Main text 7556/7000 words
Expert opinion 834 words (of min 500 words)
Abstract 199/200 words
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Risk factors, prevention and treatment of weight gain associated with the use of antidepressants and antipsychotics: a state-of-the-art clinical review

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Abstract 199/200 words

Introduction. People with severe mental illness have poor cardiometabolic health. Commonly used antidepressants and antipsychotics frequently lead to weight gain, which may further contribute to adverse cardiovascular outcomes.

Areas covered. We searched MEDLINE up to April 2023 for umbrella reviews, (network-)meta-analyses, trials and cohort studies on risk factors, prevention and treatment strategies of weight gain associated with antidepressants/antipsychotics. We developed 10 clinical recommendations.

Expert opinion. To prevent, manage, and treat antidepressant/antipsychotic-related weight gain, we recommend i) assessing risk factors for obesity before treatment, ii) monitoring metabolic health at baseline and regularly during follow-up, iii) offering lifestyle interventions including regular exercise and healthy diet based on patient preference to optimize motivation, iv) considering first-line psychotherapy for mild-moderate depression and anxiety disorders, v) choosing medications based on medications' and patient's weight gain risk, vi) choosing medications based on acute vs long-term treatment, vii) using effective, tolerated medications, viii) switching to less weight-inducing antipsychotics/antidepressants where possible, ix) using early weight gain as a predictor of further weight gain to inform the timing of intervention/switch options, and x) considering adding metformin or glucagon-like peptide-1 receptor agonists, or topiramate (second-line due to potential adverse cognitive effects) to antipsychotics, or aripiprazole to clozapine or olanzapine.

Keywords: obesity, safety, antidepressant, antipsychotic, depression, schizophrenia, bipolar disorder, weight gain, psychiatry

Highlights

- People with mental illness, who might need antidepressants or antipsychotics, should be assessed for risk factors for obesity; weight and behavioral risk factors for cardiometabolic diseases should be measured.
- Always offer lifestyle interventions tailored to patient preferences to optimize motivation, and consider psychotherapy instead of psychotropic medications for mild-to-moderate depression and anxiety, when possible.
- Tailor the prescription of antidepressants and antipsychotics to the age group and stage of treatment (acute vs long-term), and monitor ongoing effectiveness and tolerability.
- When weight gain occurs, switching to an antipsychotic or antidepressant with less weight gain potential may be beneficial.
- When weight gain occurs, consider prescribing metformin or a glucagon-like peptide-1 receptor agonist or topiramate as a second-line option.
- If the patient is receiving olanzapine or clozapine and switching is not a viable option, consider augmenting with aripiprazole.

1. Introduction

People with schizophrenia and related disorders, bipolar disorder (BD) and major depressive disorder, i.e., severe mental illness (SMI), have a ≥ 2-fold mortality rate than in the general population [1-3], and approximately 10-20 years reduced life expectancy [4,5]. This gap appears to be widening as life expectancy increases in the general population, but not among people affected by SMI [3,6,7]. The excess mortality is mainly due to non-communicable diseases, in particular cardiovascular diseases (CVDs), while unnatural causes (e.g., suicide) account for < 20% of deaths [1]. People with SMI have a CVD prevalence of approximately 10% and a 175% increased CVD-related mortality compared to the general population [8-11]. Risk factors for CVD are common in SMI and include poor diet, sedentary behavior, substance abuse, and smoking [12-14]. Type 2 diabetes mellitus (T2DM) is prevalent in people with SMI [15-17], and is associated with a two-fold excess risk of CVD and CVD-related death [18-20]. Similarly, the prevalence of T2DM, obesity, and dyslipidemia in schizophrenia is 3-5 times higher than in the general population [21]. The metabolic syndrome is also highly prevalent in SMI [22]. The metabolic syndrome was introduced to detect people at high risk for CVD and T2DM by clustering central obesity/elevated triglycerides/decreased high-density lipoprotein/hyperglycemia/hypertension [23]. The presence of a metabolic syndrome is associated with a 135% increased risk of CVD, a 140% increased risk of CVD mortality [24], and a 50% increased risk of all-cause mortality [25]. Almost one third of people with SMI have a metabolic syndrome and central obesity is found in 50% of people with SMI [22].

In addition to its link with CVD, obesity has been associated with inflammation, neuronal loss, cognitive dysfunction, and depression in the general population [26-28]. In parallel, increased inflammation has been found in schizophrenia [29-31], depression [32-35], and BD [31,36,37]. Structural and functional brain alterations and cognitive impairments have also been well documented across these conditions [38-44]. These observations suggest that obesity may affect not only the physical health of people with SMI, but also their mental condition, further emphasizing the need for appropriate assessment and management in clinical practice. To this end, several modifiable risk factors are common in SMI and contribute to obesity: i) physical inactivity and sedentary behavior [13,45,46], ii) poor diet (i.e., greater caloric intake with less nutritional benefit) [12,47,48], iii) side effects of antidepressants and antipsychotics [49-51].

Antidepressants are indicated for depression [52,53], anxiety, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder [54]. In a network meta-analysis (NMA) of randomized controlled trials (RCTs, k = 522; n = 116,477) in adults [50], virtually all antidepressants outperformed placebo in terms of efficacy for depressive disorders. Additionally, real-world data have confirmed the efficacy of antidepressants (umbrella review pooling > 1,000 studies, > 120 different meta-analytic associations of antidepressants with health outcomes) and there is highly suggestive evidence that antidepressants are protective against suicidality in adults [55]. In anxiety disorders in adults (NMA; RCTs = 89; n = 25,441), several antidepressants are effective, with duloxetine, venlafaxine, and escitalopram being particularly effective, while mirtazapine, sertraline, fluoxetine, buspirone, and agomelatine also outperforming placebo [56,57]. Antidepressants are also beneficial in the treatment of OCD in adults [58].

In children and adolescents ("youth"), only fluoxetine outperformed placebo and other active interventions for depression [59,60], alone or in combination with psychotherapies (NMA; RCTs = 71; n = 9,510) [60,61]. However, antidepressants did not improve suicidality in youth with depressive disorders, and venlafaxine even worsened it (umbrella review pooling nine NMAs, 39 meta-analyses [MAs], 90 RCTs, and eight cohort studies) [62]. Fluoxetine also improved anxiety disorders in youth [60,61].

Antipsychotics are indicated for the treatment of schizophrenia and BD in adults and youth [63-66], depression in augmentation for adults [67], and Tourette's disorder and irritability associated with autism in youth [60]. In adults with schizophrenia (NMA; RCTs = 402; n = 53,463), 26 of 32 antipsychotics outperformed placebo [51]. Clozapine was the most effective antipsychotic (standardized mean difference [SMD] = -0.89, 95% confidence interval [CI] -1.08 to -0.71) [68-70], while other antipsychotics' efficacy largely overlapped. Clozapine and other antipsychotics are also effective in reducing premature mortality [3,71]. In youth with schizophrenia (NMA; RCTs = 28; n = 3,003), clozapine outperformed all other antipsychotics in terms of efficacy, while the others were similar, except for ziprasidone which did not differentiate from placebo [60,72].

Despite their efficacy in treating SMIs, weight gain frequently occurs with antidepressants and especially antipsychotics [73,74], which not only contributes to obesity and CVD, but may also lead to medication nonadherence [49,73,75,76]. For instance, weight gain was rated as the most concerning adverse event by 46% of children treated for BD, 39% of their parents, and 70% of clinicians [77]. Moreover, SMIs are frequently comorbid with physical conditions [3,10,78-80], and those with mental disorders have poorer physical health and access to health care than people without mental disorders [81-84], calling for safe medications to treat mental disorders. Therefore, weight gain and obesity, which can be considered both health outcomes and risk factors for physical and mental disorders, should be appropriately prevented and treated in people prescribed antidepressants and antipsychotics. Knowledge of the risk factors for obesity and antidepressant/antipsychotic-related weight gain is key to their prevention/mitigation, and evidence-based management is crucial once clinically relevant weight gain has occurred [85].

Umbrella reviews summarize the evidence from MAs of observational studies and assess the credibility of published findings according to established objective and quantitative criteria to account for confounding biases [86-92]. Such an umbrella review has previously summarized risk factors for obesity in youth and in adults [93]. Regarding interventions, individual studies and meta-reviews have pooled evidence on physical health outcomes in SMI, including weight gain and obesity, from MAs of RCTs [85,94-96]. In light of these, and by conducting a comprehensive review of the most recent high-quality evidence, we aimed to provide clinical guidance on how to appropriately prevent and manage weight gain during antidepressant/antipsychotic treatment in all age groups.

2. Methods

For this narrative review, we searched MEDLINE (PubMed) and Google Scholar from database inception until April 18th, 2023, using the following search terms: ("antipsychotic"[Mesh] OR "antidepressant"[Mesh]) AND ("obesity" OR "weight"), supplemented with manual searches. Based on a best evidence-synthesis principle, we considered umbrella reviews, NMAs/MAs of RCTs, individual RCTs, and cohort studies. Recently FDA-approved antidepressants (e.g., esketamine, brexanolone, zuranolone, AXS-05) were not discussed in this review because their clinical use is not yet widespread and relatively little data are currently available, particularly in real-world settings.

The evidence was summarized separately in three sections: risk factors, prevention, and interventions. Within each section, a focus on antidepressants and antipsychotics was applied separately for youth and adults, as appropriate.

3. Risk factors for obesity

Risk factors for obesity supported by the most solid evidence, and risk factors specifically related to antidepressants and antipsychotics, are listed in Table 1. The receptor-binding profiles of antidepressants and antipsychotics related to weight gain are displayed in Table 2.

3.1 General risk factors for obesity

An umbrella review has summarized the evidence from 26 MAs of 166 observational studies reporting on risk factors for obesity [93]. Credibility of evidence was ranked into convincing, highly suggestive, suggestive, weak, and not significant, based on quantitative criteria including sample size, excess of significance bias driven by small studies, heterogeneity, and statistical significance, as done in numerous other reports (e.g., [90,97,98]). In children and adolescents, convincing evidence emerged for weight gain during the first year of life, depression, and low maternal education. In adults, convincing evidence emerged for depression. Childhood and adolescence obesity were risk factors for adult obesity supported by highly suggestive evidence. In addition, short sleep duration, which could also be a symptom of depression, was a risk factor for obesity in adults with highly suggestive evidence. A broad range of different types of childhood abuse (highly suggestive evidence), ranging from sexual to physical abuse, and neglect (suggestive evidence) were also risk factors for obesity in adults. Of note, childhood abuse is also a transdiagnostic risk factor for mental disorders, which in turn may contribute to weight gain and obesity risk [97].

Additional risk factors for obesity include unhealthy lifestyle factors, such as high intake of calorie-dense foods, reduced amounts of physical activity (with only a minority of individuals achieving the recommended amounts of 150 minutes of moderate or 90 minutes of vigorous activity per week) and high levels of 'sedentary behavior' (i.e., time spent sitting/laying down during waking hours), with recent MAs of objective data finding people with schizophrenia are sedentary over 12 hours per day [12,13,99,100]. SMIs are

associated with unhealthy dietary patterns, including sugar-sweetened beverage consumption, lower adherence to the Mediterranean diet, and lower consumption of fruit and vegetables [12,48]. Physical activity is decreased and, conversely, sedentary behaviour is increased in people with SMI [13], which shifts the energy intake and expenditure balance towards weight gain [48].

3.2 Antidepressant-related risk factors for weight gain

Loss of appetite is a common symptom of melancholic depression, and thus weight gain during treatment may be a sign of response. However, depressive episodes with atypical features are characterized by increased appetite and carbohydrate craving, and thus increased body weight during short-term treatment may be due to these persisting atypical symptoms and the natural course and consequences of the disease [73,78-80,101]. Nonetheless, antidepressants should target disease-specific symptoms (i.e., mood in depressive disorders, anxiety in anxiety disorders).

Different medications have different effects on weight, depending on their receptor-binding profiles [49,102]. For antidepressants, histamine 1-receptor (H1) antagonism, muscarinic receptor (M) and serotonin-2C receptor (5-HT2C) antagonism are considered crucial [49]. Tricyclic antidepressants, mirtazapine, and paroxetine have considerable affinity for H1- and M-receptors [49]. Antidepressants associated with greater weight gain include amitriptyline [103], mirtazapine [104,105], and paroxetine [103], whilst the ones with the most favorable weight profile are fluoxetine and bupropion (MA; 116 studies) [73,106]. Bupropion has also been associated with weight loss [107]. Mirtazapine, in particular, induces more weight gain than citalopram, fluoxetine, paroxetine and sertraline [108]. Duloxetine and other serotonin/noradrenaline reuptake inhibitors have intermediate weight gain effects [107,109,110], while vortioxetine, agomelatine, and escitalopram are considered weight neutral [104,111-113]. When it occurs, weight gain of antidepressants appears to be sustained over time [110].

There is little consensus on which patient characteristics predict weight gain during antidepressant-treatment, although there is evidence indicating that early weight gain (i.e., during the first weeks of treatment) is a solid predictor of overall weight gain [114,115].

3.3 Antipsychotic-related risk factors for weight gain

The risk of weight gain with antipsychotics depends on antipsychotic receptor-profile, demographic, clinical, and lifestyle characteristics [116-119].

Direct receptor activities that appear to be mostly responsible for weight gain include antagonism at histamine receptor H1, muscarinic receptors M1 and M3, and 5-HT2C receptors. H1-antagonism induces appetite increase and sedation [116,119-122], M1-antagonism induces sedation, and 5HT2C-antagonism induces metabolic alterations that contribute to weight gain [123,124]. Muscarinic M3 receptors are expressed notably in the pancreas (β cells) and hypothalamus, where they are involved in insulin secretion, glucose homeostasis, and body weight regulation [125]. Animal studies suggest that at least some of the

deleterious effects of olanzapine and clozapine on weight gain and development of T2DM may be mediated by blockade of M3 receptors [126,127].

Appetite alterations with antipsychotics might be mediated by several gut hormones [128,129]. While alterations in leptin, ghrelin, adiponectin, and C-peptide are most likely a consequence rather than cause of the weight gain [130-139], low levels of glucagone-like-peptid-1 (GLP-1) might play a causal role. By reducing GLP-1 secretion, second-generation antipsychotics (SGAs; clozapine and olanzapine in particular) impair glucose homeostasis, increase the risk of T2DM [140-143], and alter craving for higher-caloric carbohydrate foods [122,141]. In addition, antipsychotics could act directly on the hypothalamus, whereby an increase of the AMP-related kinase (AMPK) levels causes an orexigenic effect [144]. The increase in AMPK levels is partly dependent on H1-antagonism [121,145]. Blockade of dopamine receptors (D2/3) may likewise lead to increased AMPK levels via the D2 receptor-AMPK axis and has been implicated in increased caloric intake via suppression of satiety signals [146-148]. Additionally, 5-HT2C receptor affinity has also been correlated with orexigenic effects [149].

As expected from their receptor-binding profiles [120,150-153], yet with some differences found among recent NMAs, short and mid-term weight gain are most considerable with chlorpromazine, clozapine, followed by zotepine, olanzapine, sertindole, iloperidone, quetiapine, risperidone, paliperidone, asenapine, and brexpiprazole, while flupentixol, amisulpride, cariprazine, lurasidone, aripiprazole, ziprasidone, haloperidol, and fluphenazine did not significantly differ from placebo [51,118,154-160]. In studies reporting on body mass index (BMI)-increases in adults, the adverse effect liability went from olanzapine, clozapine, sertindole, quetiapine, risperidone and paliperidone, to lurasidone, aripiprazole, and haloperidol [154]. Similar profiles emerge with up to 18 months of follow-up, with weight gain $\geq$ 7% occurring in 30% of those receiving olanzapine vs only in 7% of people taking ziprasidone [161]. The safety profile across different antipsychotics in adults was largely confirmed in children and adolescents [72,162]. In the largest NMA to date in children and adolescents taking antipsychotics, olanzapine induced the largest weight gain, followed by quetiapine, clozapine, risperidone and paliperidone, asenapine, and aripiprazole, while haloperidol, fluphenazine, molindone, lurasidone, and ziprasidone did not significantly differ from placebo [72].

The weight gain associated with antipsychotics appears to be dose-related [163,164]. For asenapine, brexpiprazole, cariprazine, haloperidol, iloperidone, lurasidone, risperidone, there was an initial linear association that plateaued at higher doses [163]. For aripiprazole, olanzapine, and paliperidone, the initial linear increase did not plateau, suggesting that weight gain continues to increase with dose [163]. For quetiapine, sertindole, and ziprasidone, the dose-response curve was bell-shaped, with higher doses associated with less weight gain [163].

The magnitude of weight gain compared with placebo, however, differed between the two age groups. In adults, the weight gain difference between antipsychotics and placebo ranged from less than 1 kg for brexpiprazole (mean difference [MD] = 0.88 kg, 95% CI 0.06 to 1.69) to 5.13 kg for clozapine (MD = 5.13 kg, 95% CI 1.98 to 8.30) over a mean trial duration from six to more than 13 weeks [154]. The magnitude of

weight gain was larger for youth. In a cohort study involving around 90 youth with BD, schizophrenia spectrum disorders, and other non-psychotic disorders, > 70% had significant weight gain after three months [165]. A comprehensive review showed that weight gain is heterogeneous among antipsychotics, but higher than seen in adults [166]. Pooling 34 studies and 2,719 children or adolescents with schizophrenia (n = 788), BD (n = 719), or mixed disorders (n = 1,212) exposed to SGAs, weight gain ranged roughly from 4-16 kg for olanzapine, 1-9.5 kg for clozapine, 2-7 kg for risperidone, and 2-6 kg for quetiapine [166]. According to the most recent NMA on antipsychotics in youth, these figures translate into a large effect size for olanzapine (SMD = 1.24, 95% CI 0.91 to 1.57), clozapine (SMD = 0.92, 95% CI 0.22 to 1.61), and quetiapine (SMD = 0.85, 95% CI 0.61 to 1.09); medium for paliperidone (SMD = 0.73, 95% CI 0.48 to 0.97), and risperidone (SMD = 0.61, 95% CI 0.32 to 0.89); and small for asenapine (SMD = 0.43, 95% CI 0.19 to 0.68) and aripiprazole (SMD = 0.29, 95% CI 0.20 to 0.49) [72].

Importantly, not only younger age, but also early phases of disease are associated with an increased propensity for antipsychotic-related weight gain, especially in people who are antipsychotic-naive or have a first-episode of psychosis [167-172]. For example, in a 12-month trial involving patients with first-episode schizophrenia who received antipsychotics considered body weight neutral (e.g., amisulpride, ziprasidone, and low-dose haloperidol), each antipsychotic was associated with a clinically relevant weight gain (9.7, 4.8 and 6.3 kg, respectively) [173]. These findings are supported by a 3-month study of treatment with quetiapine, ziprasidone, and aripiprazole in patients with first-episode psychosis [174]. The proportion gaining ≥ 7% of baseline weight at week 24 was 23% for ziprasidone, 32% for quetiapine, and 45% for aripiprazole. A recent MA of 404 clinical trials found that weight gain associated with the use of amisulpride, aripiprazole, haloperidol, perphenazine, olanzapine, quetiapine, and ziprasidone was greater in patients who were antipsychotic naive compared with those who were previously treated [175]. A notable exception appears to be lurasidone, which in a 2-year study was associated with numerically less weight gain at last observation than expected from sex- and age-adjusted growth, both in the subgroup of adolescents with schizophrenia who were antipsychotic-naive (+ 4.5 kg vs + 5.7 kg) and those who were previously treated with antipsychotics (+ 4.6 kg vs + 6.6 kg) [176]. Off-label use of antipsychotics has also been associated with weight gain, with olanzapine leading to a weight gain of 3.2 kg (95% CI 2.57 to 3.90, p = 0.001, k = 12), and similar trends observed for quetiapine and risperidone [177].

A clinically relevant and readily available indicator of weight gain risk is early weight gain. Results from a 6-month, prospective, multinational, observational study showed that factors associated with greater weight gain when taking olanzapine were early weight gain, problematic eating psychopathology/behavior, and low physical activity [178]. Early significant weight gain after 2 months of treatment occurred in 23% of the participants and these people gained significantly more weight overall. In an exploratory multivariate analysis, 10 factors were associated with weight gain during 6 months of olanzapine therapy: country (weight gain decreased from Mexico, through China, Romania, to Taiwan, suggesting regional and/or ethnic differences), housing conditions (larger weight increase in more supervised settings, such as hospitals or other institutions vs independent living), stronger appetite, excessive amount of food needed to feel full,

eating until uncomfortably full, thoughts preoccupied with food, eating location (greater weight gain in fast food vs regular restaurants), increased meal frequency, evening snack consumption, and less vigorous exercise [178].

On the other hand, contrasting findings have been reported for other factors, including demographics, indicating that very little can be known regarding the baseline risk of weight gain prior to antipsychotic treatment initiation (other than younger age group and less prior antipsychotic exposure). For instance, while some studies suggested that baseline weight predicted weight gain, the largest recent NMA did not confirm such finding [154], although this null-finding may have been due to the fact that mostly chronically ill patients were included in the meta-analysed RCTs. Similarly, the risk of weight gain does not seem to be consistently moderated by sex nor ethnicity [154,179]. The lack of baseline indicators of weight gain proneness makes the need for early and continuous weight measurement even more important.

Those medications that induce more weight gain are also associated with worsening of several metabolic parameters [154], including HbA1c and lipid profile, ultimately increasing the risk of cardiovascular events. In this sense, weight gain is not only an outcome, but an additional risk factor of subsequent complications associated with pharmacological treatment of mental disorders [180,181].

Nevertheless, data on individual health outcomes, e.g., weight, lipids, glucose metabolism, should be assessed in the larger context of the ultimate composite health outcome, which is death. Despite the association between antipsychotics and poor metabolic health, subjects with schizophrenia that receive treatment with antipsychotics have a longer life expectancy compared with those who do not take antipsychotics [3]. This is true in particular for SGAs and long-acting injectable formulations [3]. The mismatch between the negative impact on physical health and the positive effect on life expectancy has been defined as “the antipsychotic paradox” [182]. Among other reasons, the net beneficial effect of antipsychotics on life expectancy might be mediated by a better adherence to cardiometabolic medications when on versus when off antipsychotics, in people with schizophrenia [183].

4. Prevention of weight gain due to antidepressants and antipsychotics

First, preventing weight gain in people taking antidepressants and antipsychotics requires a multidimensional approach. It can be implemented by choosing a safe first-line treatment for the underlying mental condition. Alternative treatments to antidepressants should be considered when clinically feasible. For mild forms of depression, among several effective modalities of psychotherapy [184-187], cognitive-behavioral therapy (CBT) can be considered for adults [188], and CBT or interpersonal therapy (IPT) should be considered in youth [61]. For anxiety disorders in adults, CBT should also be considered [189]. In youth, group CBT should be considered for anxiety disorders and OCD [190]. For moderate to severe depressive and anxiety disorders [191,192], BD [191], and for schizophrenia [193], pharmacological treatment, with or without CBT, is generally recommended as first-line treatment. Brain stimulation techniques including transcranial

magnetic stimulation and transcranial direct current stimulation are also effective and safe treatment options for depression [194].

When an antidepressant is indicated, in adults, agents with a lower risk of weight gain should be selected as first-line treatments, given that none of the antidepressants currently clearly or substantially outperforms the others in the treatment of depressive or anxiety disorders [50,59]. Vortioxetine, agomelatine, and fluoxetine can be first-line choices. In youth, fluoxetine remains the only approved option to treat depressive disorders, and the best choice to treat anxiety disorders.

Several antipsychotics are equally effective for treating schizophrenia in both adults and youth, with similar rankings among antipsychotics regarding weight effects in both age groups [51,72,155,162,195,196]. Clozapine and olanzapine are associated with the highest risk of cardiometabolic adverse effects, while lurasidone, cariprazine, ziprasidone, aripiprazole and lumateperone are the safest regarding weight, and should be first-line antipsychotic treatment across age groups, as approved by regulatory bodies, to minimize weight gain. When olanzapine is needed and weight gain is observed, the recently FDA-approved combination of olanzapine plus the mu opioid antagonist samidorphan can attenuate weight gain [197,198], and the risk of newly emergent metabolic syndrome or hypertension [199].

Second, as recommended by The Lancet Psychiatry Commission for protecting physical health in people with mental illness, lifestyle interventions should be provided from the initiation of medication treatment to optimize both physical and mental health outcomes of pharmacological interventions [14]. In particular, physical activity interventions aiming to help people achieve recommended amounts of moderate-to-vigorous physical activity should be offered to those with anxiety, mood disorders, and schizophrenia spectrum disorders [12,200,201]. If patients' psychiatric symptoms interfere with motivation, treatment adherence, or ability to engage with exercise, physical activity interventions may need to be provided after psychiatric symptoms have sufficiently improved with successful pharmacologic treatment, as people with mental illness benefit from weight interventions similarly to individuals with obesity in the general population [202].Third, measuring weight at baseline and monitoring weight throughout the course of treatment is a mandatory step to prevent weight gain and collect valid clinical information to guide further decision making. Along with body weight, behavioral risk factors for cardiometabolic diseases (such as physical activity, diet, and smoking) should also be assessed whenever possible. Given that several first-line antidepressants for major depression are associated with weight gain, close monitoring of weight change should be prioritized during pharmacological treatment of mood disorders [203]. Currently, there are no cardiometabolic monitoring guidelines for antidepressants in contrast to antipsychotics where well-established guidelines exist [204,205]. Thus, and given the clinically relevant risk of weight gain with some antidepressants and cardiometabolic risk associated with depressive disorder [22,206], similar monitoring guidelines for antidepressants should be adopted, balanced with available resources [203].

Finally, the early addition of a weight gain-attenuating co-treatment is another preventive option that may be considered for those with baseline risk factors for weight gain. A recent Cochrane review of preventive

pharmacologic interventions in those with schizophrenia initiating antipsychotic therapy indicated that metformin may be effective in preventing weight gain (MD = -4.03 kg, 95% CI -5.78 to -2.28; k = 4; n = 131; low-certainty evidence) and BMI increase (MD = -1.63 kg/m^2, 95% CI -2.96 to -0.29; k = 5; n = 227; low-certainty evidence) [207]. Other agents found to be potentially effective in preventing weight gain associated with antipsychotic treatment included H2 antagonists, like nizatidine, famotidine and ranitidine (MD = -1.32 kg, 95% CI -2.09 to -0.56; k = 3; n = 248; low-certainty evidence), and monoamine modulators, like reboxetine and fluoxetine (MD = -1.89 kg, 95% CI -3.31 to -0.47; k = 3; n = 103; low-certainty evidence). However, in this MA of preventative effects, topiramate was not found to be superior to placebo in preventing weight gain (MD = -4.82 kg, 95% CI -9.99 to 0.35; k = 3; n = 168; very low-certainty evidence) [207].

5. Treatment of weight gain due to antidepressants and antipsychotics

According to an umbrella review that pooled data from 128 RCTs and 47,231 participants with schizophrenia treated with antipsychotics, several options are available to treat weight gain, including non-pharmacological and pharmacological strategies [85]. In addition, individual RCTs have introduced several additional alternatives for treating obesity in people managed with antipsychotic and antidepressants, which are discussed in the following sections.

5.1 Non-pharmacological interventions

Several trials have shown that non-pharmacological interventions are effective in treating overweight or obesity or attenuating further weight gain in people taking antipsychotics [208-211]. However, findings have not been universal, and effects in motivated study participants are reduced when considering larger and more representative populations [212].

Individual lifestyle counselling (i.e., health-promoting psychoeducational interventions aimed at weight management) was the most effective of all options for reducing weight in people with schizophrenia taking antipsychotics, with a large effect size (SMD = -0.98, 95% CI -1.15 to -0.81; k = 14). Lifestyle counselling also retains efficacy when delivered in a group setting, but the effect size shrinks from large to small (SMD = -0.39, 95% CI -0.54 to -0.23; k = 19) [85]. However, not all trials were able to confirm the efficacy of healthy lifestyle instruction [213], and differences in the format of delivery of lifestyle interventions may affect their efficacy. Moreover, focusing on multiple lifestyle domains may be associated with reduced efficacy of the specific components of lifestyle interventions, i.e., improving diet and physical activity [94,212].

Dietary interventions alone had a small to moderate role in treating overweight or obesity in people with schizophrenia and taking antipsychotics (SMD = -0.50, 95% CI -0.66 to -0.34; k = 22) [85]. Psychoeducation exerted a moderate beneficial effect on weight in people with schizophrenia on antipsychotics (SMD = -0.77, 95% CI -0.98 to -0.55; k = 8) [85]. CBT alone may also reduce weight, yet with a small effect size (SMD = -

0.37, 95% CI -0.55 to -0.18; k = 11) [85], which can be larger when combined with exercise and dietary interventions [214,215]. Structured physical activity, i.e. exercise, is also one of the most effective interventions (SMD = -0.96, 95% CI -1.27 to -0.66; k = 4) for weight reduction in people on antipsychotics, with a large effect size similar to that of individual lifestyle counselling [85].

While no umbrella review has summarized the same body of evidence in people taking antidepressants, it would be reasonable to expect that the same interventions that are effective in reducing weight in people on antipsychotics would also be effective in people taking antidepressants, given that these strategies are also effective in the general population for reducing weight in people with obesity [93], and given that unhealthy lifestyles are common in people with depressive disorders and schizophrenia [12]. Several MAs have demonstrated that exercise is an effective treatment for depression, with pooled effect sizes ranging from small (SMD = -0.4) to very large (SMD = -1.4) [216-219]. Also, regarding psychological interventions, the RAINBOW study, a RCT including 409 participants with obesity and depression, revealed that compared with usual care, an integrated behavioral weight-loss treatment and cognitive-based problem-solving therapy with as-needed antidepressant medication resulted in statistically significant reductions in BMI (-0.7 vs -0.1 kg/m^2, respectively; p = .01) and depressive symptoms (-0.3 vs -0.1 on the average score for the 20 items of the Depression Symptom Checklist; score range: 0-4; p = .01) at 12 months [220].

Optimizing motivation in people with mental disorders is a key factor in the adherence and effectiveness of proposed lifestyle changes. Motivating factors and barriers towards exercise in people with SMI have been identified [221]. In a MA including 12 studies and 6,431 subjects with SMI, 91% of patients endorsed "improving health" as a valid motivation to exercise, as well as "losing weight" (83%), "improving mood" (81%), and "reducing stress" (78%). The main barriers to exercise were low mood and stress, and lack of support [221]. Hence, improving mood or negative symptoms first may be key to foster intrinsic motivation for physical activity, which itself is a crucial factor towards engaging with an exercise prescription [222-224]. Exercise is also beneficial for physical health, to mitigate weight gain or obesity that may occur during treatment with psychotropic medications [208-211]. Importantly, to maximize adherence to and effectiveness of lifestyle interventions, these should be delivered by health professionals with specific training in health behavior change and/or expertise from a health and fitness background [14,225].

In sum, rather than waiting for weight gain and comorbidities to occur, lifestyle interventions should be offered to all patients as early as possible in the course of the illness as well as antidepressant/antipsychotic treatment, as preventing further weight gain and comorbidities may be an effective strategy for maximizing the adherence, engagement and outcomes of lifestyle interventions in SMI populations [14].

5.2 Switching antipsychotic or antidepressant

Switching to an antipsychotic with a lower propensity for weight gain profile may improve weight gain or even lead to weight loss [226,227]. A recent MA included 61 studies reporting on antipsychotic switching versus staying on the previous antipsychotic with data on change in weight [227]. In a pairwise MA, only switching to aripiprazole was associated with a significant weight loss (-5.52 kg, 95% CI -10.63 to -0.42; p =

0.03), with improvements in fasting blood glucose and triglycerides, and no change in psychotic symptoms [227]. In a before-after MA, both aripiprazole and ziprasidone were associated with statistically significant weight loss (-1.96 kg, 95% CI -3.07 to -0.85; $p < 0.001$, and -2.22 kg, 95% CI -3.84 to -0.60; $p = 0.007$, respectively) without worsening of psychotic symptoms [227]. Switching to amisulpride, paliperidone/risperidone, quetiapine, or lurasidone was not associated with weight change, whereas switching to olanzapine and clozapine was associated with statistically significant weight gain. There was limited evidence to guide switching from a specific first antipsychotic to a specific second antipsychotic [227]. Any decision to switch antipsychotics in a person whose psychiatric illness is stable must be weighed against the risk that a switch may lead to a deterioration in mental status [226,227]. However, a recent NMA of antipsychotic treatment strategies in schizophrenia found that both antipsychotic continuation and switching were equally efficacious in maintaining treatment efficacy, with both strategies being superior to antipsychotic dose reduction, and with all three strategies outperforming antipsychotic discontinuation, which was associated with the greatest risk of relapse [155]. Clozapine, an antipsychotic associated with high metabolic risk [228,229], is reserved for treatment refractory schizophrenia [68,230], which is why switching from clozapine to an antipsychotic with a more favourable metabolic profile may not be feasible, risking symptom deterioration in case of treatment resistance to first-line antipsychotics.

The antipsychotic switch must always be implemented appropriately to avoid the risk of worsening the psychiatric illness, as detailed elsewhere [231,232]. In particular, the risk related to switching from a sedative (H1-antagonist) to a non-sedative medication or from a full dopamine antagonist to a D2-partial agonist may worsen psychiatric status [150,233]. Plateau cross-titration (reaching the target dose with the second, less sedating and less potent dopamine blocking agent, or the one with a longer half-life than the initial drug, and only then tapering the first agent) and progressive switching, with concomitant benzodiazepines to bridge the lack of sedation, are common strategies to avoid worsening of psychiatric symptoms [150,233]. The risk-benefit ratio of switching antipsychotic vs augmenting the current antipsychotic with other medications, for which there is limited high-level evidence [234-236], should be carefully evaluated.

For antidepressants, no high-quality evidence has identified valid options for switching from one antidepressant to another to safely and effectively induce weight loss. However, switching from those antidepressants with a higher risk of weight gain (i.e., paroxetine, mirtazapine, tricyclic antidepressants) to those that are more weight neutral (i.e., escitalopram, fluoxetine, vortioxetine) or even associated with weight loss (i.e., bupropion) is clinically reasonable.

5.3 Augmentation with psychopharmacologic medications

The best evidence among psychopharmacologic augmentation options to reduce weight in people on antipsychotics is for aripiprazole, with a moderate effect size (SMD = -0.73, 95% CI -0.97 to -0.48; $k = 9$), but only in people treated with high-risk antipsychotics, such as clozapine or olanzapine. A moderate effect size was also found for topiramate (SMD = -0.72, 95% CI -1.56 to -0.33; $k = 15$) [85,237]. However, the use of psychotropic polypharmacy is discouraged in clinical practice [236,238], and the use of topiramate for

weight loss is limited due to the risk of cognitive impairment [239,240], making topiramate a second-line option. Samidorphan, a mu opioid antagonist recently approved by the FDA in a single-pill combination with olanzapine, has also been shown to mitigate weight gain and metabolic disturbances associated with olanzapine [197-199]. Consistent with findings from a previous phase 2 trial [198], a phase 3 RCT (n = 561) reported that significantly fewer patients gained ≥ 10% of their baseline weight at 24 weeks with the combination of samidorphan/olanzapine compared to olanzapine alone (17.8% vs 29.8%; odds ratio = 0.50; p = .003) [197]. Post-hoc analyses also showed that the combination with samidorphan resulted in a better tolerability profile with respect to the development of hypertension, obesity and metabolic syndrome, although there were no differences for hyperglycemia and dyslipidemia [199].

No high-quality evidence has identified valid options for augmenting antidepressants to induce weight loss.

5.4 Augmentation with non-psychopharmacologic medications

Administration of metformin is one of the most investigated pharmacological strategies to treat antipsychotic-related weight gain, including in youth [213]. Metformin is a first-line treatment for T2DM together with lifestyle changes; it decreases intestinal absorption of glucose, increases insulin sensitivity, reduces hepatic gluconeogenesis, and suppresses appetite [203,204]. Several RCTs and MAs have found metformin to be effective, safe, and well tolerated in reducing antipsychotic-related weight gain in people with schizophrenia [241-248]. According to the most comprehensive umbrella review on this subject, metformin (SMD = -0.53, 95% CI -0.69 to -0.38; k = 29) is the most evidence-based non-psychopharmacological medication for weight loss in people taking antipsychotics with schizophrenia [85]. Metformin-associated attenuation of antipsychotic-induced weight gain may be greater in persons with first-episode psychosis than in chronically ill populations, thereby supporting early intervention approaches [249]. The overall efficacy of this strategy was also confirmed by a MA that highlighted that in six RCTs (n = 732), the metformin plus lifestyle group had significant reductions in weight and BMI compared with the metformin, lifestyle, and placebo groups [250]. Weight gain of ≥ 7% was less frequent in the combination group than in the placebo group. Among people on clozapine, the only antipsychotic indicated for treatment refractory schizophrenia, concomitant use of metformin at the time of clozapine initiation may reduce weight gain [228], while augmentation with metformin may lead to weight loss in people with pre-existing clozapine-associated obesity (-3.12 kg, 95% CI -4.88 to -1.37; p < .001) [248].

Another group of non-psychopharmacologic medications that have been shown in RCTs to reduce weight gain in people taking antipsychotics are GLP-1 receptor agonists (GLP-1RAs) (e.g., exenatide, liraglutide, semaglutide), which are currently being evaluated for antipsychotic-related weight gain. GLP-1 RAs were originally licensed for the treatment of T2DM, and more recently liraglutide and semaglutide have been approved for the treatment of obesity, albeit at higher doses than typically used in T2DM. GLP1-RAs have shown efficacy in reducing weight in people taking antipsychotics in several RCTs. While initial trials studied GLP1-RAs at the lower doses used for the treatment of T2DM, an individual participants data MA pooled data from two RCTs comparing exenatide and one comparing liraglutide with placebo in people

taking antipsychotics, showing that GLP-1 RAs were superior to placebo on weight, waist circumference, BMI, HbA1c, fasting blood glucose, and visceral adiposity [237]. Specifically, the weight loss versus placebo was -3.71 kg (95% CI -4.99 to -2.44; k = 3; n = 164), and the number-needed-to-treat for ≥ 5% body weight loss was 3.8 (95% CI 2.6 to 7.2) [237]. Importantly, weight loss was greater in patients treated with olanzapine or clozapine. A recently published RCT including 47 patients using the obesity dose of liraglutide confirmed the findings of this previous MA and reported a greater weight loss of 5.7 ± 7.9 kg [251]. Liraglutide was also found to be safe and did not worsen psychiatric symptoms in a small retrospective chart-review study [252]. In a one-year follow-up study after liraglutide withdrawal, weight was still reduced compared to baseline, but other metabolic and anthropometric indices returned to baseline values, suggesting that treatment with GLP1-RAs should likely be continued long-term to maintain the effect [253].

No high-quality evidence has identified valid options for augmenting antidepressants to induce weight loss.

6. Ten expert opinion clinical recommendations to reduce weight gain in people taking antidepressants or antipsychotics

Based on the available evidence, ten clinical recommendations regarding management options to reduce weight gain associated with antidepressants/antipsychotics are provided (table 3). These recommendations address overarching principles of good clinical practice that are equally, if not more, important than minimizing weight gain: monitoring efficacy and adverse effects, using effective medications with the least potential for adverse effects, avoiding medications that may increase the risk of suicide, and adjusting treatment based on the efficacy, tolerability, and safety profiles of antidepressants/antipsychotics.

6.1 Assess risk factors

Risk factors for obesity should be routinely assessed. The choice of antidepressants/antipsychotics should take into account the patient's baseline risk of weight gain, with particular caution in those with identified risk factors for obesity (see above).

6.2 Monitor metabolic health

Routine measurement of patients' weight by (mental) health professionals as a standard of care is not yet a global reality. The lack of routine measurement of weight and CVD risk factors (waist circumference and BMI, blood pressure, fasting blood glucose or HbA1c, triglycerides, and high-density lipoprotein cholesterol) risks failure to intervene in a timely manner. If weight is not measured routinely, detection of weight gain may go unnoticed until the patient has developed overt obesity, which is much more difficult to treat. Weight should be measured routinely before an antidepressant or an antipsychotic is prescribed and at each follow-up visit, ideally within the first month and then every 4 weeks [14]. CVD risk factors should be

measured prior to commencement of an antidepressant or an antipsychotic, at 3 months, then 6-monthly (youth, people with first-episode psychosis) or annually (low-risk patients), with a weight gain of ≥ 7% of baseline weight triggering a series of metabolic tests [14]. However, the relative weight gain should be contextualized within the absolute weight status. For instance, for those who are underweight, a change from underweight to normal weight may be beneficial. In these cases, consideration of the patient's metabolic profile along with weight status can guide appropriate clinical decision making. In addition to weight measurement, behavioral factors that may contribute to weight gain and adverse cardiovascular and metabolic outcomes, such as unhealthy diet, physical inactivity, and smoking, should also be considered.

6.3 Individual lifestyle interventions, exercise, diet

Lifestyle education, counselling, and interventions should be offered as early as possible to all patients receiving antipsychotic or antidepressant treatment (i.e., even those at the very initiation of treatment), as prevention of further weight gain and comorbidities is feasible and effective in SMI populations [14]. Exercise interventions are also a transdiagnostic treatment that improves both mental and physical health and should be available to all individuals with SMI [201]. Exercise can improve primary disease-specific symptoms of mental disorders and prevent and treat weight gain or obesity in people treated with antidepressants or antipsychotics. Engagement in physical activity and structured exercise should be encouraged and supported whenever psychiatric symptoms are sufficiently stable not to interfere with motivation/ability to engage. In all cases, lifestyle interventions promoting healthy behaviors, such as physical activity and diet, should be delivered, where possible, by staff with specific training and expertise, and should follow patients' preferences to promote enjoyable activities and social reconnection, possibly even focusing on only one lifestyle aspect to provide a simpler and more targeted approach. The pleiotropic benefits of a healthier lifestyle go beyond weight.

6.4 Non-pharmacological treatments

Non-pharmacological alternatives to antidepressants are available for anxiety disorders and mild forms of depression, alone or in combination with antidepressants. For mild depression, exercise and CBT should be considered in adults [188,219], and CBT or IPT in youth [61]. For anxiety disorders, CBT should be considered in adults [189], and CBT for anxiety disorders and OCD in youth [190]. For moderate-to-severe depression, anxiety disorders, BD, and schizophrenia, pharmacological treatment is the most commonly recommended first-line treatment, with or without psychotherapy. Ultimately, the choice of treatment depends on the informed preference of the patient and the availability of treatment.

6.5 Tailor treatment according to stage of disease, age, and prior medication exposure/weight gain

Age is a factor that can guide the choice of antidepressants and antipsychotics, as youth and treatment-naive individuals are at greatest risk for antipsychotic-related weight gain. Moreover, for children and adolescents with depression, the only antidepressant that is widely supported by the available evidence is fluoxetine. Venlafaxine should be used with caution, as it may increase the risk of suicidality [59]. The effectiveness of other antidepressants in these age groups is much lower or not evidence-based [59]. For anxiety and OCD, selective serotonin reuptake inhibitors are first-line options, of which fluoxetine causes the least weight gain [254]. Among antipsychotics, aripiprazole, brexpiprazole, cariprazine, lumateperone, lurasidone, and ziprasidone should be preferred as first-line antipsychotics to minimize the risk of weight gain, given that their efficacy largely overlaps with all other antipsychotics except clozapine [51,72]. For mood disorders, aripiprazole, brexpiprazole, cariprazine, lumateperone, and lurasidone have also demonstrated efficacy [52,64,255-261].

6.6 Monitor effectiveness

The effectiveness of any intervention should be measured and reevaluated throughout the course of treatment. If interventions that are metabolically neutral (e.g., psychological interventions, weight-neutral antipsychotics) do not produce the necessary improvements, patients may be at risk for adverse disease outcomes, including rehospitalization, deterioration, inability to manage physical health, poor lifestyle choices, substance abuse, and even suicidal behavior. In such cases, switching to alternative medications with less favorable metabolic profiles but better efficacy and effectiveness (such as clozapine for treatment refractory schizophrenia [68,70]) would be indicated.

6.7 Early intervention/prevention

Early weight gain is the most robust predictor of subsequent weight gain and should therefore be used to prompt consideration of a switch or augmentation strategy aimed at minimizing weight gain before much of it has occurred [114,115]. If weight gain of > 2 kg in 1 week or > 4 kg in 2 weeks or > 5% of weight gain occurs at any time, switching to an antipsychotic or antidepressant with a lower propensity for weight gain, where feasible, or adding metformin, is recommended.

6.8 Acute vs long-term treatment

For both antidepressants and antipsychotics, long-term treatment is indicated in many cases. Therefore, the initial medication prescribed should be chosen carefully, weighing both efficacy and potential long-term side effects, including the risk of weight gain. During an acute episode of psychosis, sedation may be required to manage aggression and agitation. Because many antipsychotics with sedative properties also carry higher

metabolic risks (notably olanzapine and quetiapine), it may be more appropriate to use antipsychotics with a lower risk of metabolic adverse effects in combination with a benzodiazepine [193]. Avoiding the initial administration of antipsychotics with a higher risk of metabolic adverse effects may avoid their long-term use. If this is not clinically feasible and there are concerns about weight gain, consideration should be given to switching to an antipsychotic with a more neutral profile once the patient is more psychiatrically stable. Of course, this would not apply to clozapine, which can be a life-saving treatment and for which weight gain is not an indication for switching if it is effective [262,263]. Nevertheless, shared decision making, involving both the patient and family where possible, should always underlie treatment choice in such instances.

Similarly, for antidepressants, while H1-antagonism, for example, may be useful to achieve sedation, treat insomnia, and stimulate appetite in the first days or weeks of treatment, in the long term, antidepressants with less sedative and weight gain-inducing properties should be chosen if unwanted weight gain occurs or daytime sedation interferes with functioning.

6.9 Switching

When an individual gains weight with an antidepressant or antipsychotic (e.g., paroxetine, mirtazapine or olanzapine, quetiapine), switching to a drug with a low risk of weight gain should be considered (e.g., bupropion, vortioxetine or aripiprazole, brexpiprazole, cariprazine, lumateperone, lurasidone, ziprasidone). Switching between different antidepressants or antipsychotics should always be done gradually, with cross-titration to avoid rebound or withdrawal effects. A shared decision-making model that weighs the risks of mental deterioration against the potential metabolic benefits should be used.

6.10 Treatment augmentation with an effective agent to reduce weight

In people taking clozapine or olanzapine, but not other antipsychotics, augmentation with aripiprazole may improve weight gain or even lead to weight loss. Topiramate can also reduce body weight, but should be considered a second-line option due to its potential adverse cognitive effects. For antidepressants, no recommendations can be made regarding psychopharmacologic augmentation options.

Regarding non-psychopharmacologic augmentation options, in people taking antipsychotics, metformin and GLP1-RAs have the best evidence for ameliorating weight gain or inducing weight loss. For antidepressants, no specific recommendation can be made, however, as liraglutide and semaglutide are licensed for the treatment of obesity in the general population, these agents can be considered within their general population licence.

Expert opinion (834 / minimum 500 words, maximum 1000)

A large body of evidence has investigated the effects of antipsychotics and, to a lesser extent, antidepressants on body weight. Information from high-quality epidemiologic and interventional studies can guide clinicians in making evidence-based decisions about patient care aimed at improving psychiatric symptoms and functionality while avoiding clinically relevant weight gain with its detrimental long-term effects.

We provide ten clinically relevant and actionable recommendations to prevent, manage, or treat weight gain with antidepressants or antipsychotics. These apply prior to medication initiation, when choosing the most appropriate antidepressant or antipsychotic, and when changing or augmenting ongoing pharmacologic treatment. When collecting the clinical history of a patient potentially in need of an antidepressant or antipsychotic, clinicians should first assess risk factors for obesity. Second, weight and relevant metabolic parameters must be measured at baseline and monitored regularly during follow-up. Such routine monitoring allows early detection of weight gain and intervention to minimize it. Third, providing lifestyle education, instruction and, if needed, interventions, including exercise and healthy eating, as early as possible is a key routine strategy that can benefit both physical and mental health outcomes. The type of lifestyle change and intervention should prioritize the motivation of the person taking antipsychotics or antidepressants. Fourth, for those with milder anxiety and depressive disorders, where pharmacologic treatment is not mandatory and where the clinical picture allows consideration of stand-alone exercise or psychotherapy, consider CBT in adults, or CBT or IPT in youth for depression, or CBT in adults, and group CBT in youth with anxiety disorders. Fifth, medications should be chosen in a shared decision-making process based on age, stage of illness, and history of weight gain. For instance, weight gain with antipsychotics is greater in youth and treatment-naive individuals, and for depression, the only effective treatment in youth is fluoxetine. Sixth, safety and avoidance of weight gain are important, but efficacy should always be a pre-requisite for any intervention. If medications with a lower risk of cardio-metabolic adverse effects do not work, switch to another antidepressant or antipsychotic. Seventh, in individuals with significant early weight gain, consider preventative early antidepressant or antipsychotic switching or augmentation with a weight-reducing agent to mitigate the risk of substantial ongoing weight gain. Eighth, for severe cases that require sedation in the acute phase, prescribe the most effective medications, but always consider long-term safety, either by adding a sedating medication to more weight-neutral and less sedating agents, or at least consider a more weight-neutral medication to maximize safety and treatment adherence once the acute phase has resolved. Ninth, if weight gain occurs, switch from weight-inducing antidepressants or antipsychotics to more weight-neutral ones if possible. Tenth, if a switch is not indicated/feasible (e.g., in the case of treatment with clozapine), augment antipsychotics with psychotropic medications, such as aripiprazole (daily dose 10-15 mg) if on clozapine or olanzapine or, as a second-line option, with topiramate (daily dose 50-400 mg in two divided doses). Finally, a more evidence-based and widely used alternative to psychopharmacologic augmentation is antipsychotic augmentation with metformin (daily dose 1000-2000 mg in two or three divided doses with meals) or a GLP-1RA such as liraglutide (starting dose 0.6 mg, then uptitration schedule of 0.6 mg per week to a daily dose of 3.0 mg or the highest tolerated dose). As data on efficacy and safety become available from

ongoing studies of semaglutide in people treated with antipsychotics, weekly subcutaneous doses (titrated to 2.4 mg over 16 weeks, as tolerated) or daily oral doses of 50 mg may be preferable to the daily subcutaneous injection of liraglutide. For antidepressants, the evidence for weight gain interventions is very weak. Therefore, future RCTs should test switching strategies or augmentation with lifestyle, and pharmacologic augmentation options to inform clinical decision making.

In the future, genetics [264], including polygenic risk scores [265,266], may help identify individuals at risk for antidepressant/antipsychotic-related weight gain, providing a baseline tool beyond early weight gain to help tailor antidepressant/antipsychotic choice or early preventive use of augmenting agents to mitigate pathologic weight gain.

In summary, it is hoped that weight gain and related adverse downstream effects can be prevented or minimized by i) ensuring that an antidepressant or antipsychotic is needed before prescribing it and that lower-risk options have been explored and/or have failed, ii) providing psychoeducation and healthy lifestyle counselling whenever an antipsychotic or antidepressant is prescribed, prioritizing patient motivation, and iii) carefully selecting effective agents that are also the most tolerable, taking into account cardiometabolic adverse effects. When weight gain and cardiometabolic adverse effects associated with increased body weight become evident, several strategies can be considered, including i) intensified healthy lifestyle instructions; ii) healthy lifestyle interventions; iii) switching to a lower-risk, more effective agent; iv) augmentation with metformin, a GLP-1RA, or topiramate (second-line); or v) augmentation with aripiprazole if the patient is on olanzapine or clozapine. Finally, new and more antipsychotics and antidepressants are needed that have minimal effects on body weight and cardiometabolic risk factors or even improve these measures from baseline, even without reversing previous antipsychotic- or antidepressant-related weight gain [267,268].

Data availability statement

Since this is a narrative synthesis and no quantitative analysis was conducted, data availability does not apply to this work. All data sources are listed in the references.

Authors' contribution statement

Marco Solmi and Christoph Correll designed the methodology of the study. Marco Solmi, Alessandro Miola, Federico Capone, Mikkel Højlund, and Christoph Correll were involved in the data collection and also drafted the first version of the manuscript. All authors critically reviewed, edited, interpreted, and approved the final version of the manuscript.

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Table 1. Risk factors associated with weight gain and obesity

General risk factors (age group with obesity)
Infancy weight gain (youth)
Lower maternal education (youth)
Depression (youth, adults)
Obesity in youth (adults)
Short sleep duration (adults)
Childhood abuse (adults)
Childhood neglect (adults)
High-density food diet
Sedentary behavior
Treatment-naiveté/early phases of disease (antipsychotics)
Early weight gain

Legend. Youth, children and adolescents. According to [73,74,117,154].

Table 2. Affinity (k_i^*) of antidepressants and antipsychotics for receptors involved in weight regulation and degree of propensity for clinical weight gain

	H1	5HT2C	M3	Clinical weight gain propensity
Antidepressants				
Agomelatine	N/A	6.2	N/A	0
Vortioxetine	N/A	N/A	N/A	0/+
Amitriptyline	0.81	4	25.9	+++
Mirtazapine	1,6	39	800	+++
Nortriptyline	7.4	8.5	50	++
Imipramine	26.5	120	60	++
Clomipramine	47	43.3	N/A	+
Desipramine	64	748	210	+
Citalopram	283	617	1430	0/+
Trazodone	1100	223	10000	0/+
Escitalopram	1973	2531	1242	0/+
Duloxetine	2300	916	3000	0/+
Fluoxetine	2683	194	1000	0/+
Bupropion	10000	10000	10000	-/0
Fluvoxamine	10000	6700	N/A	0/+
Paroxetine	10000	10000	80	0/+
Sertraline	10000	1000	1300	0/+
Venlafaxine	10000	7300	10000	0/+
Antipsychotics				
Asenapine	1	0.03	N/A	+
Clozapine	1.2	17	25	+++
Olanzapine	2	6,8	105	+++
Chlorpromazine	6	25	47	+++
Loxapine	7	9.5	122	+
Perphenazine	8	132	1848	0/+
Quetiapine	11	2502	10000	++
Risperidone	15	35	10000	++
Brexpiprazole	19	29	NA	+
Thioridazine	19	60	43	++
Fluphenazine	21	1386	1441	0/+
Cariprazine	23.2	134	NA	0/+
Aripiprazole	29.7	22.4	4677	0/+
Ziprasidone	43	13	10000	0/+
Sertindole	130	0.9	2692	++
Pimozide	692	3350	1955	0/+
Lumateperone	>1000	173	>100	0/+
Haloperidol	1800	10000	10000	0/+
Molindone	2130	10000	10000	0/+

*Legend. * lower values indicate tighter binding. K_i values according to [108,116,121,269]and https://pdsp.unc.edu/databases/pdsp.php. 5HT2C, serotonin-2C receptor; H1, histamine-1 receptor; M3, muscarinic-3 receptor. Antidepressants and antipsychotics are ordered by decreasing affinity for H1. -: weight loss; 0: no/limited effect. +: small effect; ++: medium effect; +++: large effect, according to [49,73,116,117,154].*

Table 3. Ten clinical recommendations to prevent and manage weight gain due to antidepressants and antipsychotics

Before pharmacological treatment	
1. Assess risk	Baseline risk factors for obesity should be routinely assessed.
2. Monitor metabolic health	Monitor weight and other metabolic parameters (i.e., waist circumference, BMI, blood pressure, fasting blood glucose or HbA1c, triglycerides and high-density lipoprotein cholesterol) at baseline and at every follow-up visit
3. Lifestyle behaviors	Lifestyle counselling and, whenever indicated, lifestyle interventions aiming to improve health behaviors should be offered as early as possible, ideally supervised by staff with relevant and specific training, and following patients' preferences to prioritize motivation.
4. Psychotherapy	Psychotherapy should be considered if possible. For mild cases of depression, in adults, consider CBT, in youth, consider CBT or IPT. For anxiety, in adults, consider CBT, in youth, consider group CBT.
Choosing pharmacological treatment	
5. Consider age and stage of illness	Adapt the choice of medication to the patient's age, taking into account the increased risk of weight gain in youth, treatment-naive individuals, and those in early stages of illness (e.g., first-episode psychosis).
6. No efficacy, no safety	Effectiveness is a pre-requisite for any treatment; ineffective treatments may lead to unhealthy lifestyles, substance abuse, and suicide.
Changing/augmenting pharmacological treatment	
7. Early intervention/ prevention	Early intervention is key; use early weight gain after treatment initiation as a robust and easily assessed risk factor for subsequent weight gain to prompt interventions to mitigate weight gain.
8. Acute vs long-term treatment	If sedating and weight-inducing medications are initiated in the acute phase, consideration should be given to changing medications after acute treatment to avoid weight gain in the long term, which may also compromise adherence.
9. Switching	When weight gain occurs, consider switching to an antidepressant or antipsychotic with a lower propensity for weight gain.
10. Augment with an effective agent to reduce body weight	If weight gain occurs, and non-pharmacologic lifestyle interventions have failed or are not clinically feasible, consider augmenting antipsychotics with metformin (1000-2000 mg), or a GLP-1RA (oral semaglutide - target dose 14 mg, subcutaneous semaglutide - target dose 2.4 mg; or liraglutide – target dose 3 mg), or topiramate (50–400 mg/day) (second-line), consider augmenting clozapine or olanzapine with aripiprazole (10-15 mg/day).

Legend: BMI, body mass index; CBT, cognitive-behavioral therapy; GLP-1RA, glucagon-like peptide-1 receptor agonist; IPT, interpersonal psychotherapy.