

Management of Drug-induced Weight Gain in Persons Receiving Psychotropic Drugs

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ABSTRACT

Weight gain is common in patients with severe mental illness and contributes to cardiovascular risk. Medications, such as antipsychotics, antidepressants, and mood stabilizers, are commonly associated with weight gain. In addition, antidiabetic drugs (insulin, sulfonylureas, and thiazolidinediones), antihypertensives (beta-blockers), and corticosteroids, which are commonly used to treat comorbid medical conditions, contribute to weight gain. In clinical practice, simple measures, such as body weight, body mass index, and waist circumference, can be used to monitor the metabolic risk of psychotropic drugs. Lifestyle modifications, including dietary advice and exercise, help in preventing weight gain. The clinician can choose relatively weight-neutral drugs for the treatment of psychiatric disorders. For the patients having weight gain with psychotropic drugs, several nonpharmacological and pharmacological management strategies are available.

Keywords: Metabolic syndrome, Obesity, Psychotropic drugs, Severe mental illness, Weight gain.

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INTRODUCTION

Patients with severe mental illness (SMI) experience a life span that is 15–20 years shorter compared to the general population.^{1,2} Physical conditions are a major contributor to the increased risk of mortality observed in SMI. In particular, cardiovascular diseases (CVD) account for 17.4 and 22.0% of reduced life expectancy in men and women, respectively; these figures surpass the contribution of suicide, which is pegged at 13.5%.³ Among the major contributors to an increased prevalence of CVD in SMI patients are the increased prevalence of CVD-related risk factors, such as obesity, dyslipidemia, and diabetes mellitus.⁴ These may aggravate the risk of CVD when co-occurring with genetic predispositions and behavioral factors, such as sedentary lifestyle, unhealthy food choices, and smoking.

Compounding matters further are the adverse effects of drugs, such as antipsychotics, used to treat SMI; these include weight gain, dyslipidemia, and abnormalities in glucose metabolism. The term metabolic syndrome denotes a clustering of these multiple, concurrent risk factors for CVD in an individual; the rates of metabolic syndrome in schizophrenia and bipolar disorders were 32.5%⁵ and 37.3%,⁶ respectively. Further, the prevalence of metabolic syndrome among antipsychotic-naïve and antipsychotic-treated patients with schizophrenia was estimated between 3.3–26% and 32–68%.⁷

Obesity, a component of metabolic syndrome, is defined by the World Health Organization as “excessive body fat accumulation that is associated with clear risks to health.” The measures to describe obesity are body weight and Quetelet index or body mass index (BMI); males with body weight more than 35% (in females, it is 45%) or BMI more than 30 kg/m² are considered obese. The percentage of body fat for given BMI changes with age in a curvilinear fashion; hence BMI underestimates obesity.^{8,9} Also, Indians have more body fat for a given BMI, thus making BMI cutoffs unreliable. The Indian Consensus Group suggested a cutoff BMI of 25 kg/m² for defining obesity among Asian Indians residing in India.¹⁰

The other proxy measures for obesity, specifically abdominal obesity, are waist circumference (WC) and waist–hip ratio (WHR)

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(Table 1). The WC cutoffs for high risk are 102 cm in men and 88 cm in women.¹¹ However, separate cutoffs are suggested for Asians (including Indians), with above 90 cm in males and 80 cm in females considered as high risk. WHR reflects the fat distribution of lower and upper body areas; android type of excess upper body fat is typical of males, and gynoid type of excess lower body fat is more common among females. WHR cutoffs for risk are 1 for men and 0.85 for women.¹¹ It is less useful as a measure of abdominal obesity with increasing levels of fat. Several other measures, including skinfold measurements, bioelectrical impedance analysis, hydrodensitometry, air-displacement plethysmography, dual-energy X-ray absorptiometry, and other imaging modalities, have been used for the obesity assessment in research.¹² The computed tomography and magnetic resonance imaging of body parts are more accurate methods to measure visceral obesity.¹³

Prior reviews on drug-induced weight gain in patients with SMI have either focused on generating estimates for the risk of weight gain with different psychotropic agents,¹⁴ was not focused on management aspects,¹⁵ or had a narrow focus on pharmacological management strategies.¹⁶ Instead, we have focused our review on the management that describes practical aspects of pharmacological and nonpharmacological

Table 1: Standard assessment of obesity

	Measure	Definition	Interpretation
1	Body weight	Difference from ideal body weight	>35% in males and 45% in females
2	Body mass index	Ratio of body weight in kg and surface area in m ²	>30 kg/m ² (25 kg/m ² in Asians) is obesity
3	Waist circumference	Measured at the end of expiration in a standing position at the midpoint of the lowest rib cage and the iliac crest	102 cm in men and 88 cm in women (90 cm in males and 80 cm in females in Asians) is high risk
4	Waist-hip ratio	Ratio of waist circumference and the hip circumference	1 for men and 0.85 for women

management of weight gain, as well as preventive aspects, in patients with SMI. The review is divided into five sections: in the first part, we examine the drugs implicated in weight gain in patients with SMI; next, we provide an overview of the monitoring frequency of metabolic parameters in this group; then, we discuss general principles of the weight management in SMI; this is followed by a section on lifestyle interventions that are considered the first line for weight gain in SMI; and finally, we end by discussing the evidence-based pharmacological interventions for the issue. The review is practically focused so as to aid clinical practice.

DRUGS CAUSING WEIGHT GAIN

Several classes of psychotropic medications are associated with weight gain, including antipsychotics, antidepressants, and mood stabilizers.

Antipsychotics

Atypical antipsychotics are considered responsible for the metabolic adverse effects, including weight gain, with clozapine and olanzapine having the highest risk. Among mid-risk groups are amisulpride, asenapine, iloperidone, paliperidone, quetiapine, risperidone, and sertindole, whereas aripiprazole, lurasidone, and ziprasidone have the lowest risk.¹⁷ However, given prolonged exposure (which is common for SMIs), almost all antipsychotics, including typical antipsychotics, are associated with weight gain. Weight gain is more pronounced in antipsychotic-naïve patients and adolescents; thus those receiving treatment for the first episode of psychosis are at a higher risk.¹⁸ There is a possibility that those gaining weight with antipsychotics show a good response to treatment, i.e. a metabolic threshold, similar to the concept of neuroleptic threshold.¹⁹

Antidepressants

There is a significant increase in the incidence of weight gain following antidepressant exposure, i.e. almost 21% increase over 10 years.²⁰ Weight gain is more common with tricyclic antidepressants (e.g. amitriptyline), mirtazapine, and paroxetine and becomes prominent with long-term use.²¹ In contrast, fluoxetine and bupropion are relatively weight-neutral antidepressants.

Mood Stabilizers

Weight gain is a frequent adverse effect of long-term lithium therapy.²² Several anticonvulsant mood stabilizers, including

valproate, carbamazepine, and oxcarbazepine, are associated with significant weight gain, specifically with the long-term treatment.²³

Besides the psychotropics, medications prescribed for treating comorbid medical conditions (e.g. diabetes, hypertension) among those with SMI could also contribute to weight gain. Antidiabetic medications, such as insulin, sulfonylureas, and thiazolidinediones are commonly associated with significant weight gain.²⁴ Other medications, including antihypertensives (e.g. beta-blockers) and steroids (e.g. glucocorticoids), are commonly associated with weight gain.²⁵

Monitoring/Assessment Frequency in SMI

The goal of monitoring patients with SMI is to prevent the development of risk factors for CVD. It is recommended that all patients with SMI be routinely monitored for weight gain, glycemic imbalance, dyslipidemia, blood pressure changes, and lifestyle factors, such as diet, smoking, and physical activity.²⁶ All patients with SMI must also be provided with adequate nutritional advice and encouragement to promote positive lifestyle changes.

Monitoring Frequency for Weight/BMI

The weight of all patients with SMI, regardless of whether they are on antipsychotics or not, must be measured at the baseline. Subsequently, for those with normal baseline screening and absence of CVD risk factors, weight must be checked at 6 weeks, 3 months, 12 months, and annually thereafter. Monitoring should be customized to the individual patient; for instance, it is a good practice to record weight and BMI at every visit for those with a higher risk of adverse metabolic effects of the medications. This includes the first episode, drug-naïve patients or adolescents with psychosis. Another dictum is to front-load assessments; in other words, have a greater frequency of monitoring in the first year after antipsychotic initiation when the risk of weight gain with medicines is higher.²⁷

Monitoring Frequency for Other Metabolic Risk Factors

Other key CVD risk factors, such as fasting glucose, lipid profile, and blood pressure, must be monitored at baseline, 6 weeks, 3 months, and quarterly after that.²⁷ Again, as explained earlier, monitoring frequencies must be adjusted to suit the individual patient's risk profile. A suggested scheme for monitoring metabolic risk factors in patients with SMI is shown in Table 2.

GENERAL PRINCIPLES OF WEIGHT MANAGEMENT IN SMI

Dietary Advice

Evidence suggests that compared to the general population, people with SMI are more likely to follow unhealthy dietary habits.²⁸ Therefore, all overweight or obese patients with SMI should receive adequate counseling about healthy dietary habits and nutrition.

Weight Management

Along with pharmacotherapy for specific metabolic disturbances, advice about weight reduction is intended to help overweight SMI patients to lose weight and is a key component of therapy for the management of metabolic syndrome. Weight reduction, though challenging, can be attained with lifestyle interventions detailed below with beneficial spinoffs on the metabolic risk profile.²⁷

Table 2: Monitoring of metabolic risk factors in patients with severe mental illness

Parameter	Frequency of assessment					
	First year of antipsychotic treatment				Subsequent monitoring	
	Baseline	6 weeks	3 months	12 months	Quarterly	Yearly
Personal and family history of diabetes, hypertension, CVD	✓					✓
Lifestyle factors (smoking, sedentary lifestyle, exercise, dietary patterns)	✓	✓	✓		✓	✓
Weight, waist circumference, BMI	✓	✓	✓		✓	
Blood pressure	✓	✓	✓		✓	
Fasting glucose	✓	✓	✓			✓
Fasting lipid profile	✓		✓	✓		✓

CVD, cardiovascular disease; BMI, body mass index. Source: Adapted from De Hert et al.²⁷

Encouragement to Increase Physical Activity

Aggressive lifestyle modifications and encouragement to increase physical activity occupy a central role in the lifestyle interventions package that is usually tailored to the needs of the individual SMI patient. This ties in with the evidence that people with SMI are more likely to follow sedentary lifestyles with reduced physical activity, placing them at a greater risk of metabolic disorders, such as diabetes and CVD.²⁹

Selection of Treatment Strategy (Separately for Drug-naïve Patients and Those Already on FGA/SGA)

The treatment principles for metabolic risk factors in patients with SMI are broadly similar, regardless of whether they are taking antipsychotics or not. In those who are already on treatment with a first-generation or second-generation antipsychotic (FGA/SGA), the difference is that changes in the treatment regimen should be considered as a first-line strategy, i.e. (a) dose reduction—for those in whom the current clinical status and treatment history permits, clinicians may consider an appropriate dose reduction of antipsychotics under close supervision for symptom relapse and (b) switching antipsychotics—for those with more severe or unacceptable weight gain and dyslipidemia with the ongoing agent, a switch to an antipsychotic agent with better metabolic profile (such as aripiprazole or ziprasidone) is associated with better weight loss and lipid profile outcomes.^{22,30,31}

LIFESTYLE INTERVENTIONS FOR OVERWEIGHT OR OBESE PATIENTS WITH SMI

People with SMI follow lifestyles that put them at a higher risk of obesity and adverse cardiovascular events.^{32,33} The aim of lifestyle interventions in people with SMI is to prevent or attenuate cardiovascular risk factors, such as weight, physical activity, and blood pressure. Needless to say, the package of lifestyle interventions must be tailored to the requirements of the individual patient.

For patients with SMI who are overweight or obese, either lifestyle interventions or medications are possible treatment options with the lifestyle advice preferred as the first-line intervention among those who are willing, motivated, and capable of executing the advice given. The major components of lifestyle interventions for people with SMI are detailed below and summarized in Table 3:

Psychoeducation

In this context, psychoeducation should emphasize nutritional counseling where adequate education is given about the caloric

Table 3: Components of various lifestyle interventions for overweight or obese patients

Intervention	Key components/advice
Psychoeducation	<ul style="list-style-type: none"> • Nutritional counseling • Recommended diet composition • Healthy snack options
Dietary and physical activity modification	<ul style="list-style-type: none"> • Avoid sugar and soft drinks with artificial sweeteners • Limit fast foods and processed foods • 30 minutes of moderately vigorous physical activity for most days a week • Incorporate exercise into daily routines (e.g. use staircase instead of the elevator)
Learning skills of behavior self-management	<ul style="list-style-type: none"> • Set goals that are • Specific • Measurable • Attainable • Realistic • Timely
Motivational enhancement	<ul style="list-style-type: none"> • Engage the patient • Interview with open-ended questions • Affirmative statements • Reflection • Summary statements • Formulating immediate plan of action

value of food items that are regularly consumed by the patient. The goal is to help patients to recognize the calorie-dense items that may be inadvertently contributing to their weight problem, for example, aerated soft drinks or fast foods. Patients also benefit from knowing the recommended composition of diet and healthy snack options when they are hungry. Culturally appropriate e-resources that provide this information may be shared with patients.

Dietary and Physical Activity Modification

Changes in dietary habits can have substantial benefits on weight and other metabolic indices. A 5% or greater reduction in weight is associated with a reduction in cardiovascular risk and disease. Further, physical activity can improve metabolic indices even in the absence of weight reduction.³⁴

Specific suggestions that can be given in this context are (a) avoid juices and soft drinks containing sugar and artificial sweeteners; (b) avoid fat-rich and calorie-dense foods, such as fast or processed foods; (c) choose healthy snack options when there is a need to munch; (d) advice 30 minutes of moderately vigorous



activity (a brisk walk) for most days a week; and (e) innovative ways to get the daily recommended physical activity, i.e. incorporate exercise into daily routines (e.g. using staircase instead of elevators, parking the car farther away from the entrance) or partnering with an exercise buddy to motivate each other.

Learning Skills of Behavioral Self-management

Self-management refers to the process by which individuals feel empowered to take active steps in recognizing and managing their health issues on their own, thus taking greater responsibility for their health and recovery. In behavior self-management, the goal is to facilitate goal setting for healthy behaviors and lifestyle changes to reduce the cardiometabolic risk.³⁵ The goals that are set must follow the following principles: (a) Specific—this includes defining the goal and how it is intended to be achieved; (b) Measurable—how will the individual know that the goal has been accomplished? (c) Attainable—is the goal attainable for the individual? (d) Realistic—is the goal realistically achievable for the individual? Is the individual willing to work to achieve it? and (e) Timely—is the time frame set for the task motivating enough or is it unrealistic and demotivating?

Motivational Enhancement

The role of motivational enhancement assumes significance when patients are ambivalent about making the necessary changes in their behavior and lifestyle. Motivational enhancement strategies for lifestyle changes follow the same framework as used for substance use disorders in exploring and resolving ambivalence about behavioral changes.³⁶ Brief steps are listed below: (a) Engage the patient by asking for their permission to discuss about their health/smoking/weight issues; (b) Open-ended questions—how do you feel about your smoking/weight? This question allows the patient to express himself/herself; (c) Affirmative statements—this is meant to support positive behaviors. “You have already taken steps to reduce weight. I can see how important this is for you;” (d) Reflection—to allow the patient’s concerns to be aired. “You seem to be trying your best to make time for exercise but evidently it has been hard for you to do that. Tell me a bit more about it;” (e) Summary statements—to convey that you have understood the patient correctly and allow patients to come up with next steps of change. “You have evidently taken the issue seriously and have tried a number of things that did not quite seem to work. You seem unsure about what next to do;” (f) Make an immediate plan by discussing next steps—“What would be the next thing that you want to do for your weight problem?” and (g) Close on a positive note by promoting self-efficacy and highlighting change talk—“It is commendable that you have recognized your weight problem and want to do something about it. You are also ready to make changes in your diet and lifestyle choices to meet your goals and have already started implementing them. Let us meet about 2 weeks from now to discuss the progress on this and meanwhile you can try out the steps that we have discussed today.”

PHARMACOLOGIC INTERVENTIONS

Recent evidence on the management of weight gain among subjects who have recently been initiated on antipsychotics suggests possible benefits for more aggressive management with medications.³⁷ Pharmacologic interventions may also be useful for patients who are not adequately motivated to change their lifestyles or behaviors. There is preliminary evidence for some agents in promoting weight loss in patients with SMI. These are discussed below:

Metformin

Metformin has the widest body of evidence for this indication in patients with SMI. A recent meta-analysis of pharmacological interventions for the treatment of weight gain in patients with SMI found 14 trials (pooled $n = 864$) of which 12 studies (pooled $n = 843$) yielded data for analysis. The pooled effect size (ES) was—3.27 kg [95% confidence interval (CI), -4.49 to -2.06], supporting metformin.³⁸ Lesser evidence is available for the preventive use of metformin; one randomized controlled trial found lower mean weight gain in patients with first-episode schizophrenia initiated on olanzapine plus metformin compared to olanzapine plus placebo over 12 weeks.³⁹ It is also useful for weight gain related to other medications, such as lithium.⁴⁰

Common adverse effects of metformin are nausea, diarrhea, vomiting, and abdominal discomfort. Less frequent, but potentially dangerous, adverse effects are hypoglycemia, vitamin B12 deficiency, and lactic acidosis; the last one is usually among patients with congestive heart failure, hypoxia, or sepsis, in whom it is not recommended for use. Metformin should also be avoided in patients with hepatic and renal dysfunction, alcohol use disorder, and pregnant women. Metformin should be dosed initially at 500 mg once a day in the morning and increased by 500 mg every week, as tolerated, till 1000 mg twice daily. The higher dosages are associated with greater benefits on weight gain, hence every attempt must be made to reach the maximum tolerated dose.^{38,41}

Topiramate

Six studies (pooled $n = 469$) have examined the efficacy of topiramate for weight gain in patients with SMI. The pooled ES was 5.33 kg (95% CI, -7.20 to -3.46), favoring topiramate.³⁸ Based on the ES reported, topiramate appears to be promising for this indication though, admittedly, only short-term trials (<12 weeks) are available. Common side effects of topiramate are sedation, dizziness, difficulties with cognition, and tingling of hands/feet. Rare, but dangerous, side effects include urolithiasis, metabolic acidosis, secondary angle-closure glaucoma, and hyperammonemia. Suggested dosing is to start with 25 mg at night for a week, increase to 50 mg nightly at week 2, and then increase by 50 mg every week, as tolerated, till 100 mg twice daily.⁴²

Aripiprazole

A meta-analysis of three clinical trials (pooled $n = 266$) found benefits for aripiprazole in ameliorating antipsychotic-induced weight gain; the pooled ES was 2.13 kg (95% CI -2.87 to -1.39).⁴³ The agent has been studied in patients receiving clozapine and experiencing weight gain, with reported side effects, including nausea, anxiety, and akathisia.⁴⁴ The recommended dosing is 5 mg at night for a week and to increase by 5 mg every week, as tolerated, till 15 mg at night.

Liraglutide

A glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide has preliminary evidence for the efficacy on weight loss in patients with SMI; a 16-week randomized controlled trial found a decrease of 5.3 kg (95% CI -7.0 to -3.7) with liraglutide compared to placebo among overweight or obese patients with schizophrenia spectrum disorders.⁴⁵ The agent is commonly associated with nausea and diarrhea and rarely with pancreatitis,⁴⁶ cholecystitis, and cholelithiasis. The recommended starting dose is 0.6 mg subcutaneously every day for a week, 1.2 mg per day for week 2, and then titrate to a target dose of 1.8 mg per day, as tolerated.

Table 4: Evidence-based key pharmacologic agents in management of drug-induced weight gain for patients with severe mental illness

Agent	Target dose range (daily)	Adverse effects	Monitoring
Metformin	1500–2000 mg	Common—Nausea, vomiting, diarrhea, abdominal discomfort Rare—Headaches, myalgia, low vitamin B12, hypoglycemia	Biannual e-GFR Annual LFT Monitor alcohol use
Topiramate	100–200 mg	Common—Paraesthesia, sedation, memory difficulties Rare—nephrolithiasis/angle-closure glaucoma, metabolic acidosis	eGFR, LFT, Serum bicarbonate 3 months after starting treatment and repeat every 6 months
Aripiprazole	15 mg	Akathisia, nausea, anxiety (when taken with clozapine)	For mentioned side effects
Liraglutide	1.8 mg	Common—nausea, diarrhea, and abdominal discomfort Rare—pancreatitis, cholelithiasis, and cholecystitis	For hypoglycemia
Samidorphan	Fixed dose combination with olanzapine (10 mg samidorphan with 5–20 mg olanzapine)	Somnolence, increased appetite, and dry mouth	For sedation and dizziness

GFR, glomerular filtration rate; LFT, liver function test

Sibutramine

A total of three studies ($n = 66$) examined the efficacy of sibutramine; the pooled ES was 2.86 kg (95% CI, -4.72 to -1.01), favoring sibutramine.³⁸ The drug is contraindicated in patients with CVD as in those with hepatic and renal dysfunction.⁴⁷ Concerns about its cardiovascular safety have impacted its use for weight loss, and the drug is no longer available in some countries.⁴⁸

Samidorphan

Samidorphan is an investigational opioid antagonist with preliminary evidence for ameliorating olanzapine-induced weight gain in a single randomized controlled trial ($n = 561$); adverse effects in the trial were sedation, dry mouth, and increased appetite.⁴⁹ Due to the lack of sufficient evidence, it is not recommended for clinical use yet.

Others with Insufficient Evidence

Agents with limited or insufficient evidence for weight loss in patients with SMI include orlistat,⁵⁰ L-carnitine,⁵¹ fluoxetine,⁵² reboxetine,⁵³ and naltrexone.⁵⁴

Given the side effect profile of the agents listed above, their use must follow the due process of risk-benefit evaluation for every patient. After initiation, patients should be monitored both for clinical efficacy and adverse effects outlined above. Table 4 lists the pharmacotherapeutic agents that have been studied for weight gain among patients initiated on antipsychotics.

MANAGEMENT OF WEIGHT GAIN DUE TO OTHER CAUSES (ATYPICAL DEPRESSION/SLEEP DEPRIVATION)

Other causes of weight gain in patients with SMI include atypical depression⁵⁵ and sleep deprivation.⁵⁶ No specific trials for weight management in these conditions are available. Therefore, the management should be directed at the underlying condition, for instance, management of the depression with pharmacotherapy or other modalities as appropriate and sleep hygiene advice for sleep-related issues. Additionally, dietary counseling and general health promotion advice (such as exercise and physical activity) may be beneficial.

SUMMARY

Weight gain is common with the treatment of psychiatric disorders with antipsychotics, antidepressants, mood stabilizers, as they

require long-term treatment. In addition, the treatment with antidiabetic drugs and corticosteroids for comorbid medical conditions contributes to the risk. Clinical measurement of obesity is important to identify those at risk and monitor them during treatment for early identification and treatment. Simple anthropometric measures, such as body weight, BMI, WC, and WHR, may be routinely incorporated into practice. Psychoeducation and lifestyle modifications, including diet and exercise, should be a part of the treatment of SMIs. Choosing relatively weight-neutral drugs (e.g. aripiprazole, bupropion) may be helpful if clinically feasible. The pharmacological treatment for drug-induced weight gain includes metformin, topiramate, aripiprazole, liraglutide, and samidorphan, but the actual weight reduction with these agents is limited.

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