associated cardio-metabolic risk factors: A systematic review and individual participant data meta-analysis. Diabetes Obes Metab 2019; 21(2):293-302.
(74) Wichniak A, Dudek D, Heitzman J, et al. Metabolic risk reduction in patients with schizophrenia treated with antipsychotics: recommendations of the Polish Psychiatric Association. Psychiatr Pol 2019; 53(6):1191-1218. DOI:10.12740/PP/113222.