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Psychotropic Medications Weight Gain: A Clinical Dilemma Looked Through the Lens of Therapeutic Challenges, Complementary Approaches and Pharmacotherapies

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Psychotropic drugs especially second generation of antipsychotics and antidepressants are used in psychiatric patients with severe mental disorders. These disorders are associated with weight gain and obesity that poses clinical challenges. This needs individualised-tailored integrative interventions including the promotion of health and wellbeing.
Objective: The review critically assimilates evidence-based data on several aspects of psychotropic-induced weight gain with a focus on therapeutic challenges and multidimensional integrative management strategies along with pharmacological interventions.
Methods: Electronic searches of three databases (from 2000 to 2018) using Boolean operators and keywords retrieved thousands of peer-reviewed articles published in scientific journals. Based on exclusion and inclusion criteria 141 pertinent articles were retained for this review.

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Results: Overweight in psychiatric patients on weight increasing psychotropic medications is associated with a variety of adverse consequences and therapeutic challenges. Overweight and obesity is reported to need a multimodal patient-centred approaches regarding lifestyle changes, dietary modifications and medicinal herbs, cognitive behavioural therapy, motivational psychotherapy and weight controlling pharmacological interventions. Multimodal treatment directed towards overweight is often delivered by a multidisciplinary team in well-equipped clinical settings. Symptom relief from the primary psychiatric illness is necessary for this strategy to work.
Conclusion: Although overweight or obesity secondary to psychotropic medication poses a number of treatment challenges, an integrative intervention that combines complementary therapies with conventional medications appears to work best. This review calls for comparative research to determine the most effective strategies to combat weight gain in psychiatric populations.

Keywords: Weight gain; obesity; severe mental disorder; psychotropic medications; complementary therapies; antiobesity medications.

1. INTRODUCTION

There is converging evidence that weight gain related to antipsychotics [1] and non-antipsychotics [2] prescribed in psychiatric practice is successfully manageable using modern medications combined with complementary (integrated) approaches. Besides psychotropic medications, other dynamic etiological factors including genetic and environmental also contribute simultaneously to the weight gain in the psychiatric population [3]. This multifactorial trend (Table 1) tends to posit multiple therapeutic challenges concerning overweight and obesity in general, but especially in a psychiatric population. In such scenarios, therapeutic intervention should target either a single or multiple etiological factors underlying weight gain. Hence, related detailed evidence-based therapies are required to manage the weight gain in psychiatric or nonpsychiatric population successfully. The study aims on the treatment of weight gain or morbid obesity from psychotropics prescribing in psychiatric population. However, overweight, and obesity will be addressed succinctly in the nonpsychiatric population including children, adolescents and adults whose health is affected adversely throughout their life trajectories [4].

Table 1. Predictive risk factors of weight gain

Factors	Remarks
Psychotropic drugs	All antipsychotic medications and antidepressants, mood stabilisers, and some natural antidepressants increase weight gain [1,2,5]. Cannabis use leads to psychosis, weight gain and poor outcome as found in some studies [6,7].
Psychiatric disorders	Various psychiatric diagnoses including schizophrenia, schizoaffective disorder and related psychotic disorders, autistic disorders, anxiety, post-traumatic stress disorder (PTSD), severe depression and co-occurring psychiatric conditions [5,8-11].
Initial BMI	Increasing insulin resistance [12,13].
Cognition	Lower cognitive functions associated with weight gain [14]
Genetic	Multiple genes are involved in drug-induced obesity as well as obesity not by psychotropic drugs [15-17]
Gender	Females are susceptible to greater weight gain compared to their counterparts [5,18] and parity [19].
Age	Adolescents and adults vulnerable to greater weight gain [5,20] than any other age category
Services	Lack of healthcare clinics concerning overweight and obesity [21].
Physical disorders	Thyroid disease, Cushing disease and other diseases [5, 22-24].
Biological	Neuroinflammation, alteration in neurometabolism and oxidative stress, hormones in the brain, Biological-gastrointestinal tract (GIT) and fat cells, gut microbiota-brain-axis, modulation of mitochondria [25,26].
Body constitutions	Genetic endowment and impact on behaviour [27].

Factors	Remarks
Dietary habits	Overeating with a craving to different foods and increased calories intake [28].
Insomnia	Sleep less than 5 to 6 hours [29,30].
Lifestyle	Sedentary, i.e., lack of exercise [31] and high intensity and moderate exercise tends to reduce weight gain [32] and smoking cessation [33].
Geographic region	Influences the type of psychiatric medication prescribed and the psychiatric diagnoses [5].
Environment	Fast food outlets, violence-infested neighbour and pesticides, lack of recreational centres and parks, lack of safe walking and biking routes and food addiction [13,30,34].
Breastfeeding	Breastfeeding (initial one year or more) protects children from obesity and allergic diseases [35,36].
Socioeconomic position	African-American women gain weight associated with cumulative socioeconomic position [37].

Overall antipsychotic medications and biopsychosocial factors in tandem tend to increase weight gain in clinical populations and overweight gain is linked to physical and psychiatric disorders, increased burden and mortality [38-41]

1.2 Aim of the Study

This study aims to

(i) review critically conventional and integrative interventions directed towards psychotropics-induced weight gain in psychiatric population.
(ii) to focus on patient-centered health promotion and
(iii) to focus on wellness and prevention strategies together with common complementary therapies in the management of weight gain attributed or not to psychotropic drugs.

1.3 The Relevance and Significance of the Study

This research avenue is linked with a wide variety of physical and psychological adverse consequences of weight gain or obesity concerning psychiatric medications prescribed to mentally ill people. This work also searches to manage this globally increasing epidemic is relatively ignored in Arabian Gulf countries.

This is the first of its kind work in Saudi Arabia. Also, it will bridge the knowledge gaps of mental health professionals and related physicians concerning psychotropic prescribing and weight gain in psychiatric population. It is expected that all should benefit from this review including patient population and public at large.

2. METHODS

2.1 Search

Boolean operators were used to search specific data (from 2000 to 2018) on psychotropic medications linked to weight gain and obesity. Electronic searches of three databases and three open access publishing houses (Google Scholar, MEDLINE/ PubMed, OvidSP and Dovepress.com, Hindawi.com & Sciencedomian.org) were conducted. Keywords such as psychotropic medications weight gain AND integrative modalities OR complementary therapies OR conventional interventions OR prevention OR psychiatric disorders were used. Additional searches used keywords such as psychotropic medications weight gain AND obesity adverse effects OR physical diseases OR Case reports OR observational studies OR randomised clinical trials (RCTs) OR systematic reviews OR meta-analysis for retrieving pertinent articles published in English literature. The e-searches were modified whenever needed and compatible with databases.

3. RESULTS

3.1 Search Results

A large number of articles (n=37,987) were retrieved. A quick screening by a single author (NAQ) excluded 32721 articles that did not focus on weight gain associated with psychotropic medications prescribing and its treatment approaches. Then both authors (NAQ and YSA) independently reviewed the available data (n= 5266) for extracting relevant articles. Consequently, unrelated articles (n=2052), inaccessible papers (because of high price tag) (n=360), articles cited in systematic reviews and meta-analysis (n=86), no abstract available (n=63), duplications (n=2462), and irrelevant information (n=98) were excluded. A total of 145 articles remained, which were screened further for eligibility. Articles which did not focus on psychotropic medications weight gain, overweight, obesity and treatment intervention approaches were excluded (n=4). Thus, the total number of working articles is 141 (Fig. 1).

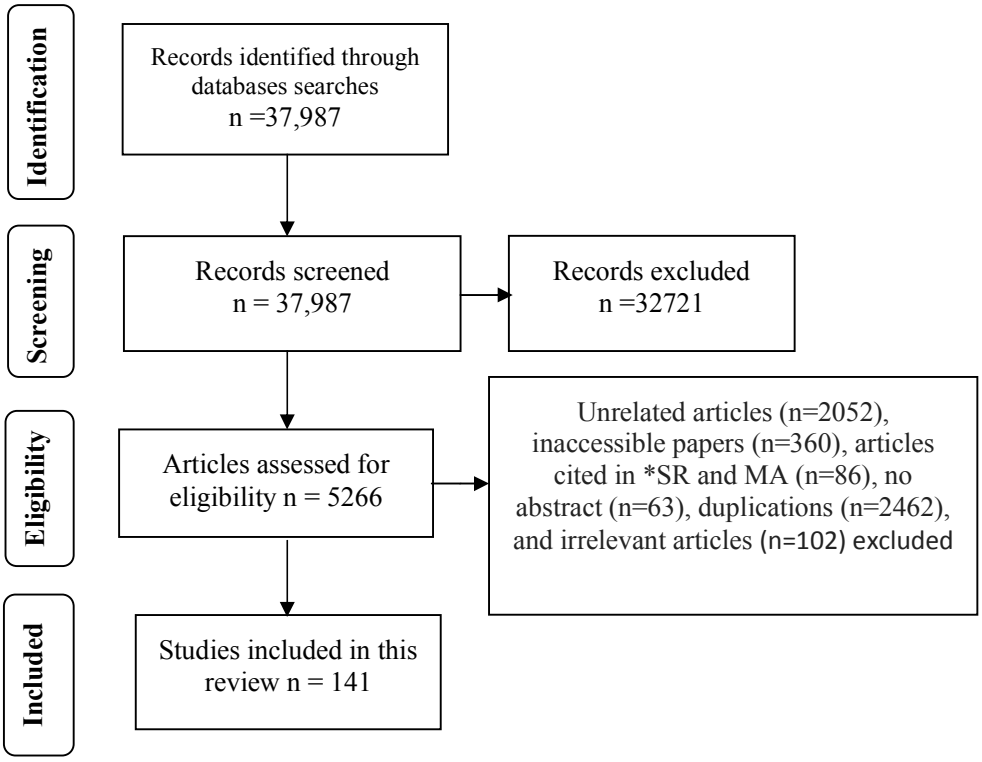

Fig. 1. Prisma diagram summarising the flow of search results
*(*SR=systematic review & MA=meta-analysis)*

3.2 Definition of Weight Gain

The prevalence and definitions of weight gain and obesity tend to guide researchers to precisely assess, treat and monitor the weight in the healthy and mentally ill population [1]. Weight gain mainly measured in kilograms is an increase in body weight involving muscle mass, fat deposits, and excess fluids including water. The average body weight is a minimum of 57.7 kg to a maximum of 87.7 kg. The global adult population is 4.63 billion with an average weight of 62 kg and overweight population constitutes 34.7% of the total population [42]. Overweight and obesity are globalised and are linked to cardiovascular diseases, diabetes mellitus, metabolic syndrome, musculoskeletal disorders, cancers, neurological diseases, psychiatric disorders, disabilities and impairment of social body functioning [43,44]. Conversely, many of these physical diseases are important causes of obesity and overweight. The several psychiatric disorders including depression, anxiety disorders, post-traumatic stress disorder (PTSD), eating disorders such as binge-eating disorders and night-eating syndrome, and severe psychiatric conditions such as schizophrenia, bipolar disorders and adult attention deficit hyperactivity disorder (ADHD) may also affect overweight and obesity [45-47]. Body mass index (BMI, formula = weight in kg/square of height in meters), a simple weight measurement tool for male and female adults are frequently used to classify overweight (BMI≥25) and obesity (BMI≥30). Abdominal obesity is defined as waist circumference >102 cm in men or >88 cm in women [48]. The weight gain is defined as a mean weight gain of 1.9 kg to 20.1 kg. A normal BMI is between 18.5 and 24.9, a BMI between 25 and 29.9 is classified as overweight, and 30 to 39.9 denotes obesity. Patients with a BMI above 40 are considered extremely obese [49]. Recently, American Association of Clinical Endocrinologists (AACE) defined overweight and obesity based on BMI and clinical complications (Table 2) [50]. In sum, the normal weight, weight gain, overweight and obesity are well-defined concepts in obesity research including psychotropic medications-weight gain paradigm.

Table 2. Overweight and obesity staging and risk stratification based on complication-specific criteria [50]

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Overweight Staging	BMI	Checklist of Obesity-Related Complications#; risk stratification based on complication-specific criteria
Overweight stage 0	≥25-29.9*	No complications
Obesity Stage 0	≥30	No complications
Obesity Stage 1	≥25	One or more mild-to-moderate complications**
Obesity Stage 2	≥25	One or more severe complications***

In certain ethnicities BMI<23; **or may be treated effectively with moderate weight loss;* requires significant weight loss for effective treatment;# Prediabetes, metabolic syndrome, type 2 diabetes, dyslipidemia, hypertension, cardiovascular disease, nonalcoholic fatty liver disease, polycystic ovary syndrome, female infertility, male hypogonadism, obstructive sleep apnea, asthma/reactive airway disease, osteoarthritis, urinary stress incontinence, gastroesophageal reflux disease and depression*

3.3 Prevention Strategies, Overweight and Obesity

Prevention is much better than treatment because it is cost-effective and prevents the onset and adverse consequences of a particular disease. Obesity is a public health problem and on the rise at an alarming rate around the world. Obesity is associated with a variety of comorbidities including various cancers and psychiatric disorders with overall high morbidity and mortality (Table 3). Obesity needs effective public health strategies for promoting health and wellness, reducing risk factors and its prevention (Tables 4 and 5) [51-53]. In particular, 5As approach used successfully in quitting cigarette and addiction. It was also applied for preventing and managing obesity in general healthcare settings. The 5As strategy includes the following steps; 1) discuss weight with the patient (**A**SK); 2) assess health status, comorbidities and causes of weight gain (**A**SSESS); 3) advise on treatment options (**A**DVISE); 4) agree on weight loss expectations and treatment plan (**A**GREE) and 5) assist the patient in the continuous process of weight management (**A**SSIST) [54,55]. Weight counselling embedded in the 5As theory-driven program and online tool tends to stimulate doctor-patient interaction and motivation to lose weight. The use of this tool around the world will possibly address complex therapeutic as well as research issues of obesity in all age groups including children and adolescents. Previous researches suggest that the most common psychiatric and non-psychiatric treatment interventions used in promoting health and reducing weight of all categories are behavioral modifications, lifestyle changes including dietary changes and regular exercise, multi-pronged school-and community-based programs, social media strategies and a variety of medications associated with good outcome and quality of life [40,51-58]. Overall, from complementary and integrative medicine or holistic perspective, aforesaid approaches make substantial sense of complementary therapies. If combined with modern medicines, it will definitely result in better therapeutic benefits to a psychiatric or non-psychiatric population with weight gain or obesity in all age groups.

3.4 Basic Management Guide

Before treatment begins, mental health professionals should take written consent from the patient if mentally competent, otherwise from his/her guardian. Prior to the start of psychotropic medications inform the patient that there is a possibility of slight weight gain, which is of low impact compared to clinical gain [59,60]. Furthermore, assessment and monitoring of weight gain including blood pressure and pulse rate need to be done at a regular interval in patients on psychiatric medications. Besides, tailoring antipsychotic doses in line with the needs of each individual patient (patient-centred approach) is equally important to stabilise the patient, to minimise the weight gain and metabolic syndrome [59-61]. Professionals need to choose psychiatric medications including antipsychotics that cause the least weight gain or decrease it especially in initially obese patients with psychiatric disorders [62]. Furthermore, safe psychiatric medications and complementary treatments effective in reducing weight gain need to be continued among mentally ill patients. This is done to stabilise their clinical condition, to prevent disruptive relapses, weight gain and maintain good drug compliance. Besides assessing weight gain, regular monitoring of early indicators of a metabolic syndrome characterised by high lipids, blood sugar, blood pressure, uncontrolled glycemia and abdominal girth is also required among patients on antipsychotic drugs [63]. Like in general hospitals, psychiatric treatment centres need to

have outpatient weight control clinics for serving not only outpatients but also in patients having psychotropics-induced overweight or obesity problems [64,59]. Overall, in addition to these fundamental principles of controlling overweight or obesity in psychiatric patients on psychotropic drugs, other drug-free programs and strategies used in children and adolescents need to be applied to an adult population with or without mental disorders. In the subsequent sections, multiple approaches that reduce weight gain in psychiatric population will be discussed in detail.

3.5 Life Style Changes

Lifestyle behaviours play an important role in the causation of obesity and diabetes mellitus in patients with major or minor mental illness. Multidimensional lifestyle interventions, important component of complementary therapies, are reported to target various poor lifestyle behaviours. These include sedentary life, smoking, alcohol and other drug use disorders, high calorie food and perceived barriers that promote weight gain, poor adherence, and metabolic syndrome among patients not only with SMI [62,65,66] but also major depression, bipolar I and II disorders, anxiety disorders including PTSD, personality disorders, ADHD and autistic spectrum disorder [67,68]. In particular, more than the 12-month duration of lifestyle program was found to be more effective than 6-month timeline program in seriously ill patients of schizophrenia [69]. Clinicians need to assertively inform patients about the usefulness of daily exercise and dietary changes, i.e., low-calorie diet and behavioural modifications such as quitting smoking that needs their full commitment and motivation. Portion control behaviours, i.e., to eat less at every meal also help in reducing weight gain. A successful weight reduction program reflects a loss of 0.23 to 0.45 kg. of body weight per week, which is considered safe and acceptable. Exercise-only interventions are reported to have a significant positive impact on depressive symptoms and a reduction in weight gain [70]. Prophylactic exercise and diet control are two very effective complementary methods to proactively check on weight gain among patients intending to take weight increasing psychiatric medications or normal population of all age categories especially children and adolescents with overweight and obesity.

Table 3. Relative risk of physical health problems associated with obesity [52]

Relative risk >3	Relative risk 2−3	Relative risk 1−2
Type II diabetes	Coronary heart disease	Cancer
Gallbladder disease	Hypertension	Reproductive hormone abnormalities
Dyslipidemia	Osteoarthritis	Polycystic ovary syndrome
↑Insulin resistance	Hyperuricemia and gout	Impaired fertility
Breathlessness		Low back pain
Sleep apnea		Increased risk of anaesthesia complications
		Fetal defects (associated with maternal obesity)

Comorbid psychiatric disorders associated with obesity: schizophrenia-spectrum disorders, mood disorders, anxiety disorders & PTSD, eating disorders, autistic disorders, ADHD, and some personality disorders [5,8-11]

Table 4. Strength of evidence on factors that might promote or protect against weight gain and obesity [53]

Increased risk	Decreased risk	Strength of evidence
Sedentary lifestyle	Regular physical activity	Convincing
High intake of energy-dense foods	High dietary intake of fibre	
Adverse socioeconomic conditions-developed countries	Home and school environments that support healthy food choices for children	Probable
Large portion sizes	Breastfeeding	
A high proportion of food prepared outside the home-developed countries	Low glycemic index foods	Possible
Rigid restraint/periodic disinhibition eating patterns	The increased eating frequency with intake of a small quantity of healthy food (portion control behaviour)	
Alcohol use		Insufficient

Table 5. Recommendations for the prevention of obesity and overweight in the normal population [56]

Infants and pre-school children#	Early and middle school years##	Adolescence ###
Nutrition	**Nutrition**	**Nutrition**
	Varied, balanced diet::	Same recommendations as here ##
• By age 1, meals should be taken seated with the family	• Ample beverages (water or unsweetened, sugar-free drinks)	Early and middle school years
• Introduction to new, healthy foods	• Plentiful varied plant-based foods (vegetables, fruit, whole grain products, potatoes)	Early and middle school years
• Positive mealtime conditions (e.g. positive atmosphere, no outside distractions: e.g. TV)	• Limited animal-derived products (milk/milk products, meat, fish, eggs)	Early and middle school years
• A varied diet with plenty of beverages (water or unsweetened, sugar-free drinks)	Very limited sugar and sweets, age-adjusted portion sizes	Early and middle school years
•.Ample plant-based foods (vegetables, fruit, potatoes, whole grain products)	• Limitation or elimination of sweetened drinks	Early and middle school years
• Limited animal-derived products (milk and milk products, fish, eggs)	• No snacking	Early and middle school years
• Very limited added sugar and sweets	• Creation of a healthy, balanced school meal program	Early and middle school years
• Careful observation of the sugar content in food and drinks		Early and middle school years
Physical activity and sports	**Physical activity and sports**	**Physical activity and sports**
1.For children 3–5 years: at least 60 min of structured physical activity daily	• Daily physical activity of at least 90 minutes (possible also in periods of 15 minutes for endurance and interval training)	• Daily physical activity of at least 90 minutes (possible also in periods of 15 minutes for endurance and interval training)
2.≥ 3 years: From 60 min to several hours of unstructured physical activity; limit inactivity to less than 60 minutes at a time, outside of sleep	• Minimum of 12,000 steps per day	• Minimum of 12,000 steps per day
3.School-age: a minimum of 60 min of moderate to intensive physical activity daily or at least 10,000 steps per day	• Limit sedentary activity to a maximum of 2 h/day	• Limit sedentary activity to a maximum of 2 h/day
4.Adolescence: a minimum of 90 min of moderate to intense physical activity daily or at least 10,000 steps per day		4.Adolescence: a minimum of 90 min of moderate to intense physical activity daily or at least 10,000 steps per day
5.Acquisition of basic motor skills as the basis for future physical dexterity and activity		5.Acquisition of basic motor skills as the basis for future physical dexterity and activity
Promoting access to indoor and outdoor exercise areas		Promoting access to indoor and outdoor exercise areas
6.Education of parents and caregivers on the importance of physical activity		6.Education of parents and caregivers on the importance of physical activity
Media consumption	**Media consumption**	**Media consumption**
1.No TV in children´s bedrooms	• Limit media consumption as well as sedentary leisure time according to age	Limit media consumption as well as sedentary leisure time according to age:

		For adolescents age 12 years and older. 120 min maximum per day
2. Limit access to media and in general reduction of leisure time spent sitting according to age: 3.For children under 3 years: 0 min 4.For children 3–6 years: 30 min maximum	• For children 7–11 years: 60 m maximum	

#&## In addition: interventions as well as targeted education of teachers and parents; ###In addition: direct transfer of knowledge on obesity-related aspects to adolescents

3.6 Psychological Methods and Overweight

Psychosocial therapies that also constitute mainstream of complementary and alternative medicine (CAM) modalities contribute to the reduction in psychotropics related weight gain among patients with major and minor psychiatric problems. Several behavioural modification techniques and other psychological interventions tend to reduce weight gain. Sometimes a weight loss of 0.5 kg to 0.7 kg per week [40]. In one study, the effect of cognitive behavioural therapy (CBT) on weight gain due to psychotropic medications was studied in six young adult patients with schizophrenia. The mean BMI decreased from 29.6 kg to 25.1 kg in the post-treatment group. In addition, CBT has also been helpful in reducing overweight among children and adolescents with or without mental disorders. Furthermore, the addition of CBT to a diet controlled method produced better results. Nonpharmacologic interventions including dietary counselling, exercise and fitness programs and cognitive and behavioural strategies appear to be equally effective in individual and group therapy formats [62]. In an observational study involving patients with psychosis-spectrum disorders, other psychiatric disorders and no psychiatric disorders, Zhang et al. (2012) reported greater weight loss linked to CBT interventions in patients with psychotic disorders. This study suggested that anti-obesity strategies including CBT should also target non-adherence and concomitant depression among patients with diverse psychotic disorders [71]. Overall, the available literature suggests that behavioural modifications, lifestyle changes, CBT, anti-obesity medications and their integrated modalities are of considerable help in effecting weight loss in psychiatric population using psychotropic medications linked with weight gain (Table 6) [40]. On the other hand, huge literature evidenced the fact that the multidimensional programs are effective in non-psychiatric child and adolescent population with obesity and overweight [56,57]. Notably, patients with complex psychiatric disorders especially psychotic conditions associated with physical and psychiatric comorbidities need greater motivation to adhere to non-pharmacological or medication programs directed toward improving their overweight or obesity [5].

3.7 Pharmacotherapy - Role of Anti-obesity Drugs

Antiobesity medications (AOM): Some are considered of great potential to reduce weight gain in psychiatric as well as nonpsychiatric population (Table 6). Therefore, AOM needs to be considered in case a patient who has obesity with a BMI of 27 kg/m^2 to 30 kg/m^2 associated with metabolic syndrome or obstructive sleep apnea. Anorectic agents act centrally by suppressing appetite or increasing satiety and cause weight loss but reported to have a variety of dangerous adverse effects including potential for abuse, stroke and cardiac arrhythmias [73]. Sympathomimetic agents such as phendimetrazine, phentermine, mazindol, ephedrine, cathinone, and phenylpropanolamine, as well as controlled substances such as amphetamine, dextroamphetamine, levoamphetamine and methylphenidate also impact CNS and are used not only in patients with obesity (BMI>29) with variable efficacy [74,75] but also sleep apnea, narcolepsy, and ADHD [74]. Interestingly amphetamine analogues and others psychostimulants are found in different plants [76]. Some of these drugs are produced illegally for recreational purpose and associated with fatal events and methamphetamine certainly not a prescription drug. Similarly, phenylpropanolamine is taken off from the market as it produces a hemorrhagic stroke. Also, the role of sympathomimetic drugs in overweight or obese patients on psychotropic drugs is minimal (or negative impact) because of several potential adverse effects especially abuse potential and cardiac effects, and their dangerous interactions with psychotropic medications [40,73].

Table 6. Weight reduction strategies in psychiatric population [40,72]

Drug/Non-drug strategies	Weight loss	Duration & remark
Behaviour modification	0.5–0.7 kg/week	—
Behaviour modification#	The mean BMI-SDS decreased by 0.15 kg/m ^{2}	12 weeks
Cognitive-behavioural therapy	4.5 drop in BMI	—
Naltrexone Plus bupropion	4%	—Bupropion (antidepressant) off-label,
Phentermine*Plus Topiramate	9%	1 year, Sympathomimetic and mood stabiliser
Phentermine*Plus Fenfluramine	Yes	Sympathomimetic and serotoninergic
Sibutramine*	10–15% due to increased satiety.	<1 year, safer, mix of SSRIs and SNRIs, increase in BP& heartrate is removed from the market
Orlistat**	8.8 to 34.6%	1-2 years, lipase inhibitor, unpleasant side effects
Orlistat	>10%	2 years, lipase inhibitor, unpleasant side effects
Orlistat	34.6%	lipase inhibitor, unpleasant side effects
Amantadine	3.5 kg	3–6 months, 300mg/day, also used in Parkinson's disease and flu (influenza A). Acts on dopamine and has anticholinergic activity and interferes with viral protein M2.
Nizatidine	Yes (3kg less than those without it)	16 weeks, H_2 antagonist, 300mg twice daily
Naltrexone (Zonisamide + Bupropion	5 kg	8 weeks, opioid antagonist, weight loss as a side effect, decreases hunger and craving for sweet,
Topiramate augmentation	10–15 lbs	— Off-label, mood stabiliser
Metformin	15/19 patients lost weight	12 weeks, used in T2DM
Chromium picolinate-Brewer's yeast richest source	+/-with 600 to 100mcg/day	Works with insulin in the body to metabolise carbohydrates and improves insulin sensitivity
Fluoxetine	Yes	Off-label, SSRI
Diethylpropion**	Yes	An amphetamine-like analogue used on short basis (up to 12 wks.)
Reboxetine	Yes	selective noradrenaline reuptake inhibitor (NARI)
α-glucosidase inhibitors	Yes	Glucose lowering agent
sodium-glucose cotransporter 2 inhibitors	Yes	Glucose lowering agent
Pramlintide	Yes	Injectable, Glucose lowering agent,
Glucagon-like peptide (GLP) -1 receptor agonists	Yes	Glucose lowering agent,

*#through parents and caregivers, *including rimonabant (serious psychiatric side-effects including severe depression and suicide ideations), 2,4-dinitrophenol (linked to death) and aminorex (causes pulmonary hypertension) removed from the market due to such severe side effects and unfavourable risk-benefit ratio, **FDA approved*

Of note, the serotonergic agents such as fenfluramine and dexfenfluramine were also withdrawn from the US market over concerns about valvular heart disease. Sibutramine, a SNRI causes 5% to 15% weight loss in obese persons. Sibutramine use is discontinued around the world since 2010 because it causes an increase in blood pressure and heart rate. Sympathomimetic drugs also induce serotonin syndrome if combined with SSRIs, SNRI and amphetamine derivatives. Serotonin syndrome is a polypharmacological potentially serious condition caused by synergistic adverse interaction of serotonergic drugs and needs early diagnosis and intervention for better outcome [77,78].

Orlistat, a lipase blocker with safe good efficacy profile, available in 60 mg and 120 mg capsules, acts on GIT. Specifically, it inhibits gastric and pancreatic lipases by binding covalently to the serine residue at the active site of these enzymes [79], which allows fat not to be absorbed by the GIT including intestines. Orlistat needs to be taken with low-calorie meals only by overweight adults. Children under 12 year and persons with kidney diseases and cholestasis should not use lipase blockers. Orlistat is

associated with unpleasant adverse GIT effects including oily spotting, flatus with discharge and faecal urgency [79,80].

The drug reboxetine (NARI) 4mg daily for 6 weeks is effective for weight prevention while topiramate (100-200 mg daily for 12 weeks) is useful for both prevention and established weight-gain in patients with schizophrenia [81,82]. Reboxetine is primarily used to treat depression but has also been found useful in the treatment of narcolepsy and panic disorder. Additional research has shown that the use of topiramate combined with valproate or clozapine results in substantial weight loss in patients with schizophrenia [83].

Patients with schizophrenia having antipsychotic-induced weight gain also tend to benefit from metformin compared to placebo [84]. According to a meta-analysis of RCTs for the most studied antiobesity agents to estimate mean weight loss, metformin was reported to show the most reliable evidence in patients with schizophrenia [85] and also improved vascular risk factors beyond obesity. Accordingly, topiramate is reported to decrease weight gain and improvement in psychotic symptoms among patients refractory to antipsychotic treatment. A marginal benefit is seen with NARIs, and any vascular benefits from such weight loss may be counteracted by increases in blood pressure or heart rate. Pharmacological therapies may offer benefits as a means of supplementing the effects of lifestyle changes for weight loss. However, the existing evidence provides little evidence of specificity for pharmacological therapies to antipsychotic-induced weight gain. However, any link between benefits from weight loss and reduced incidence of diabetes mellitus or any cardiovascular outcomes remained unexplored [86] and need further relevant research in future.

There are now many newer medications developed for the management of obesity; selective central cannabinoid-1 receptor blockers, selective central 5-hydroxytryptamine 2C receptor agonists, and central acting incretin mimetic drugs [44,87]. Furthermore, other newer agents associated with beneficial changes in appetite expression in the obese population include GLP-1 analogs such as liraglutide (Saxenda 3mg/day), an amylin analog davalintide, the 5-HT(2C) receptor agonist lorcaserin, and the trimonoamine re-uptake inhibitor tesofensine (a serotonin–noradrenaline–dopamine reuptake inhibitor from the phenyltropane family of drugs). Also, some combination therapies such as pramlintide and metreleptin, bupropion and naltrexone, phentermine and topiramate, and bupropion and zonisamide are also used in the obese population [88-91]. These anti-obesity medications when combined with a low-calorie diet, exercise and behavioural interventions (integrative approaches) result in additional weight loss [91-93]. Ranitidine (histamine-2 receptor blocker) used as adjunctive is also reported to reduce weight gain and negative symptoms in patients with schizophrenia [94]. Overall, psychiatric patients on weight increasing psychotropic medications may better benefit from new anti-obesity drugs [79] when combined or not with CAM therapies including acupuncture, cupping therapy (Hijamah), medicinal herbs and natural antidepressants and spiritual and religious therapies [95-98]. Notably, most of the natural antidepressants summarised below are weight neutral or associated with weight loss. On longterm use, they may cause weight gain and, therefore, may presumably be used on short term basis among patients with depression and weight gain induced by psychotropic drugs (Table 7).

3.8 Multidisciplinary Approach and Weight Loss

Evidently, a multidisciplinary approach is appropriate for those overweight patients on weight increasing psychiatric medications. Morbid obesity is a complex condition that also needs a multidisciplinary approach. Furthermore, many healthcare disciplines have identified numerous risk factors that contribute to the development of morbid obesity, and overweight in the psychiatric population [45,105,106]. A combination of suitable diet, exercise, behaviour modifications, and weight reducing medications would be the ideal strategy for reducing the weight gain in the mentally ill patients on antipsychotic medications [62,65,91, 105]. In particular, mentally ill persons often show poor compliance with rigorous diet and exercise regimen due to their disturbing psychiatric symptoms. Furthermore, besides antipsychotic medications, the association between overweight and depression, bipolar disorders, schizophrenia, and PTSD is mediated by a change in eating, current smoking, lack of exercise and many other factors including insomnia [107,108]. Other integrated strategies that include switching the psychotropic medication to one less likely to cause weight

gain. The addition of newer anti-obesity medication further help to reduce weight gain in mentally ill patients [62,107,108]. Similarly, natural acetylcholinesterase inhibitors (NACIs) used in dementia and other disorders (Table 8) are associated with anorexia. The side effect might be utilised in reducing weight among patients with cognitive dysfunctions found in diverse conditions such as schizophrenia, mood disorders including major depression, bipolar I and II, and dementia.

In conjunction with weight loss drugs such as metformin, topiramate, sibutramine, aripiprazole, reboxetine, and orlistat, modification of dietary habits together with physical activities might be of more significant help in reducing weight gain in psychiatric population taking olanzapine, clozapine, valproate and risperidone [62,113-118]. These are linked with greatest weight gain. However, other psychotropics associated with the lowest risk of weight gain in psychiatric patients are ziprasidone, lurasidone, and burpropion. Weber and Wyne implemented a cognitive-behavioural group intervention matching with the Diabetes Prevention Project in a group of patients with schizophrenia or schizoaffective disorder taking atypical antipsychotics. After 16 weeks it was found that the intervention group lost more weight (2.9% of body weight) than a control "treatment as usual" group (0.6% body weight). The intervention group was delivered weekly sessions which centred on various strategies including goal setting, discussions on barriers to change and plans to increase physical activity. Participants in the intervention also had to keep a food and activity records, which was submitted at each weekly session [118]. Thus, multidimensional interventions prevent weight-gain and associated health risks in individuals exposed to antipsychotic drugs [119,120]. However, given the modest effect of these interventions, appraising metabolic risk is a critical first step to preventing weight-gain in patients starting on antipsychotics or antidepressants [81,121]. Additionally, in extreme cases, surgery remains an option when other weight control methods have failed and obesity-related co-morbidities and mortality become a major problem [122, 123].

Table 7. Psychotropic drugs (natural antidepressants) and weight gain/loss variations

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Natural Antidepressants				
St. John's Wort	A flowering shrub (hypericin)	Wt. loss/ neutral	300mg TID, up to 1500 mg /day	Wt. loss due to appetite suppressant effect & increased brain serotonin levels; used in depression, anxiety, insomnia, and menopausal symptoms. Average dose 1300 mg/day [99,100].
S-adenosylmethionine	Natural Chemical Found in the body, Nutraceutical	Wt +/-	200 mg to 1,600 mg/day	Speculative! On longterm use wt. gain? Used in depression, osteoarthritis (400 to 1200 mg/day), fibromyalgia and liver disease (800 to 1000 mg/day) [101].
Omega 3 fatty acids (OFAs)	Essential fatty acids, Nutraceutical	Wt.-		Causes fat loss; found in water fish (salmon), decrease cholesterol and LDL in the blood. EPA and DHA are major OFAs.
Saffron	Natural herb	Wt+/-	30 mg/day in divided doses	Obese people lose weight, Saffron stigmas used in persons with underweight, depression, cancers Alzheimer's dis. MD, & Parkinsonism and other diseases (PMS) [102,103].
5-HTP	Help in the synthesis of serotonin	Wt.-	300 to 500 mg daily	Decreases carbohydrate and starch intake and early stomach fullness & used in depression, anxiety, migraine, PMS, insomnias, obesity and ADHD.
DHEA (precursor to testosterone & estrogen)	Endogenous steroid hormone from adrenal glands	Wt. -	25 to 100 mg in divided doses	Helps in depression, obesity, lupus, and adrenal insufficiency, osteoporosis, vaginal atrophy, erectile dysfunction, and dementia [104].

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Ginkgo biloba	Nootropic	Wt. +/-	40 to 240 mg divided doses	Used (its standardised extract of 24% flavone glycosides and 6% terpene lactones) in elderly with cognitive impairment, anxiety, schizophrenia, TD, and wt. the loss may also be due to associated physical diseases elderly people tend to suffer.

+=mild to moderate weight gain, ++=moderate to marked weight gain, -=wt. loss; 5HTP=5-hydroxytriptophan; DHEA=Dehydroepiandrosterone; EPA=eicosapentaenoic acid, DHA=docosahexaenoic acid, MD=macular degeneration, PMS=premenstrual syndrome; TD= tardive dyskinesia

Table 8. Psychotropic drugs (Anti-dementia drugs) and weight gain variations

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Natural ACIs				
Galanthamine	NACIs	Anorectic agents/ wt. loss	16 to 24 mg/day, max. dose	Tried in nerve pains, poliomyelitis, facial paralysis and schizophrenia. A better option for treating dementia (AD) with initial overweight [109]. Maximum dose: 16 to 24 mg/day[110]
Quercetin#	NACIs	+/-	25 to 50 mg QD	Used in many physical diseases and schizophrenia; increase weight in lean persons but reduces weight in high BMI people
Timosaponin AIII	NACIs	+/-	Manufacturers suggest using three to six 500 mg capsules two to three times daily as a tea.	Used in many diseases and has anticancer, anti-inflammatory, antithrombotic activities and improves memory deficits [111, 112].

+=mild to moderate weight gain, ++=moderate to marked weight gain; ACIs=Acetylcholinesterase inhibitors

In a nutshell, a program that combines pharmacotherapy with non-pharmacological approaches including herbal preparations will result in weight loss among patients with major psychiatric disorders, and will also impact the outcome of associated physical and psychological problems [5]. Further research is required to determine which methods of intervention show the best long-term effects on overweight. In the same vein, what individual differences influence the type of intervention that will be robustly effective in reducing overweight among psychiatric patients on weight increasing medications.

3.9 Prevention and Management of Weight-gain in Clinical Practice

The weight-gain and other adverse effects that result from antipsychotic medications may force some patients to discontinue treatment, inhibiting their potential for improved mental health [124]. Consequently, these patients develop numerous serious biopsychosocial problems and complications [125,126] and, therefore, pract-itioners must identify and monitor patients at higher risk for substantial weight-gain and psychiatric and physical comorbidities [126]. In this way, overweight and obesity linked with excessive morbidity and mortality might be prevented prior to causing a considerable burden on the healthcare system. Switching antipsychotic medication is another strategy to reduce body weight, although this may not be clinically feasible in all cases of psychiatric disorders. Moreover, switching from one drug to another linked with less weight gain is a clinical decision that depends on several factors, e.g. tolerance, safety and efficacy of a drug. Such critical decision needs to be taken in the best interest of the patient based on the existent state of knowledge, and to which the patient must agree. Notably, evidence for the effectiveness of switching or adjunctive medication strategies is conflicting. However, evidence-based non-pharmacological interventions combined with psychotropics are better holistic approaches for an individual patient with psychotic disorders with overweight/obesity [126-130]. From the perspective of antiobesity pharmacotherapies, orlistat produces weight loss of 7-10% of initial body weight [58], but other antiobesity drugs

including sibutramine are no more used in patients with psychoses due to their life-threatening adverse effects including deaths [44,131]. Overall, patients with psychosis spectrum disorders need continuous monitoring of weight gain and holistic approaches for preventing metabolic syndrome and optimising their treatment outcome and weight control in clinical settings.

3.10 Herbs and Overweight or Obesity

Herbs and herbal medicines are commonly used globally in reducing weight and obesity. Huge literature has emerged on herbs and natural products that are frequently used by healthy and physically or psychologically ill population with overweight or obesity around the world [97,98]. The diverse herbs are used as foods, spices, teas, fluids, medicines, dietary supplements or whole herb formulations, juices, oils, soup and salads. Herbs are reported to have anti-anxiety properties, adaptogenic features, antidepressant effects and attributes of stress reduction. A diet infused with medicinal herbs provides an effective formulation for weight loss [44,132,133]. Ayurvedic formulations and concentrated extract supplements made of herbs are primarily used as complementary remedies to control overweight and obesity. Hemp and ephedra with abuse potential need careful use in psychiatric clinical practice. Herbs tend to cause weight loss in psychiatric or nonpsychiatric population through a number of means. This includes gene expression, a reduction in appetite, food intake, ghrelin hormone that stimulates hunger, insulin resistance, fatty synthesis and an increase in GLP-1 and thermogenesis that are mediated by enteric and central nervous systems [134-140]. From a cultural perspective, numerous herbs (Table 9) have an impact on overweight and obesity [135-141]. Overall, herbs and natural products used in different traditional medical systems since ancient times. Herbal products either combined or with conventional medications have significantly contributed to the management of overweight and obesity among patients with or without psychiatric disorders.

4. DISCUSSION

This review describes critically therapeutic strategies-conventional and integrative- directed towards overweight and obese patients on psychotropic drugs. Of note, obesity, is a complex public health conundrum determined by multifactorial aetiology and well defined dynamic predictive factors embedded in individual biological, psychosocial and cultural milieu [1-41]. These weigh causing factors are fairly common denominators both in psychiatric and non-psychiatric population. Antipsychotics and antidepressants have the greatest potential to increase weight among patients with schizophrenia-spectrum conditions and mood disorders [1-3,5-7,12,13,81,121,126-128]. Unlike morbid obese people without psychiatric disorders [4,105], patients with SMI on psychotropics pose additional therapeutic challenges concerning overweight and obesity [1-3,40]. This is because of multifactorial aetiology, lack of motivation, severe psychotic symptoms, side-effects, and poor compliance to prescribed integrated interventions directed towards overweight and obesity [1-41,59,65-67,69,115,119-121]. Psychiatric patients on

Table 9. Herbs with weight loss effects

Herbs	Used in different forms
Fish oils, glucosamine, St. John's wort, ginger, and peppermint.	Supplements
Ginger, cayenne pepper (capsaicin), and fennel	Spices
Chamomile, gentian, or dandelion root	Bitter herbs
Dried nettle leaf, spaghetti sauce, sprouted fenugreek, and dandelion leaf, water socked fenugreek seeds	Salad, carbohydrate metabolizer
Siberian, American, and Chinese ginsengs, holy basil, schizandra, ashwaganda, licorice, and codonoposis	Adaptogens
Fennel, licorice, chamomile, lemon balm, peppermint, catnip, aniseed, and damiana, aloe resin, senna, cascara, rhubarb, yellow dock	Weight loss formulations
Linden, gravel root, dandelion, or boldo	Diuretic herbs
Caffeine, pseudoephedrine, or phenylephrine (and other sympathomimetic)	Supplements with concentrated dose extracts but have abuse potential
Bitter melon, fenugreek, garcinia, gymnema	Thermogenic supplements
Ayurvedic formulations	Containing multiple herbs
Guarana, bitter orange, green tea, and yerba mate	Not advised in concentrated dose extract

psychotropics with overweight need special care concerning the promotion of health and wellbeing, suitable community-and public health-based prevention strategies and complementary and integrative interventions that should be provided by a multidisciplinary team [4,40]. However, a patient-focused approach that targets the unique needs of the individual person with the mental disorder is of great therapeutic value in overweight and obesity caused by prescribed medications. Huge data address the problems of obesity in children, adolescents, adults and elderly people not on weight increasing psychotropic drugs [4], and the discussion of which is beyond the scope of this paper.

There is converging evidence that the integrative non-pharmacological approaches are the most useful, safe, cost-effective in reducing overweight and obesity in psychiatric populations [40,62,71,72,118,129,130]. Also, other CAM approaches such as acupuncture, Hijamah (cupping), herbal formulations combined with safe, conventional antiobesity medications such as metformin result in significant weight reduction in mentally ill people [95-98,129-140]. Furthermore, several new antiobesity medications were developed and most of them were reported to cause life-threatening events such as severe depression, suicidal ideation, arrhythmias and myocardial infarction, stroke and deaths and are not sold in the free, open market around the world [40,44, 73,77,78131].

In the clinical setting, mental health professionals and physicians should take some additional precautions concerning overweight and obesity in the psychiatric population. Collection of comprehensive data about history, predictive risk factors, lifestyle, dietary habits, and complete physical, systemic and mental status examination along with the history of heart disease, arrhythmia, or syncope, and prolonged QT syndrome or early sudden cardiac death is imperative [40,61]. Furthermore, monitoring of weight and metabolic parameters throughout treatment is also highly desirable [59-61]. However, in the case of emerging metabolic syndrome, it is vital to review psychiatric medications and carefully manage it [31,40,43,62-65,87]. The patient-centered approach must also guide mental health professionals to select the most suitable programs including a minimum number of safe psychiatric medications linked with very low or no weight gain in conjunction with antiobesity drugs to obtain adequate remission of psychiatric disorder and reversal of metabolic syndrome [45,85,95-98,105,106,129-140]. An electrocardiogram should be done to each patient before initiation of antipsychotic and antidepressant medications [40,61].

This narrative review has some limitations. The most important is selection and publication biases. This is not a comprehensive and systematic review of diverse therapeutic interventions directed towards overweight and obesity in the psychiatric population. Moreover, the reviewed studies vary widely with regards to methodology and patient populations. This review has multiple strengths. This is the first review of psychotropic-induced weight gain with a focus on therapeutic challenges, conventional treatments and complementary therapies in Saudi Arabia. This review also updated the predictive risk factors of weight gain associated with or without psychotropic prescribing in mentally ill and normal population globally. This review might bridge the knowledge gap of mental health professionals and paramedical staff, physicians and mental healthcare users concerning psychotropic-induced weight gain, and its predictive risk factors in psychiatric and physical ill population across the world.

5. CONCLUSION

The overweight or obesity associated with psychotropic medication use in patients with major or minor psychiatric disorders is a complex clinical dilemma. This needs multidimensional individualised treatment approach tailored to meet the multiple needs of each patient. Regular monitoring of weight gain, a continuation of psychiatric medications in conjunction with effective integrative CAM interventions, and antiobesity pharmacotherapies with the safe clinical profile is reported to control weight gain in a psychiatric population with stabilisation of psychiatric condition. Future comparatives studies are needed for optimising the treatment of overweight and obesity and its adverse consequences in the psychiatric population around the world.

CONSENT

Prior to the start of psychotropic medications, written consent from the patients or from his/her guardian was taken.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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