**Thesis**

# WEIGHT GAIN UNDER ANTIPSYCHOTIC AND MOOD STABILIZING TREATMENT: A NARRATIVE REVIEW ABOUT MECHANISMS AND FUTURE OPTIONS


submitted by

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# Zusammenfassung in Deutsch

*Hintergrund*

Die medikamentöse Behandlung psychischer Erkrankungen kann paradoxerweise die körperliche Gesundheit beeinträchtigen. Zu den besorgniserregendsten Nebenwirkungen zählen Gewichtszunahme sowie damit verbundene Herz-Kreislauf- und Stoffwechselerkrankungen. Das Verständnis und die Abschwächung der metabolischen Folgen antipsychotischer und stimmungsstabilisierender Behandlungen sind daher entscheidend für die Verbesserung der langfristigen Gesundheit von Menschen mit schweren psychischen Erkrankungen wie Schizophrenie und bipolarer Störung. Diese Literaturübersicht konzentriert sich auf die zugrunde liegenden Mechanismen, die Antipsychotika und Stimmungsstabilisatoren mit der Gewichtszunahme bei bipolarer Störung in Verbindung bringen. Aktuelle Erkenntnisse zu pharmakologischen und nicht-pharmakologischen Strategien zur Prävention dieser Nebenwirkung werden ebenfalls berücksichtigt.

*Methoden*

Von Februar bis April 2025 wurde eine Literaturrecherche in PubMed und Google Scholar durchgeführt. Die elektronische Suche wurde durch eine manuelle Suche nach weiteren Artikeln in Referenzlisten und früheren Reviews ergänzt. Relevante Reviews, Kohortenstudien, Metaanalysen und randomisierte kontrollierte Studien wurden berücksichtigt.

*Ergebnisse*

Unsere Ergebnisse belegen, dass verschiedene Stimmungsstabilisatoren und Antipsychotika über unterschiedliche biologische Mechanismen zur Gewichtszunahme beitragen, darunter Stoffwechselstörungen, Appetitmodulation und hormonelle Veränderungen. Nicht-pharmakologische Interventionen wie Ernährungsumstellungen, körperliche Aktivität sowie kognitive und verhaltensbezogene Strategien spielen eine entscheidende Rolle bei der Bekämpfung der medikamenteninduzierten Gewichtszunahme. Pharmakologische Ansätze, einschließlich begleitender Medikamente, bieten Potenzial zur

Eindämmung der Gewichtszunahme, ihre Wirksamkeit und Sicherheitsprofile müssen jedoch noch weiter untersucht werden.

*Schlussfolgerung*

Für die Behandlung von antipsychotika- und stimmungsstabilisatorbedingter Gewichtszunahme sollten individuelle Behandlungspläne in Betracht gezogen werden, die auf die Bedürfnisse, Präferenzen, Ziele und Umstände jedes Patienten zugeschnitten sind.

## Abstract in English

*Background*

Pharmacological treatment for mental illness can paradoxically compromise physical health, with weight gain and related cardiovascular and metabolic diseases among its most concerning side effects. Understanding and mitigating the metabolic consequences of antipsychotic and mood stabilizing treatments is therefore crucial for improving long-term health outcomes in individuals with severe mental illness such as schizophrenia and bipolar disorder. This literature review focuses on the underlying mechanisms linking antipsychotics and mood stabilizers to weight gain in bipolar disorder. Current evidence on both pharmacologic and nonpharmacologic strategies to prevent this side effect is also addressed.

*Methods*

A literature search was conducted from February - April 2025 using PubMed and Google Scholar. The electronic search was complemented by a manual search for additional articles in reference lists and previous reviews. Relevant reviews, cohort studies, meta-analyses and randomized controlled trials (RCTs) were reviewed.

*Results*

Our results support that different mood stabilizers and antipsychotics contribute to weight gain through distinct biological mechanisms, including metabolic dysregulation, appetite modulation, and hormonal changes. Nonpharmacologic interventions, such as dietary modifications, physical activity, cognitive and behavioral strategies, play a crucial role in counteracting medication-induced weight gain. Pharmacologic approaches, including adjunctive medications, offer potential in mitigating weight gain, but their effectiveness and safety profiles require further evaluation.

*Conclusion*

Customized treatment plans tailored to each patient's needs, preferences, goals and circumstances should be considered for the treatment of antipsychotic and mood stabilizer-associated weight gain.

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# Abbreviations and their Explanations

SMI: severe mental illness

RCT: randomized controlled trial

SREBP-1c: sterol regulatory element-binding protein 1c

SREBP-2: sterol regulatory element-binding protein 2

H1: histamine receptor 1

5-HT2C: 5-hydroxytryptamine receptor 2C

D2: dopamine receptor D2

M3: muscarinic acetylcholine receptor M3

DRD2: dopamine receptor D2

MC4R: melanocortin 4 receptor

HTR2C: serotonin 2C receptor gene

PI3K/Akt: phosphoinositide 3-kinase/protein kinase B

GSK3: glycogen synthase kinase-3

GABA: gamma-aminobutyric acid

ADH: antidiuretic hormone

ACP: American College of Physicians

BMI: body mass index

GLP-1: glucagon-like peptide-1

GLP-1 RA: glucagon-like peptide-1 receptor agonist

LDL-CH: low-density lipoprotein cholesterol

CHOL: cholesterol

MEN 2: multiple endocrine neoplasia type 2

GI: gastrointestinal

GWAS: genome-wide association studies

BDNF: brain-derived neurotrophic factor

ADRA2A: adrenoceptor alpha 2A

INSIG2: insulin-induced gene 2

CNR1: cannabinoid receptor 1

EPA: European Psychiatry Association

GLP-1/GIP: glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide

## Glossary

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# Introduction

## Introduction to the Topic

Stabilizing the mind might sometimes strain the body. Pharmacological treatment for mental illness can paradoxically compromise physical health, with weight gain and related cardiovascular and metabolic diseases among its most concerning side effects. Medication-naive people with severe mental illness (SMI) such as schizophrenia, bipolar disorder and depressive disorders have a shorter lifespan than the general population, often due to adverse somatic comorbidities.1-3 Understanding how commonly used medications can lead to weight gain is therefore crucial, not only for health care practitioners but also for patients themselves, as it may help to prevent health complications and improve treatment adherence in this vulnerable population.

## Identification of the Knowledge / Research Gap

Individuals with SMI, such as schizophrenia and bipolar disorder, face a significantly higher risk of metabolic syndrome, driven by a combination of medication side effects (increased appetite, disturbances in lipid and glucose metabolism), lifestyle factors (more sedentary lifestyle), and potential genetic predisposition.[4-5] Among these, weight gain is a major contributor, leading to obesity and increasing the risk for cardiovascular disease.[5] While second-generation antipsychotics are most frequently associated with metabolic complications, mood stabilizers – particularly valproate and lithium – also play a significant role.[5] A systematic review on the effects of antipsychotics and mood stabilizers on health outcomes reported a 2.8 to 4.4 likelihood of being obese in individuals with schizophrenia, whereas those with bipolar disorder or major depression had a 1.2 to 1.7 higher likelihood.[5] Among antipsychotics, clozapine has been identified as the antipsychotic with the greatest potential to induce weight-gain, whereas ziprasidone appears to have the least impact.[6] Similarly, a multiple-treatments meta-analysis associated olanzapine with producing more weight gain than most other antipsychotics.[7] Additionally, a meta-analysis comparing second-generation antipsychotics revealed that both olanzapine and

clozapine were linked to the greatest increases in weight, cholesterol and glucose levels, reinforcing their role in metabolic disturbances.[8]

More updated systematic reviews and meta-analyses ranking on the basis of degree of weight gain have also validated these findings - clozapine and olanzapine as part of the agents producing more weight gain than most other drugs.[9-10] The longer the antipsychotic use, the more the weight gain was in antipsychotic-naive patients with olanzapine showing the greatest weight gain after 38 weeks, whereas clozapine had the most severe weight gain in antipsychotic-switch patients (in less than 6 weeks and after 38 weeks)[11] - in this meta-analyses, antipsychotic-switch patients were defined as those who had ever used an antipsychotic before the study began and were randomized into an antipsychotic.[11]

Though antipsychotics are the primary drivers of weight gain and metabolic complications, mood stabilizers also contribute significantly. Valproate in particular has been associated with weight gain, further compounding the risk of cardiovascular morbidity and mortality in these patients.[5]

Although lithium-treated patients find weight gain the most distressing side effect,[13] the extent of weight gain associated with lithium has not been consistent across studies. Prior results have linked about 20% of patients reporting weight gain exceeding 10 kg,[14] with another study showing an average gain of 6.3 kg in 77% of lithium-treated patients.[15] Nevertheless, a more recent systematic review and meta-analysis evaluating weight change between lithium treated patients compared to baseline did not reach statistical significance (weight gain of 0.462 kg in the lithium group);[16] still weight gain seemed to be significantly greater in interventions of 12 weeks or less.[16] Similarly, another contemporary systematic review and meta-analysis did not report lithium as one of the pharmacotherapeutic agents associated with a higher incidence of weight gain.[17]

Anticonvulsants such as valproate, lamotrigine, carbamazepine and topiramate are other medications that are used as mood stabilizers, with valproate-related weight gain being the most well characterized in studies. A prior study on weight gain during treatment with valproate reported an increase of more than 4 kg in

57% of adult participants.[18] A more recent study estimated a similar amount of weight gain in 70% of the valproate group with the increase being characterized as sustained and socially significant to patients.[19] Weight gain has been associated with valproate for several years.[20] Lamotrigine, however, has been linked to stable body weight during one year of treatment.[21] Two double-blind, placebo-and lithium-controlled, 18-month studies in patients with bipolar I disorder found a non-significant difference in weight with lamotrigine vs. placebo at week 52 (-1.2 kg vs. +0.2 kg; $p$ = 0.237).[21] On the other hand, very few studies have reported weight increase with carbamazepine therapy which seems to be an uncommon event: 2 out of 178 carbamazepine-treated patients in a multicenter prospective trial[22] and 9% in a multicenter, double-blind trial of 480 patients.[23] In the case of topiramate, it has been associated with weight loss.[24-25]

## Justification of the Research Question

Given these findings, understanding and mitigating the metabolic consequences of antipsychotic and mood stabilizing treatments is critical for improving long-term health outcomes in individuals with SMI. Thus, this literature review focuses on the underlying mechanisms linking antipsychotics and mood stabilizers to weight gain in bipolar disorder. In addition, current evidence on both pharmacologic and nonpharmacologic strategies to prevent this side effect will be discussed, providing a comprehensive overview of available interventions.

## Objectives and Limitations / Demarcations

This paper aims to inform clinical decision-making and highlight future directions for research in optimizing treatment strategies for individuals with schizophrenia and bipolar disorder.

The major limitations included: (1) The lack of literature directly assessing interventions in treating mood stabilizer-associated weight gain. Due to this gap in literature, we occasionally had to rely on extrapolations from studies done on antipsychotics. (2) Selecting relevant studies for a narrative review can be more of a subjective approach, which can possibly result in the selection of a representative, but not complete, sample of the literature. (3) The selectivity of the

presented results was based on a non-systematic approach. While this flexibility has advantages, it also increases its susceptibility to potential bias because of the heterogeneity of the included studies with regard to various variables such as treatment duration, patient demographics and diagnostic categories.

## Description of the Research Contribution

This work not only improves mechanistic understanding but also points toward actionable strategies. Future options may include tailored pharmacotherapy, adjunctive agents targeting metabolic pathways, or preemptive lifestyle interventions.

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REVIEW Open Access

# Weight gain under antipsychotic and mood stabilizing treatment: a narrative review about mechanisms and future options

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**Abstract**

**Background** Pharmacological treatment for mental illness can paradoxically compromise physical health, with weight gain and related cardiovascular and metabolic diseases among its most concerning side effects. Understanding and mitigating the metabolic consequences of antipsychotic and mood stabilizing treatments is therefore crucial for improving long-term health outcomes in individuals with severe mental illness such as schizophrenia and bipolar disorder. This literature review focuses on the underlying mechanisms linking antipsychotics and mood stabilizers to weight gain in bipolar disorder. Current evidence on both pharmacologic and nonpharmacologic strategies to prevent this side effect is also addressed.

**Methods** A literature search was conducted from February—April 2025 using PubMed and Google Scholar. The electronic search was complemented by a manual search for additional articles in reference lists and previous reviews. Relevant reviews, cohort studies, meta-analyses and randomized controlled trials (RCTs) were reviewed.

**Results** Our results support that different mood stabilizers and antipsychotics contribute to weight gain through distinct biological mechanisms, including metabolic dysregulation, appetite modulation, and hormonal changes. Nonpharmacologic interventions, such as dietary modifications, physical activity, cognitive and behavioral strategies, play a crucial role in counteracting medication-induced weight gain. Pharmacologic approaches, including adjunctive medications, offer potential in mitigating weight gain, but their effectiveness and safety profiles require further evaluation.

**Conclusion** Customized treatment plans tailored to each patient's needs, preferences, goals and circumstances should be considered for the treatment of antipsychotic and mood stabilizer-associated weight gain.

**Keywords** Antipsychotics, Mood stabilizers, Bipolar disorder, Weight gain, Psychotropic drug-related weight gain, Nonpharmacologic interventions, Weight-reducing agents

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## Background

Stabilizing the mind might sometimes strain the body. Pharmacological treatment for mental illness can paradoxically compromise physical health, with weight gain and related cardiovascular and metabolic diseases among its most concerning side effects. Medication-naive people with severe mental illness (SMI) such as schizophrenia, bipolar disorder and depressive disorders have a shorter lifespan than the general population, often due to adverse somatic comorbidities (Brown et al. 2010; Roshanaei-Moghaddam and Katon 2009; Laursen 2011). Understanding how commonly used medications can lead to weight gain is therefore crucial, not only for health care practitioners but also for patients themselves, as it may help to prevent health complications and improve treatment adherence in this vulnerable population.

Individuals with SMI, such as schizophrenia and bipolar disorder, face a significantly higher risk of metabolic syndrome, driven by a combination of medication side effects (increased appetite, disturbances in lipid and glucose metabolism), lifestyle factors (more sedentary lifestyle), and potential genetic predisposition (Dayabandara et al. 2017; Correll et al. 2015). Among these, weight gain is a major contributor, leading to obesity and increasing the risk for cardiovascular disease (Correll et al. 2015). While second-generation antipsychotics are most frequently associated with metabolic complications, mood stabilizers—particularly valproate and lithium—also play a significant role (Correll et al. 2015). A systematic review on the effects of antipsychotics and mood stabilizers on health outcomes reported a 2.8 to 4.4 likelihood of being obese in individuals with schizophrenia, whereas those with bipolar disorder or major depression had a 1.2 to 1.7 higher likelihood (Correll et al. 2015). Among antipsychotics, clozapine has been identified as the antipsychotic with the greatest potential to induce weight-gain, whereas ziprasidone appears to have the least impact (Allison et al. 1999) Similarly, a multiple-treatments meta-analysis associated olanzapine with producing more weight gain than most other antipsychotics (Leucht et al. 2013). Additionally, a meta-analysis comparing second-generation antipsychotics revealed that both olanzapine and clozapine were linked to the greatest increases in weight, cholesterol and glucose levels, reinforcing their role in metabolic disturbances (Rummel-Kluge et al. 2010).

More updated systematic reviews and meta-analyses ranking on the basis of degree of weight gain have also validated these findings—clozapine and olanzapine as part of the agents producing more weight gain than most other drugs (Huhn et al. 2019; Pillinger et al. 2020). The longer the antipsychotic use, the more the weight gain was in antipsychotic-naive patients with olanzapine showing the greatest weight gain after 38 weeks, whereas clozapine had the most severe weight gain in antipsychotic-switch patients (in less than 6 weeks and after 38 weeks) (Bak et al. 2021)—in this meta-analyses, antipsychotic-switch patients were defined as those who had ever used an antipsychotic before the study began and were randomized into an antipsychotic (Bak et al. 2021). Based on current evidence, Table 1 illustrates the likelihood of weight gain with different antipsychotics.

Though antipsychotics are the primary drivers of weight gain and metabolic complications, mood stabilizers also contribute significantly. Valproate in particular has been associated with weight gain, further compounding the risk of cardiovascular morbidity and mortality in these patients (Correll et al. 2015).

Although lithium-treated patients find weight gain the most distressing side effect (Gitlin 2016), the extent of weight gain associated with lithium has not been consistent across studies. Prior results have linked about 20% of patients reporting weight gain exceeding 10 kg (Vestergaard et al. 1980), with another study showing an average gain of 6.3 kg in 77% of lithium-treated patients (Chengappa et al. 2002). Nevertheless, a more recent systematic review and meta-analysis evaluating weight change between lithium treated patients compared to baseline did not reach statistical significance (weight gain of 0.462 kg in the lithium group) (Gomes-da-Costa et al. 2022); still weight gain seemed to be significantly greater in interventions of 12 weeks or less (Gomes-da-Costa et al. 2022). Similarly, another contemporary systematic review and meta-analysis did not report lithium as one of the pharmacotherapeutic agents associated with a higher incidence of weight gain (Kishi et al. 2022).

**Table 1** Risk of weight gain with antipsychotics*

| Antipsychotic | Propensity to cause weight gain |
|---|---|
| Clozapine<br>Olanzapine | High |
| Chlorpromazine<br>Olanzapine/samidorphan<br>Paliperidone<br>Quetiapine<br>Risperidone | Moderate |
| Amisulpride<br>Aripiprazole<br>Asenapine<br>Brexpiprazole<br>Cariprazine<br>Haloperidol<br>Iloperidone<br>Ziprasidone | Low |
| Lurasidone | Low (Rummel-Kluge et al. 2010)/ Neutral or weight loss (McIntyre et al. 2024) |

*Risk categorization is based on the evidence discussed in this review and information found in the next cited references (Dayabandara et al. 2017; Rummel-Kluge et al. 2010; McIntyre et al. 2024)

Anticonvulsants such as valproate, lamotrigine, carbamazepine and topiramate are other medications that are used as mood stabilizers, with valproate-related weight gain being the most well characterized in studies. A prior study on weight gain during treatment with valproate reported an increase of more than 4 kg in 57% of adult participants (Dinesen et al. 1984). A more recent study estimated a similar amount of weight gain in 70% of the valproate group with the increase being characterized as sustained and socially significant to patients (Corman et al. 1997). Weight gain has been associated with valproate for several years (Jallon and Picard 2001). Lamotrigine, however, has been linked to stable body weight during one year of treatment (Sachs et al. 2006). Two double-blind, placebo-and lithium-controlled, 18-month studies in patients with bipolar I disorder found a non-significant difference in weight with lamotrigine vs. placebo at week 52 (– 1.2 kg vs. + 0.2 kg; $p = 0.237$) (Sachs et al. 2006). On the other hand, very few studies have reported weight increase with carbamazepine therapy which seems to be an uncommon event: 2 out of 178 carbamazepine-treated patients in a multicenter prospective trial (Richens et al. 1994) and 9% in a multicenter, double-blind trial of 480 patients (Mattson et al. 1992). In the case of topiramate, it has been associated with weight loss (Ben-Menachem et al. 2003; Kirov and Tredget 2005). Table 2 shows the risk of weight gain with the mood stabilizers lithium and used anticonvulsants.

Given these findings, understanding and mitigating the metabolic consequences of antipsychotic and mood stabilizing treatments is critical for improving long-term health outcomes in individuals with SMI. Thus, this literature review will focus on the underlying mechanisms linking antipsychotics and mood stabilizers to weight gain in bipolar disorder. In addition, we will discuss current evidence on both pharmacologic and nonpharmacologic strategies to prevent this side effect, providing a comprehensive overview of available interventions. Specifically, we hypothesize that:

**Table 2** Likelihood of weight gain with lithium and anticonvulsants*

| Lithium and anticonvulsants | Propensity to cause weight gain |
|---|---|
| Valproate | High |
| Lithium | Conflicting evidence—possibly low (Kishi et al. 2022) |
| Carbamazepine | Low |
| Lamotrigine | Neutral or weight loss |
| Topiramate | |

*Risk categorization is based on the evidence discussed in this review and the most current information found in the cited references (McIntyre et al. 2024; Kishi et al. 2022)

1. Different mood stabilizers and antipsychotics contribute to weight gain through distinct biological mechanisms, including metabolic dysregulation, appetite modulation, and hormonal changes.
2. Nonpharmacologic interventions, such as dietary modifications, physical activity, and behavioral strategies, play a crucial role in counteracting medication-induced weight gain, though adherence remains a challenge.
3. Pharmacologic approaches, including adjunctive medications, offer potential in mitigating weight gain, but their effectiveness and safety profiles require further evaluation.

By addressing these aspects, this review aims to inform clinical decision-making and highlight future directions for research in optimizing treatment strategies for individuals with schizophrenia and bipolar disorder.

## Methods

A literature search without year restriction was conducted by H.T.S. from February—April 2025 using PubMed and Google Scholar. The following search terms were employed: antipsychotics, weight gain, weight-reducing agents, metabolic, treatment adherence; bodyweight gain AND anticonvulsants; adverse effects of medication, anticonvulsants, antipsychotics, psychotropic drug-related weight gain; lifestyle intervention, psychosis, bipolar disorder, weight outcomes; nonpharmacologic interventions, antipsychotics, metabolic. The electronic search was complemented by a manual search for additional articles in reference lists and previous reviews. 66 articles were selected. Inclusion criteria were: publications in English, reviews, cohort studies, meta-analyses and randomized controlled trials (RCTs), studies addressing weight gain, metabolic effects, or interventions in the context of antipsychotics, mood stabilizers or psychotropic medication. Exclusion criteria were: case reports, opinion pieces or editorials without original data, studies not addressing psychotropic drug-related weight changes, non-English publications. The quality of the included articles was not systematically assessed since this work was not designed as a systematic review.

## Results

### Potential mechanisms of weight gain

#### *Antipsychotic-induced weight gain*

Weight gain under antipsychotic treatment appears to result from a complex interaction of metabolic, neuroendocrine and genetic factors (Table 3). Central mechanisms include adipose tissue dysregulation—characterized by increased lipogenesis, reduced lipolysis, and insulin resistance (Gonçalves et al. 2015; Hakami et al. 2022)—as well as altered neuropeptide signaling

**Table 3** Overview of mechanisms in antipsychotic-induced weight gain

| Mechanism | Description | Involved substances/receptors/genes |
|---|---|---|
| Adipose Dysregulation | Increased lipogenesis, reduced lipolysis, heightened insulin resistance | Visceral fat tissue, insulin, triglycerides (Gonçalves et al. 2015; Hakami et al. 2022) |
| Altered Neuropeptides | Disruption of hunger/satiety signaling | ↓ Leptin, ↓ Adiponectin, ↑ Ghrelin (Dayabandara et al. 2017) |
| Lipogenic Gene Expression | SREBP activation enhances fatty acid and cholesterol synthesis | SREBP-1c, SREBP-2 (Kristiana et al. 2010) |
| Receptor-Mediated Hyperphagia | Monoamine receptor antagonism increases appetite and food intake | H1, 5-HT2C, D2, M3 (Dayabandara et al. 2017; Gonçalves et al. 2015; Roerig et al. 2011) |
| Pharmacogenetics | Genetic variation influences individual weight gain response | *HTR2C*, *ADRA2A*, *DRD2*, *MC4R*, etc. (Zhang et al. 2016) |

**Table 4** Overview of mechanisms in valproate-induced weight gain

| Mechanism | Description | Involved substances/enzymes |
|---|---|---|
| Hypoglycemia | ↑ Availability of long-chain fatty acids stimulates insulin secretion<br>Hinder of gluconeogenesis | ↓ Affinity of serum albumin for palmitate (Brodersen et al. 1990)<br>↓ Carnitine, ↓ Beta-oxidation (Breum et al. 1992) |
| Neurotransmitter-mediated | Appetite stimulation for carbohydrates, ↓ energy use | GABA (Jallon and Picard 2001) |
| Adiponectin expression | Weight gain associated insulin resistance | Histone deacetylase, etc. (Abosi et al. 2018) |

involving leptin, adiponectin, and ghrelin (Dayabandara et al. 2017). Antipsychotics also activate lipogenic transcription factors such as SREBP-1c and SREBP-2, contributing to increased lipid synthesis (Kristiana et al. 2010).

Moreover, receptor-level interactions—particularly antagonism at histamine H1, serotonin 5-HT2C, dopamine D2, and muscarinic M3 receptors—are implicated in hyperphagia and weight gain (Dayabandara et al. 2017; Gonçalves et al. 2015; Roerig et al. 2011). Individual susceptibility varies significantly, with pharmacogenetic studies identifying polymorphisms in genes such as HTR2C, DRD2, and MC4R as relevant modulators of weight-related side effects (Zhang et al. 2016).

#### *Lithium and anticonvulsants-induced weight gain*

Postulated lithium mechanisms include polydipsia and intake of high-calorie drinks along with possibly sodium and water retention (McIntyre et al. 2024). A recent study connected lithium's therapeutic effect to insulin signaling pathways (PI3K/Akt and GSK3) with a dysregulation potentially providing light into illnesses that are associated with impaired glucose metabolism (Campbell et al. 2022). Other suggested mechanism involves lithium's effect on leptin and adiponectin levels (Dolab et al. 2020). Its effect on the hypothalamic region of the brain and regulation of the release of neurohormones involved in synchronizing the neuroendocrine axis (such as GABA, glutamate) have also been explored (Rijal et al. 2021).

Valproate-associated weight gain appears to result from a complex interaction of metabolic and neuroendocrine factors (Table 4). Lowered blood glucose level is one potential theory. Hypoglycemia-related proposed mechanisms include increased availability of long-chain fatty acids, which stimulate insulin secretion, and a reduction of beta-oxidation of fatty acids and gluconeogenesis (Brodersen et al. 1990; Breum et al. 1992). In addition, neurotransmitter-mediated interactions, particularly GABA-mediated, are implicated in appetite stimulation for carbohydrates and energy expenditure reduction (Jallon and Picard 2001). Valproate may induce weight gain through suppression of adiponectin expression and insulin resistance (Abosi et al. 2018).

Weight gain by water retention and possible fat deposition has been associated with carbamazepine. It has been suggested that carbamazepine-associated water retention is an ADH-like effect and even if carbamazepine-treated patients have a normal plasma sodium level and osmolality, their ability to excrete a water load may be impaired (Jallon and Picard 2001; Perucca et al. 1978). Increased appetite and subsequent weight gain due to fat deposition through the involvement of neurotransmitters has also been hypothesized, however the underlying mechanism remains unclear (Jallon and Picard 2001).

### Counteracting antipsychotic and mood stabilizer-related weight gain

#### *Nonpharmacologic interventions*

These strategies include diet, exercise, cognitive and behavioral components (Table 5). Strategies that attempt to discourage maladaptive dietary habits and include daily caloric restriction that are part of common eating plans for weight loss per ACP (American College of Physicians) (Gilden et al. 2024). Some guidelines for overall health even suggest moderate-to high intensity exercise for weight management (Gilden et al. 2024).

A meta-analysis of 25 RCTs that compared lifestyle interventions (involving nutritional, exercise and/or psychological components) to control conditions in patients with psychotic disorders illustrated that these interventions were effective for both weight loss (effect size = − 0.52, $p < 0.0001$) and weight gain prevention

**Table 5** Nonpharmacologic interventions to counteract medication-related weight gain

| Strategies | Description |
|---|---|
| Cognitive | Focus on understanding eating behaviors and physical well-being (Dayabandara et al. 2017) |
| Behavioral | Involve problem-solving, goal setting and keeping track of exercise and eating patterns (Dayabandara et al. 2017) |
| Diet | Include daily caloric restriction by 500–1000/day and limitation of fat to < 30% of total calories (Dayabandara et al. 2017; Gilden et al. 2024) |
| Exercise | Include at least 150 min per week of moderate-intensity aerobic activity (Dayabandara et al. 2017) |

(effect size = – 0.84, $p = 0.0002$) (Bruins et al. 2014). Additionally, these interventions had positive effects on waist circumference, triglycerides, fasting glucose and insulin (Bruins et al. 2014). Another RCT that compared early behavioral intervention to routine care in preventing antipsychotic-induced weight gain in drug-naive first-episode psychosis patients also found this intervention effective—participants in the behavioral strategy group gained significantly less weight (mean = 4.1 kg, SD = 4.0) than those receiving routine care (mean = 6.9 kg, SD = 4.5) during the 3-month follow-up stage (Alvarez-Jiménez et al. 2006). An updated meta-analytic comparison of RCTs to the latter also highlighted a significant reduction of weight (– 3.12 kg, $p < 0.0001$) and body mass index (BMI, – 0.94 kg/m$^2$, $p = 0.0003$) in the non-pharmacological interventions group (cognitive behavioral therapy, nutritional and/or exercise interventions) compared with control groups (Caemmerer et al. 2012).

### *Pharmacologic interventions*

**Metformin** Metformin is a biguanide derivative, antihyperglycemic agent that has been used for many decades. Literature supports its use as first choice among pharmacological agents to counteract antipsychotic-associated weight gain because of its positive effects on body weight, insulin resistance and lipids (Mizuno et al. 2014). It prevents and decreases weight gain and insulin resistance in individuals starting antipsychotics and those previously experiencing weight gain after their chronic use (Silva et al. 2016; Wu et al. 2012, 2016; Jarskog et al. 2013; Siskind et al. 2016). Updated evidence in the form of a retrospective cohort study has reaffirmed the concomitant use of metformin leading to reduced weight gain–its simultaneous use resulted in a significant reduction of antipsychotic-induced weight gain with a mean change of – 0.04 kg, whereas the antipsychotic group had a 2.5 kg mean increase (Hakami et al. 2022). Metformin has the most evidence to support its initiation along with an antipsychotic to prevent weight gain (mean difference – 4.03 kg) and increases in BMI (mean difference – 1.63 kg/m$^2$) (Agarwal et al. 2023).

**Glucagon-like peptide-1 receptor agonists (GLP-1 RA)** GLP-1 stimulates insulin release in the pancreas and inhibits glucagon secretion (Dayabandara et al. 2017). Through effects in the central nervous system, semaglutide and liraglutide slow gastric emptying and decrease appetite (Gilden et al. 2024). Data on liraglutide supports its potential use to mitigate cardiometabolic adverse effects associated with second-generation antipsychotics. A 16-week double-blind placebo-controlled study evaluating the effects of liraglutide treatment on prediabetes, overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder reported significant improvements in glucose tolerance ($p < 0.001$), body weight (– 5.3 kg) and cardiometabolic disturbances (waist circumference reduction – 4.1 cm, systolic blood pressure – 4.9 mmHg, visceral fat – 250.19 g, low-density lipoprotein levels – 15.4 mg/dL) compared with the placebo group (Larsen et al. 2017).

The use of semaglutide in patients with antipsychotic-induced weight gain seems promising given its potential benefits in obese patients—a 26-week double-blinded, randomized, placebo-controlled trial is planned to evaluate the effects of semaglutide in schizophrenia spectrum disorder patients on clozapine or olanzapine (Sass et al. 2023). Exenatide, another GLP-1 RA, may be another beneficial agent for glycemic control and weight loss in patients treated with clozapine—a different randomized controlled study showed that compared with regular care, clozapine-treated obese adults with schizophrenia on exenatide had greater mean weight loss (– 5.29 vs – 1.12 kg; $p = 0.015$), BMI reduction (– 1.78 vs – 0.39 kg/m$^2$; $p = 0.019$) and other metabolic benefits (reduced fasting glucose – 0.34 vs 0.39 mmol/L and glycated hemoglobin levels – 0.21% vs 0.03%) (Siskind et al. 2018).

An updated meta-analysis has reinforced prior findings—body weight loss with GLP-1 RAs exenatide and liraglutide was greater for clozapine/olanzapine-treated patients than other antipsychotics (4.70 kg vs 1.5 kg;; $p < 0.001$) (Siskind et al. 2019). A more recent last year systematic review and meta-analysis has re-classified exenatide and liraglutide as promising drugs for inducing weight loss in patients with antipsychotic-induced weight gain (exenatide mean weight loss – 2.48 kg; $p = 0.07$ vs liraglutide – 4.70 kg; $p < 0.001$), without affecting psychiatric symptoms (Bak et al. 2024).

**Orlistat** A lipase inhibitor that limits the gastrointestinal absorption of fats (De et al. 2023). Orlistat, however, does not appear to lead to significant weight loss in clozapine or olanzapine-treated patients with associated

**Table 6** Pharmacologic treatments and associated side effects

| Agent | Side effects/notes |
|---|---|
| Metformin | No significant major side effect (mild gastrointestinal – GI – upset) (De et al. 2023); cost-effective (McIntyre et al. 2024) |
| GLP-1 RA | *Liraglutide*: GI tract effects/common side effects (nausea, constipation, abdominal pain, etc.) (Larsen et al. 2017); contraindicated with history of medullary thyroid cancer or pancreatitis, family history of MEN 2 (Gilden et al. 2024)<br>*Semaglutide:* Similar to liraglutide (Gilden et al. 2024)<br>*Exenatide:* Similar to liraglutide (Gilden et al. 2024) |
| Orlistat | GI side effects (flatulence, fecal incontinence, oily feces, oil leakage from the anus) (De et al. 2023; Xie et al. 2024); use with caution in those taking agents that need reliable absorption (warfarin, levothyroxine, immunosuppressants, etc.) (Gilden et al. 2024) |
| Phentermine-topiramate | Paresthesia, change in taste, dry mouth, constipation, insomnia, anxiety, depression (Gilden et al. 2024; De et al. 2023); teratogenic (Gilden et al. 2024); mood and sleep disturbance-related side effects could cause additional disease burden (De et al. 2023) |
| Bupropion-naltrexone | Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea, sleep disorders (De et al. 2023); limited evidence of its efficacy in SMI |

obesity (De et al. 2023). An updated last year randomized, placebo-controlled, double blind trial suggested similar but also new findings—orlistat did not affect weight or BMI in people with schizophrenia, but it was associated with lower slopes of weight (contrast = – 1.32) and BMI (contrast = – 0.94) in those with bipolar disorder (Xie et al. 2024). Furthermore, their results showed that orlistat could control serum lipids in antipsychotic-treated participants with schizophrenia (CHOL, contrast = – 0.93; LDL-CH, contrast = – 0.87) and bipolar disorder (CHOL at week 8, contrast = – 0.79) (Xie et al. 2024).

**Phentermine-topiramate** A combination drug that causes reduced appetite and is used as an adjunct to exercise and a low-calorie diet (Gilden et al. 2024; De et al. 2023). Phentermine is a sympathomimetic agent while topiramate acts mainly in the central nervous system, thereby causing dysgeusia (Gilden et al. 2024). Phentermine combinations showed the largest average reduction in weight (15.8 ± 3.3%) and waist circumference (16.4 ± 6.1 cm) when compared to the groups without phentermine in people with mental illness (Lee et al. 2022).

**Naltrexone-bupropion** A combination agent that stimulates the secretion of anorectic neuropeptides (De et al. 2023). A 24-week pilot RCT focused on examining whether naltrexone and bupropion combination treatment can help weight loss and smoking cessation in male adults with schizophrenia found no significant difference between these two groups in changes in weight, BMI, fasting lipids or cigarette smoking ($p$'s > 0.05) (Lyu et al. 2018). A more contemporary systematic review, however, reported different findings in adults with a mental health diagnosis (schizophrenia, bipolar disorder, etc.)—an average weight reduction of 10.9 ± 5.2% and waist circumference of 7.9 ± 2.2 cm in naltrexone-bupropion subjects after 52 weeks of treatment (Lee et al. 2022).

The above pharmacologic treatments discussed to counteract antipsychotic and mood stabilizer-related weight gain as well as a description of their associated side effects are listed in Table 6. Agents that are also known as antiobesity medications, except for metformin (Gilden et al. 2024).

## Discussion

The outlined mechanisms emphasize the multifactorial nature of antipsychotic-induced weight gain. Adipose tissue dysregulation appears central, with metabolic shifts such as increased insulin resistance and lipid accumulation potentially acting as both consequences and amplifiers of weight gain (Gonçalves et al. 2015; Hakami et al. 2022). The direct modulation of appetite-related neuropeptides suggests that energy balance may be disrupted independently of caloric intake (Dayabandara et al. 2017).

Receptor binding profiles provide insight into why agents like clozapine and olanzapine are associated with particularly high weight gain. Clinically, antipsychotics with lower affinity for H1 and 5-HT2C receptors might be preferable when metabolic risk is a concern (Dayabandara et al. 2017; Roerig et al. 2011). Nevertheless, considerable interindividual variability in weight gain responses highlights a likely genetic component—twin and sibling studies, as well as genome-wide association studies (GWAS), consistently demonstrate a heritable component to antipsychotic-induced weight gain, with specific single nucleotide polymorphisms in genes such as HTR2C, MC4R, BDNF, DRD2, ADRA2A, INSIG2, CNR1, and others showing significant associations with increased risk and greater magnitude of weight gain (Sicard et al. 2010; Kao and Müller 2013; Schreyer et al. 2023; Franz et al. 2024).

Pharmacogenetic studies have identified several candidate gene variants—especially HTR2C—that may influence susceptibility to metabolic side effects (Zhang et al. 2016). While not yet used routinely in clinical practice,

such findings pave the way toward more personalized antipsychotic prescribing.

Mood stabilizers contribute to weight gain through distinct biological mechanisms. The mechanisms that might explain how valproate induces hypoglycemia are also centered on decreased lipolysis, increased lipogenesis and appetite stimulation, with the reduction of fatty acid oxidation leading to the increased need for glucose as an energy source (Brodersen et al. 1990; Breum et al. 1992). Metabolic dysregulation and hormonal changes also provide insight into the nature of lithium and carbamazepine-associated weight gain.

Overall, lifestyle interventions provided to individuals with any mental health condition have been linked to significant improvements to weight, BMI, waist circumference and physical activity (Bradley et al. 2022). This is further reinforced by recent EPA (European Psychiatry Association) recommendations not only remarking the importance of these combined lifestyle strategies (behavior change techniques, dietary changes and physical activity) for reducing weight and other metabolic syndrome components in adults with SMI, but also as a way to improve overall functioning in this vulnerable population (Maurus et al. 2024).

When nonpharmacological strategies alone are not sufficient and switching antipsychotics, mood stabilizers to relatively weight-neutral agents is not an option, pharmacological interventions to counteract metabolic side effects should be considered. In general, metformin is the best-studied adjunctive pharmacological agent for treating weight gain in the SMI population (De et al. 2023). Not only it has been shown to reverse insulin resistance in treatment-resistant bipolar depression while improving clinical outcomes, but it is also well-tolerated and affordable (McIntyre et al. 2024; Calkin et al. 2022).

No studies were found evaluating GLP1's potential benefits on mood stabilizer-treated patients, but the promising evidence from GLP-1 RAs could provide an avenue of research for the purposes of targeting metabolic comorbidities in SMI (De et al. 2023). Nevertheless, access and availability of these agents is not widespread. Reluctance to self-inject can be a barrier to use. Additionally, gastrointestinal side effects can be treatment limiting for some patients.

The mixed evidence behind naltrexone-bupropion makes it difficult to interpret. The published pilot RCT showed no significant difference on weight loss (Lyu et al. 2018). It is possible, however, that the exclusion of females and smoking cessation acted as confounders—given that smoking cessation can lead to subsequent weight gain (Lee et al. 2022). Taking this into consideration, one can suggest that perhaps the results listed in the systematic review can be considered more reliable (Lee et al. 2022). More research is needed to fully understand its efficacy for weight loss in adults experiencing mental illness. One could also speculate that this combination agent could be beneficial for those with untreated depression given that clinically, bupropion is used in patients with schizophrenia for comorbid depression (Lyu et al. 2018).

Moreover, the combined constellation of side effects seen with phentermine-topiramate could limit its use in the SMI population (De et al. 2023). Orlistat's very noticeable GI symptoms could also limit its use and patient compliance, in addition to increasing the risk of fat-soluble vitamin deficiency (Gilden et al. 2024; De et al. 2023). Pharmacologic approaches offer potential in mitigating weight gain, but their effectiveness and safety profiles require further evaluation.

Despite increased efforts to expand research evidence on interventions to address poor physical health in individuals with bipolar disorder and schizophrenia, the evidence for the effectiveness of non-pharmacological and pharmacological interventions in preventing and treating these conditions remain limited (Vancampfort et al. 2019). Furthermore, behavioral change can be challenging in this patient population (Deenik et al. 2019).

#### Limitations

The major limitations in this review included: (1) The lack of literature directly assessing interventions in treating mood stabilizer-associated weight gain. Due to this gap in literature, we occasionally had to rely on extrapolations from studies done on antipsychotics. (2) Selecting relevant studies for a narrative review can be more of a subjective approach, which can possibly result in the selection of a representative, but not complete, sample of the literature. (3) The selectivity of the presented results was based on a non-systematic approach. While this flexibility has advantages, it also increases its susceptibility to potential bias because of the heterogeneity of the included studies with regard to various variables such as treatment duration, patient demographics and diagnostic categories.

#### Future directions

Our findings not only improve mechanistic understanding but also point toward actionable strategies. Future options may include tailored pharmacotherapy, adjunctive agents targeting metabolic pathways, or preemptive lifestyle interventions.

Specific future research areas include: (1) Addressing the efficacy of GLP-1 RAs and GLP-1/GIP (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide) in mitigating mood stabilizer-related weight gain with studies still needed to evaluate GLP-1/GIP on antipsychotic-associated weight gain. (2) Assessing the magnitude of the effects of GLP-1 RAs when combined

with non-pharmacologic interventions. (3) Developing novel selective agents targeting HTR2C and M3 receptors.

## Conclusions

Weight gain under antipsychotic and mood stabilizing treatments is a complex and multifaceted issue. Most studies have evaluated antipsychotics, but there is limited evidence on weight mitigation strategies with other psychotropic medications, warranting the need for future research, especially long-term comparative studies. In order to treat antipsychotic and mood stabilizer-associated weight gain, practitioners should consider developing customized treatment plans that combine both non-pharmacologic and proven safe pharmacologic interventions, tailoring them to the individual patient's needs, preferences, goals and circumstances. Integrating molecular, clinical, and genetic data could ultimately lead to more individualized and metabolically safer psychiatric treatment strategies.

### Author contributions

CRediT author statement—HTS: Conceptualization, Methodology, Investigation, Resources, Writing—Original Draft, Writing—Review & Editing, Visualization. FF: Conceptualization, Writing—Review & Editing. DP: Conceptualization, Writing—Review & Editing. EZR: Conceptualization, Writing—Review & Editing, Visualization, Supervision. All authors read and approved the final manuscript.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Competing interests

The authors declare no competing interests.

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