

# Obesity and psychiatric disorders

## Otyłość a choroby psychiczne

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### KEYWORDS:

- obesity
- eating disorders
- mental disorders
- psychopharmacology

### ABSTRACT

Obesity and mental disorders belong to the most alarming health concerns in the modern era, and when they co-occur, they can pose a significant threat to patients' overall health and well-being. It has been shown that obesity increases the risk of developing psychiatric conditions, and individuals with mental illness are more likely to become obese. The relationship between psychiatric illness and weight is complex and involves multiple factors, including neurobiological, psychological, and social aspects. Eating disorders may directly lead to obesity. They impede effective obesity treatment making it challenging for individuals to follow a healthy lifestyle. Another undisputable association between obesity and mental illness is the iatrogenic weight gain caused by psychopharmacological treatment. Managing weight in individuals with mental illness and obesity should involve prescribing weight-neutral medications for managing psychiatric symptoms, evaluation of associated comorbidities and metabolic risk factors, utilization of behavioral weight management techniques, and potentially adding obesity pharmacotherapy if needed.

### SŁOWA KLUCZOWE:

- otyłość
- zaburzenia odżywiania
- choroby psychiczne
- psychofarmakologia

### STRESZCZENIE

Otyłość oraz choroby psychiczne należą do najważniejszych problemów zdrowotnych współczesnego społeczeństwa, a ich współwystępowanie może stanowić poważne zagrożenie dla chorych. Wykazano, że otyłość wiąże się z podwyższonym ryzykiem chorób psychicznych, z kolei pacjenci dotknięci zaburzeniami psychicznymi są bardziej narażeni na rozwój otyłości. Związek między chorobami psychicznymi a masą ciała jest złożony i obejmuje różnorodne czynniki, w tym neurobiologiczne, psychologiczne, społeczne. Zaburzenia odżywiania mogą bezpośrednio prowadzić do wzrostu masy ciała. Utrudniają skuteczne leczenie otyłości, uniemożliwiając pacjentom przestrzeganie zaleceń dotyczących zdrowego stylu życia. Iatrogeny wzrost masy ciała wywołany przez leczenie farmakologiczne zaburzeń psychicznych stanowi dodatkowy czynnik wśród powiązań między chorobami psychicznymi a otyłością. Kontrola masy ciała u otyłych pacjentów dotkniętych chorobami psychicznymi powinna obejmować wybór leków o neutralnym wpływie na metabolizm, regularną ocenę chorób towarzyszących oraz czynników ryzyka metabolicznego, zastosowanie terapii poznawczo-behawioralnej oraz w razie konieczności włączenie farmakoterapii otyłości.

### Introduction

Obesity is a chronic disease marked by a rise in body fat accumulation, defined as a body mass index (BMI) of 30 kg/m<sup>2</sup> or higher. Over the past few decades, its prevalence has grown to epidemic proportions worldwide, posing significant challenges for clinicians and the public (1). In 2016, approximately 13% of adults worldwide were classified as obese, with 11% of men and 15% of women falling under this category. The global prevalence of obesity has nearly tripled from 1975 to 2016. Obesity is frequently linked with health issues. People who are obese have an elevated risk

of various physical conditions, including certain types of cancer, diabetes, hypertension, heart disease, and stroke (2). In addition, high BMI is often associated with mental health concerns and social challenges. A significant amount of evidence indicates that psychological factors play a substantial role in the onset and persistence of obesity.

Eating disorders are mental conditions characterized by abnormal eating behaviors and attempts to control weight. They are often linked with weight gain over time and an increased risk of metabolic dysfunctions, including diabetes. Studies prove a higher rate of eating disorders among those overweight or obese compared with those of normal

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weight. Patients with a mental illness are at a 2- to 3-fold higher risk of obesity, and obese individuals have a documented risk of developing a mental illness ranging from 30% to 70% (3). Obesity has been linked to several psychiatric conditions, such as mood disorders, anxiety, personality disorders, attention deficit hyperactivity disorder (ADHD), and schizophrenia. There is an undeniable link between weight and chronic mental illness that stems from the unintended effects of treatment. Although variations in weight-gain potential can be observed both between and within classes of psychiatric medications, most widely used mood stabilizers, atypical antipsychotics, and antidepressants have been associated with some degree of weight gain.

Through this review, we attempt to provide a comprehensive resource for approaching the psychiatric aspects of obesity in a more informed manner, while also providing guidance on how to manage patients who have comorbid mental illness and obesity.

### Psychiatric disorders that lead to obesity

Eating disorders (EDs) are extreme disturbances to a person's eating behaviors, feelings, and thoughts concerning food, body image, and weight. Some EDs are characterized by increased food intake and may lead to obesity. These include bulimia nervosa, listed in ICD-10 (International Statistical Classification of Diseases and Related Health Problems) and DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) classifications, binge eating disorder, also listed in DSM-5, and others: diabulimia, night eating syndrome, food or eating addiction and emotional eating (4).

Bulimia nervosa (BN) is characterized by episodes of uncontrolled consumption of a large amount of food in a short time (so-called binges) followed by compensatory behaviors undertaken to get rid of consumed food, such as self-induced vomiting, laxatives, and diuretics misuse, fasting or intense physical activity. It is estimated that bulimia nervosa affects around 1% of the population and 2% of patients with obesity (5). According to a 2012 cross-sectional study, 31.2% of enrolled patients with BN were obese (6). Fluctuation of weight is typical for bulimia nervosa. The average weight suppression, which is the difference between a patient's highest weight and current weight, is between 9.6 kg and 12.0 kg, compared to 2.7 kg for healthy controls (6). Patients with high weight suppression were found to suffer from more intense binge eating and greater weight gain. They are also at higher risk of obesity and have an overall poorer treatment outcome in bulimia nervosa.

Binge eating disorder (BED) is characterized by binge eating episodes which, contrary to bulimia nervosa, are not followed by compensatory behaviors. Patients consume large amounts of food in a short period with a subjective loss of control over eating with subsequent feelings of guilt, shame, or disgust. The prevalence of BED is reported as 1-6.6% (6) of the general population, and up to 40% (7) of obese patients. 87% of BED patients are obese (4). Around 80% of them suffer from a comorbid mental illness, predominantly mood and anxiety disorders and psychoactive substance use (7, 8).

Night eating syndrome (NES) is characterized by recurrent episodes of evening hyperphagia and/or nocturnal eating after awakening from sleep. The diagnosis of NES requires awareness and recall of the episode. Patients experience a strong urge to eat before and/or during sleep and

may report the conviction of the necessity of eating as a condition to fall asleep. NES affects around 1.5% of the general population (9) and 8-15% of obese patients (4). In a 2021 study, the incidence of obesity among patients with NES was 62% (10).

Food or eating addiction is characterized by excessive and uncontrolled consumption of palatable foods with accompanying symptoms typical for other addictions including disturbance of an individual's psychosocial functioning (4, 11). Patients obsess about desired substances in a way that negatively affects relationships, school, and work; eating becomes the sole source of relief and well-being. Usually, the object of food addiction is highly processed products rich in sugar, fat, and salt (sweets, salty snacks, fast food). It is estimated that food/eating addiction affects 5.4-11.4% of the general population and 25-42% of obese patients (4, 12).

Emotional eating is characterized by episodes of overeating that serve to relieve intense emotions, both negative and positive (13). Emotional eating is not a typical eating disorder but rather a maladaptive coping mechanism that increases the risk of developing binge eating disorder and other EDs. In a 2022 cross-sectional survey study that included 9052 respondents living in 12 European countries, 37.9% of individuals struggled with emotional eating (14).

Many obese patients suffer from eating disorders, especially binge eating disorder and food/eating addiction. Effective obesity treatment and obtaining long-lasting results are impossible without coexisting eating disorder therapy. The incidence of eating disorders is notably high among individuals qualified for bariatric surgery, with 2-53% of patients suffering from binge eating disorder (14), 2-20% – of night eating syndrome (4, 15), and 14-57.8% – of food/eating addiction (16). A comorbid ED is related to poorer surgical outcomes, and additional interventions may be needed to improve long-term outcomes (17).

It should be a physician's responsibility to identify patients showing symptoms of eating disorders and refer them to psychiatrists and psychotherapists. For this purpose, it is recommended to use screening questionnaires such as the emotional eating survey proposed by the Polish Association for the Study on Obesity (18), or, if needed DEBQ (The Dutch Eating Behavior Questionnaire) (19), and TFEQ-13 (Three-Factor Eating Questionnaire) (20). All the mentioned above questionnaires have been translated and adapted for the Polish population.

The diagnosis of eating disorders substantially influences the choice of appropriate pharmacological obesity treatment. The bupropion/naltrexone combination acts synergistically in the hypothalamus as well as in the mesolimbic dopamine circuit (reward system) to promote satiety, reduce food intake and diminish food cravings. The use of this medicine has been found to be effective and is recommended as a drug of the first choice for obese patients with comorbid eating disorders such as binge eating disorder, food/eating addiction, and emotional eating (21).

The process of screening and diagnosing eating disorders is further underscored by the emergence of pharmaceutical interventions tailored for the treatment of these disorders. Lisdexamfetamine (LDX) is the first and only drug that has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe binge eating disorder (BED) in adults. Initially employed to tackle attention-deficit hyperactivity disorder (ADHD), LDX exerts its effects as a central nervous system stimulant, primarily by inducing the release of dopamine and norepinephrine

from their storage areas in presynaptic nerve terminals. Clinical evidence has proven that LDX effectively reduces the number of weekly binge days (22). The medication's impact on BED likely arises from its interactions with catecholaminergic and serotonergic pathways, influencing key aspects such as appetite, satiety, reward mechanisms, and cognitive functions. While LDX has expanded its availability to regions like Europe, including Poland, it has yet to secure approval for BED treatment in these areas.

### Psychiatric disorders that co-occur with obesity

Increasing evidence indicates that patients with numerous mental illnesses are at significantly elevated risk for obesity and metabolic syndrome (23). Obesity shows a bidirectional relationship with psychiatric disorders, representing not only a possible vulnerability factor but also a consequence of chronic nervous system dysregulation.

The most researched mental illnesses regarding their association with obesity are mood disorders, including major depressive disorder (depression) and bipolar disorder. According to a meta-analysis of 15 longitudinal studies, individuals suffering from depression have a 58% higher risk of obesity than healthy controls (24). This phenomenon is due to several factors. Patients with mood disorders more often practice maladaptive coping behaviors including emotional eating and thus are at higher risk of binge eating disorder (25). During depressive episodes, they experience abulia that appears as reduced spontaneous movement and difficulty in initiating purposeful actions. It may result in an unhealthy lifestyle with diminished physical activity and more frequent use of ready-to-go, highly processed food (26). Furthermore, the long duration of depression or bipolar disorder is associated with higher obesity incidence (27). One of the reasons may be neuroendocrine disturbances accompanying mood disorders, especially chronically elevated cortisol levels and disruption in cortisol circadian rhythm (4, 28). Lastly, the use of certain psychiatric drugs may cause weight gain in some patients.

The comorbidity of mood disorders and obesity is associated with poorer treatment outcomes compared to patients without obesity. Kloiber et al. found that overweight or obese patients with depression showed a significantly slower clinical response to antidepressant therapy (29). Several studies show that the concomitance of bipolar disorder and obesity is linked to a worse prognosis, namely shorter remission, more depressive and manic episodes in a lifetime, and a higher risk of recurrence (27).

Furthermore, studies show a positive association between obesity and other mental disorders, namely: schizophrenia, attention deficit hyperactivity disorder (ADHD), and certain anxiety disorders.

Patients with schizophrenia are especially predisposed to develop a somatic disease (30). The most common are cardiovascular disease and metabolic syndrome including diabetes mellitus type 2, hypertension, hyperlipidemia, and obesity, with up to 60% of schizophrenia patients being obese (31). It is commonly believed that mentioned complications are due to antipsychotic treatment. However, it has been proven that other factors, including hormonal, inflammatory, and genetic, significantly contribute to the development of obesity and other metabolic disorders (32). Ryan et al. have shown that even first episode, drug-naïve patients with schizophrenia had over three times as much visceral fat

as BMI-matched healthy controls (33). In a different study, it has been proven that patients before antipsychotic treatment have impaired fasting glucose tolerance and higher levels of plasma glucose, insulin, and cortisol than healthy comparison subjects (34). It has been hypothesized that these abnormalities are the results of psychosis – its direct impact on the central nervous system or via the hypothalamus-pituitary-adrenal axis. In a 2016 research, increased levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor (TNF) have been found in first-episode psychosis patients (35). These inflammatory markers have been implicated in adipose tissue dysfunction, a pro-inflammatory state occurring in obesity (36). Lastly, new evidence suggests shared genetic risk for schizophrenia and cardiovascular disease risk factors, including obesity (37).

According to a 2015 meta-analysis of forty-two studies that included a total of 728,136 individuals, the pooled prevalence of obesity was increased by about 70% in adults with ADHD compared with healthy controls (38). Individuals receiving pharmacological treatment for ADHD were not at higher risk of obesity. Studies indicate that the main mechanism leading to weight gain in ADHD patients are reduced physical activity and abnormal eating patterns, including binge eating, eating between-meal snacks, skipping breakfast, and choosing unhealthy products (38).

Anxiety disorders that have been proven to co-occur with obesity include panic disorder, specific phobia, agoraphobia, and post-traumatic stress disorder (39). Findings concerning underlying mechanisms are unclear and so far the main focus is put on unhealthy behaviors, including the use of psychoactive substances, reduced physical activity, and emotional eating.

### Psychopharmacology – obesity as a complication of psychiatric treatment

Weight gain is a typical side effect of psychopharmacological treatment. It contributes to medical comorbidity and patient noncompliance and may lead to symptomatic relapse. The most significant body weight change is induced by antipsychotics.

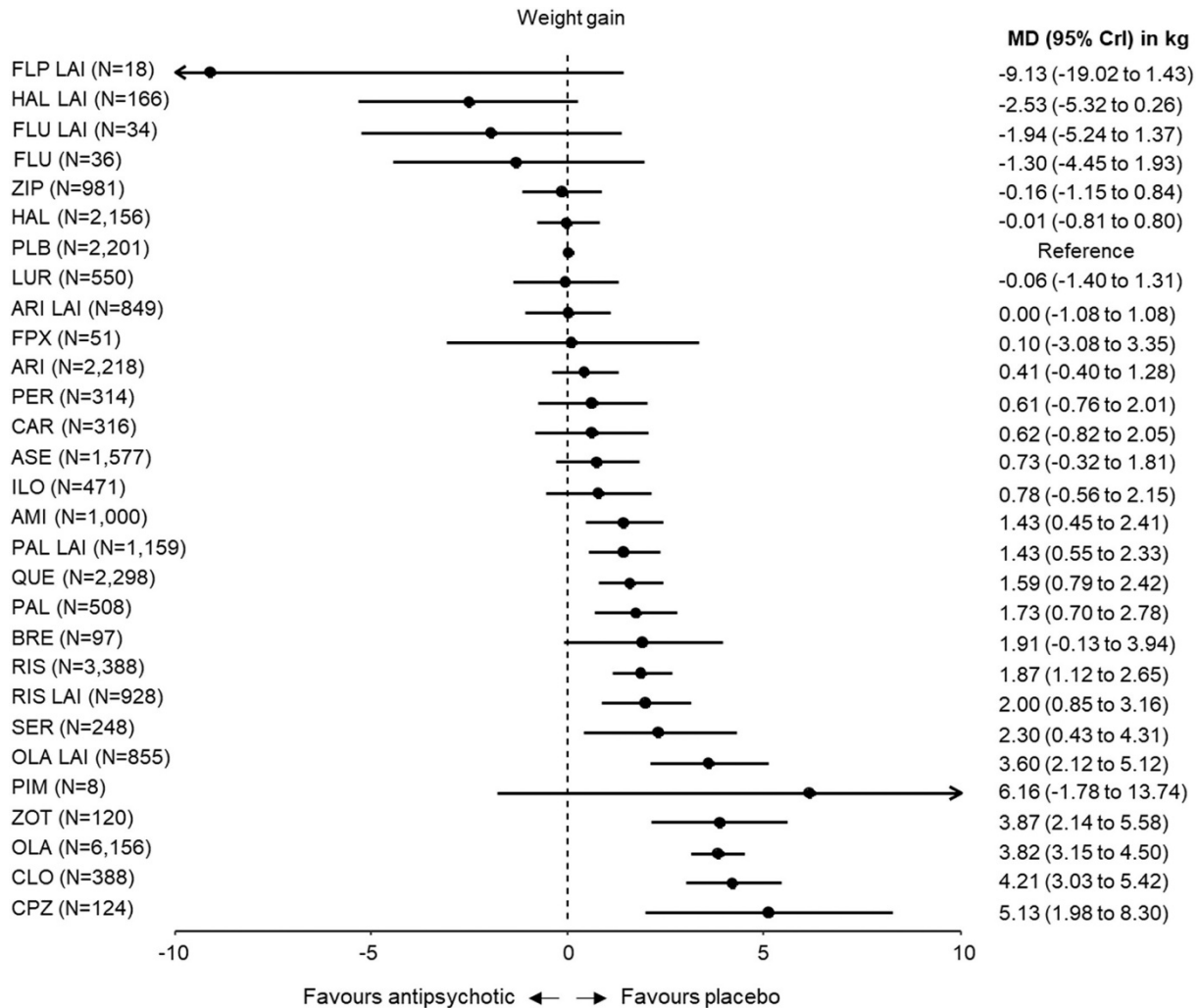
Antipsychotic medications are commonly used in patients with mental illnesses, most of all in schizophrenia and other psychotic disorders, as well as in bipolar disorder. There are two groups of antipsychotics – first-generation, known as typical antipsychotics, and second-generation, known as atypical antipsychotics. Drugs of both generations block dopamine receptors in the brain, but only atypical antipsychotics block serotonin receptors 5-HT<sub>2</sub> as well.

According to a meta-analysis including 257 studies, almost all out of thirty-two studied antipsychotics were found to cause significant weight gain (>7%) during long-term use (>38 weeks), except for aripiprazole, amisulpride, and ziprasidone (40). Clozapine and olanzapine caused significant weight gain at the greatest rate of patients: 27-50% and 20-40%, respectively. Atypical antipsychotics more frequently caused significant weight gain compared to first-generation drugs.

Table 1 and Table 2 present antipsychotic medications arranged by the iatrogenic risk of weight gain based on the results of two distinct meta-analyses (40, 41).

Allison et al. have estimated the mean weight gain in patients receiving standard doses of antipsychotics over 10 weeks: the mean increases were 4.45 kg with clozapine,

**Table 1. The risk of antipsychotic-induced weight gain. Based on the proportion of patients who experienced >7% weight gain during >38 weeks of antipsychotic treatment.**



4.15 kg with olanzapine, 2.92 kg with sertindole, 2.10 kg with risperidone, and 0.04 kg with ziprasidone (42).

The mechanism of weight gain induced by antipsychotics is complex and still not fully understood. The effect is associated with the antagonism of the serotonin receptors 5-HT<sub>2c</sub>, the dopamine receptors D<sub>2</sub>, the histamine receptors H<sub>1</sub> and the muscarine receptors M<sub>3</sub>, and agonism of the serotonin receptor 5-HT<sub>1A</sub> and the histamine receptors H<sub>3</sub>. In consequence, the medications influence the secretion of hypothalamic feeding neurotransmitters and diminish sympathetic nervous system activity. This leads to increased food intake, a rise in the calorific value of meals, and reduced energy expenditure.

Antidepressant medications are used to treat depression and anxiety disorders which are the most prevalent mental illnesses in the general population. Although their negative impact on metabolism is less significant than antipsychotics, they may have a greater overall potential for iatrogenic weight gain as their prescription volume is much higher. In Table 3, antidepressant medications are ranked according to the iatrogenic risk of weight gain (4).

A population-based cohort study with 10 years of follow-up included 294 719 participants with 53 110 (18.0%) who were prescribed antidepressants in their first calendar

year of study entry (43). During the entire period of follow-up, the risk of ≥5% weight gain was 21% higher during antidepressant treatment than at other times. The risk of weight gain was substantially increased during the second and third years of treatment. Less than 12 months' use of antidepressants did not appear to be associated with weight gain.

Selective serotonin reuptake inhibitors (SSRIs) are the most widely used class of antidepressants as they are characterized by high efficacy and safety. The evidence concerning SSRIs' influence on body weight is inconclusive with various studies showing significantly different results on weight gain during SSRIs treatment (44). According to a 4-year follow-up study, the mean annual weight gain was 0.48 kg bigger in SSRI users than in non-users (45). The exception is fluoxetine which has been found to have a neutral effect or even cause weight loss (46). According to available data the SSRI most associated with weight gain is paroxetine (43).

Tricyclic antidepressants and mirtazapine are associated with the most significant weight gain in their users (43). Studies prove that tricyclic antidepressants substantially increase the risk of metabolic syndrome, including type 2 diabetes and obesity (47). In the already mentioned population-based cohort study mirtazapine was associated with the highest incidence rate ratio of weight gain (43). Due

**Table 2. The risk of antipsychotic-induced weight gain. Based on the mean weight gain difference (measured in kilograms) between a treatment group and a placebo group.**

Antipsychotic medication	Risk of weight gain
chlorpromazine	↑↑↑
clozapine	↑↑↑
olanzapine	↑↑↑
sertindole	↑↑↑
risperidone	↑↑
quetiapine	↑↑
amisulpride	↑↑
asenapine	↑
perphenazine	↑
aripiprazole	↑
haloperidol	N
ziprasidone	N

↑↑↑ – more than 2 kg weight gain in excess to placebo  
 ↑↑ – 1 and 2 kg weight gain in excess to placebo  
 ↑ – less than 1 kg weight gain in excess to placebo  
 N – similar weight gain to placebo or weight loss

Source: Burschinski A, Schneider-Thoma J, Chiocchia V, et al. Metabolic side effects in persons with schizophrenia during mid- to long-term treatment with antipsychotics: a network meta-analysis of randomized controlled trials. *World Psychiatry*. 2023 Feb;22(1):116-128. doi: 10.1002/wps.21036.

to its effect on appetite and body weight mirtazapine is found to be a possible agent in avoidant and restrictive food intake disorder (ARFID).

Bupropion is an antidepressant known for its weight-reducing effect (46). A 2018 study has demonstrated that patients taking bupropion lost significantly more weight than controls (4.4 kg vs. 1.7 kg during 26 weeks of treatment) (48). This finding has become the basis for the decision to introduce the drug in combination with naltrexone for the treatment of obesity in 2014.

Other antidepressants (serotonin-norepinephrine reuptake inhibitors (SNRIs), trazodone, agomelatine, vortioxetine, and moclobemide have not been proven to significantly influence body weight (4).

Mood stabilizers with the greatest risk of weight gain include lithium and valproic acid. In a study including 214 participants, patients receiving either lithium or valproate gained a mean of 6.3 kg (8.2% of their baseline body weight) and 6.4 kg (8.5% of baseline body weight), respectively, whereas patients receiving topiramate lost a mean of 1.2 kg (0.7% of baseline body weight) (49).

**How to treat obesity in a patient with comorbid mental illness?**

To receive effective outcomes in the treatment of obesity, it is necessary to have a multidisciplinary treatment team that includes at least a physician, a dietician, and a mental health professional. In the case of comorbid mental illness, it is crucial to involve a psychiatrist.

**Table 3. The risk of antidepressant-induced weight gain.**

Antidepressant medication	Risk of weight gain
mirtazapine	↑↑
tricyclic antidepressants	↑↑
paroxetine	↑↑
SSRI	↑
vortioxetine	N
trazodone	N
agomelatine	N
moclobemide	N
SNRI	N
fluoxetine	N/↓
bupropione	N/↓

↑↑ – high risk of iatrogenic weight gain  
 ↑ – moderate risk of iatrogenic weight gain  
 N – no risk of iatrogenic weight gain  
 N/↓ – no risk of iatrogenic weight gain or probability of weight loss

Source: Dudek D, Wasik A, Gorostowicz A, et al. Otyłość i zaburzenia psychiczne. [In:] Olszanecka-Glinianowicz M, [edit.] *Obesitologia kliniczna*. In α-medica press; 2021; 468.

The general approach to treating a mentally ill patient with obesity is to choose pharmacologic agents that are efficacious for the patient’s primary mental disorder and that are weight neutral or, if available, associated with weight loss. If weight loss cannot be accomplished through adjusting the psychotropic drug regimen and using behavioral modification, then switching to medications with less weight-gaining liability or adding pharmacotherapy specifically for weight loss should be considered. For patients with depression and anxiety disorders, weight-neutral or even weight decreasing medications include fluoxetine, duloxetine, venlafaxine, bupropion, trazodone, agomelatine, vortioxetine, and moclobemide. For patients with bipolar disorder and schizophrenia, antipsychotics such as aripiprazole, amisulpride and ziprasidone have the lowest risk of weight gain. Another strategy that can be considered is adding a medication that enables weight loss. The most researched methods of weight reduction in patients who are being treated with antipsychotics are the addition of metformin and, as a secondary option, topiramate (50). Based on current evidence, the use of metformin and topiramate as pharmacological add-ons seems to be well-tolerated and safe. However, it’s important to highlight that the observed weight loss outcomes subsequent to the introduction of these medications are relatively modest, prompting ongoing scrutiny regarding their overall utility and appropriateness in this therapeutic context. According to recent studies, the administration of GLP-1 analogs, such as liraglutide, appears to be a tolerable and effective approach to managing obese patients receiving antipsychotic treatment (51). Nevertheless, further research is warranted before this method can be widely adopted as a standard of care.



## Conclusions

It is recommended that all patients with obesity be screened for eating disorders, with a particular focus on conditions such as binge eating disorder, night eating syndrome, and food/eating addiction. To facilitate this screening, validated questionnaires should be utilized. Psychotherapy, specifically cognitive-behavioral therapy, has been proven to be effective for patients diagnosed with eating disorders and may offer significant benefits (52).

Bupropion/naltrexone is a recommended treatment option for obese patients with binge eating disorder, night eating syndrome, and food/eating addiction. However, it is important to note that this combination therapy is not recommended for patients who are concurrently taking anti-psychootics. In such cases, metformin, GLP-1 analogs or orlistat – alternative drugs approved to treatment of obesity, if possible, as an addition to lifestyle modification should be taken into consideration.

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