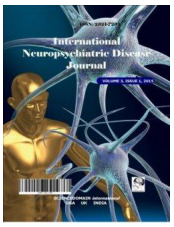

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Psychotropic Medication-induced Weight Gain or Loss Looked through the Lens of Age and Psychiatric Diagnoses: A Narrative Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors NAQ, DSD, SOS OAK and SMS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NAQ and SMS managed the analyses of the study. Authors NAQ, SOS OAK and SMS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: There is a myriad of risk factors associated with overweight and obesity in the psychiatric population.
Objective: The review aimed at looking at the psychotropic medications induced weight gain or loss through the lens of age categories and psychiatric diagnoses.
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, and based on exclusion and inclusion criteria 155 pertinent articles were retained for this review.
Results: No age is immune to weight gain provided patients are treated either with standalone

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antipsychotic medications, antidepressants, mood stabilizers or their combinations. These medications are mostly used in adult patients with schizophrenia, mood disorders, other related psychoses and anxiety disorders resulting in more significant weight gain. Children and adolescents with similar mental disorders are also prone to develop weight gain when exposed to similar psychotropic drugs on a longterm basis. Unlike those two age categories, elderly patients with dementia or carry-on psychoses (residual psychosis) treated with psychotropic similar medicines tend to have minimal weight gain. Children and adult patients with attention deficit hyperactivity disorder exposed to psychostimulants, by and large, develop a significant reduction in weight. Similarly, elderly patients with dementias managed with acetylcholinesterase inhibitors develop a decrease in weight.

Conclusion: Although results of several studies concerning psychotropic drugs use in special age categories and several diagnoses are inconsistent across the board, more studies with rigorous methodologies are needed to further clarify the contributions by age and psychiatric diagnoses to weight gain in a psychiatric population exposed to psychotropic medications.

Keywords: Psychotropic drugs; schizophrenia; mood disorders; psychostimulants, acetylcholinesterase inhibitors; weight gain or loss.

1. INTRODUCTION

There is converging evidence that weight gain, overweight and obesity are linked to multiple predictive risk factors, which are psychotropic medications, their doses, duration of use, psychiatric diagnoses, gender and age, and cognitive functioning [1-7]. Other non-psychotropic drug predictive risk factors include genetics, individual sociodemographic, non-psychotic disorders such as depression, anxiety and personality disorders, alcohol and other drug abuse, culture, dietary habits, sedentary life, poverty, cannabis use, and internal (gut microbiota) and external environment [7-21]. When mentally ill patients with major psychiatric disorders are exposed to antipsychotic drugs, all above factors in one way or the other tend to contribute to the economic, social and humanistic burden of weight gain. Such a clinical scenario further exaggerates the risks of developing psychiatric and physical comorbidities, and premature mortality [7,12,22] in related psychiatric population. This paradigm also applies to patients with minor psychiatric disorders exposed to other psychotropic drugs including traditional and newer antidepressants, mood stabilizers, natural antidepressants [6,7]. Antipsychotic medications are often combined with aforesaid psychotropic drugs in a myriad of other mental conditions such as schizoaffective disorder and other psychoses, dementia, resistant depression and bipolar disorders, chronic anxiety disorders, autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), impulse control disorders, drug abuse and personality disorders. Studies have found that antidepressants lead to an increase of weight anywhere between 24-100% of patients, an average weight gain of 0.57 to 1.37 kg/month of treatment [23,24]. Lithium monotherapy or combined with other mood stabilizers or antipsychotic drugs is also associated with significant weight-gain, with some studies reporting a gain of over 10 kg in 20% of patients [25-27]. It should be noted that not all psychotropic drugs lead to weight-gain, and some have even been shown to decrease weight, such as serotonin - reuptake inhibitors (SSRI) during the first few weeks of use [28], felbamate [29], topiramate [30], and acetylcholine cholinesterase inhibitors [31,32], and some natural antidepressants such as Ginkgo biloba [33]. Ginkgo biloba is also reported to increase weight gain [34]. Memantine with glutamatergic and dopaminergic effects is associated both with weight gain and loss; the latter effect was on clozapine-induced weight gain [35,36]. In sum, overweight and obesity are caused by psychotropic medications, and need to be looked at from different perspectives including age and mental illnesses because it is a multidimensional and multifactorial complex problem [37].

The psychiatric medications are prescribed to millions of people, up to 25% of world population of all age groups who have mental disorders of variable severity attributed to multiple risk factors [38-40]. The psychotropic drugs mostly increase weight gain but weight loss as well involving multiple neuroreceptors in the brain [41-43]. Interestingly, Schaefer et al. reported that 83% of people tend to develop non-enduring mental health problems, which means most people will develop a diagnosable mental disorder during lifetime [44]. Psychotropic drugs classified

Table 1. Predictive risk factors of weight gain or loss

Factors	Remarks
Psychotropic drugs	All antipsychotic medications and antidepressants, mood stabilizers, and natural antidepressants increase weight gain [6,7,20]. Cannabis use leads to psychosis, weight gain and poor outcome as found in some studies [14,59].
Psychiatric disorders	Various psychiatric diagnoses including schizophrenia, schizoaffective disorder and related psychotic disorders, Autistic disorders, anxiety, PTSD, severe depression and co-occurring psychiatric conditions [4,16-18.20,]
Initial BMI	Increasing insulin resistance [60,61].
Cognition	Lower cognitive functions associated with weight gain [3]
Genetic	Multiple genes are involved in drug-induced obesity as well as obesity not by psychotropic drugs [13,62,63]
Gender	Females are susceptible to greater weight gain compared to their counterparts [11,20] and parity [64].
Age	Adolescents and adults vulnerable to greater weight gain [2,20] than any other age category
Services	Lack of healthcare clinics concerning overweight and obesity [47].
Physical disorders	Thyroid disease, Cushing disease and other diseases [20, 65-67].
Biological	Neuroinflammation, alteration in neurometabolism and oxidative stress, hormones in the brain, GIT and fat cells, gut microbiota-brain-axis, Modulation of mitochondria [68, 69].
Body constitutions	Genetic endowment and impact on behavior [19].
Dietary habits	Overeating with a craving for different foods and increased calories intake [21].
Insomnia	Sleep less than 5 to 6 hours [70, 71]
Lifestyle	Sedentary, i.e., lack of exercise [72] and high intensity and moderate exercise tends to reduce weight gain [73] and smoking cessation [74].
Geographic region	Influences the type of psychiatric medication prescribed and the psychiatric diagnoses [20].
Environment	Fast food outlets, violence – infested neighbor and pesticides, lack of recreational centers and parks, lack of safe walking and biking routes and food addiction [61,71,75]
Breast-feeding	Breast feeding (initial one year or more) protects children from obesity and allergic diseases [76, 77].
Socioeconomic position	African-American women gain weight associated with cumulative socioeconomic position [78].

Overall antipsychotic medications and biopsychosocial factors in tandem tend to increase weight gain in clinical populations and overweight gain is linked with physical and psychiatric disorders, increased burden and mortality [79-82]

differently are the mainstay of treatment for patients having minor and major mental illnesses [45,46]. In a nutshell, weight gain is associated with a variety of predictive risk factors in a psychiatric population exposed to numerous psychotropics (Table 1), and age and diagnosis are, interalia, the two risk factors that are the focus of this study.

This review critically describes the psychotropic medications prescribed to children and adolescents, adults and elderly people with major to minor psychiatric diagnoses that are associated or not with weight gain, overweight and obesity. In other words, patients at what age and with what diagnosis are highly vulnerable to weight gain or loss when managed by psychotropic medications. We considered the following common psychiatric diagnoses largely managed by antipsychotics, antidepressants, mood stabilizers, psychostimulants and acetylcholinesterase inhibitors; schizophrenia and related psychoses, mood disorders, dementia, and anxiety disorders, ADHD and added a particular note on pregnancy in women with schizophrenia and other psychoses. The secondary objective is to update predictive risk factors of weight gain in general and not limited to the psychiatric population only. The relevance of this review is that this potentially important research avenue with a wide variety of adverse consequences of weight gain or obesity concerning psychiatric medications is ignored in Arabian Gulf countries. The significance of this review underlies the fact that it will bridge the knowledge gaps of mental health professionals and physicians concerning psychotropic treatment and weight gain or loss in relation to age and diagnosis, and all should benefit from this review including patient population and public at large.

2. METHODS

2.1 Search

Boolean operators were used to searching specific data (from 2000 to 2018) on antipsychotic and other psychotropic medications linked or not to weight gain and obesity or weight loss. Electronic searches of three databases and three open access publishing houses (Google Scholar, MEDLINE/PubMed, Ovid SP and Dovepress.com, Hindawi.com and Sciencedomian.org) were conducted using keywords such as antipsychotic medications AND psychotropic drugs AND weight gain AND predictors OR overweight OR obesity OR loss OR psychiatric major diagnoses OR psychiatric minor diagnoses OR children OR adolescents OR adults OR elderly. We arbitrarily divided age into three categories: children and adolescents, adults and elderly and psychiatric diagnosis into major and minor psychiatric disorders. Additional searches were made using keywords such as antipsychotic medications AND other psychotropic drugs OR weight gain OR obesity adverse effects 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 searches were modified whenever needed and compatible with databases.

3. RESULTS

A large number of articles (n=38,087) were retrieved. A quick screening by a single author excluded 32721 articles that did not focus on weight gain associated with typical and atypical antipsychotics and other psychotropic medications. Then two authors (NAQ and SOS) independently reviewed the available data (n= 5366) for extracting relevant articles. Consequently, unrelated articles (n=2082), 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=2492), and irrelevant information (n=98) were excluded from this study. The remaining were 185, which were screened further for eligibility, and those articles which did not focus on antipsychotic medications and other psychotropics concerning weight gain, overweight, obesity and types of antipsychotic medications, age and diagnoses were excluded (n=30). Thus, the total articles included in this narrative review were 155 (Fig.1).

3.1 Weight Gain in Different Populations

3.1.1 Children and adolescents

Patients both different ages and significant diagnoses on psychiatric medications are not immune to weight gain. Weight gain due to second-generation antipsychotics (SGAs) is reported in children and adolescents. McIntyre and Jerrell (2008) found a higher prevalence of obesity or weight gain in the treated cohort with an odds ratio of 2.13. The pre-treatment rates of obesity were 6%; however, newly developed incidence attributed to SGAs was 14%. The risk

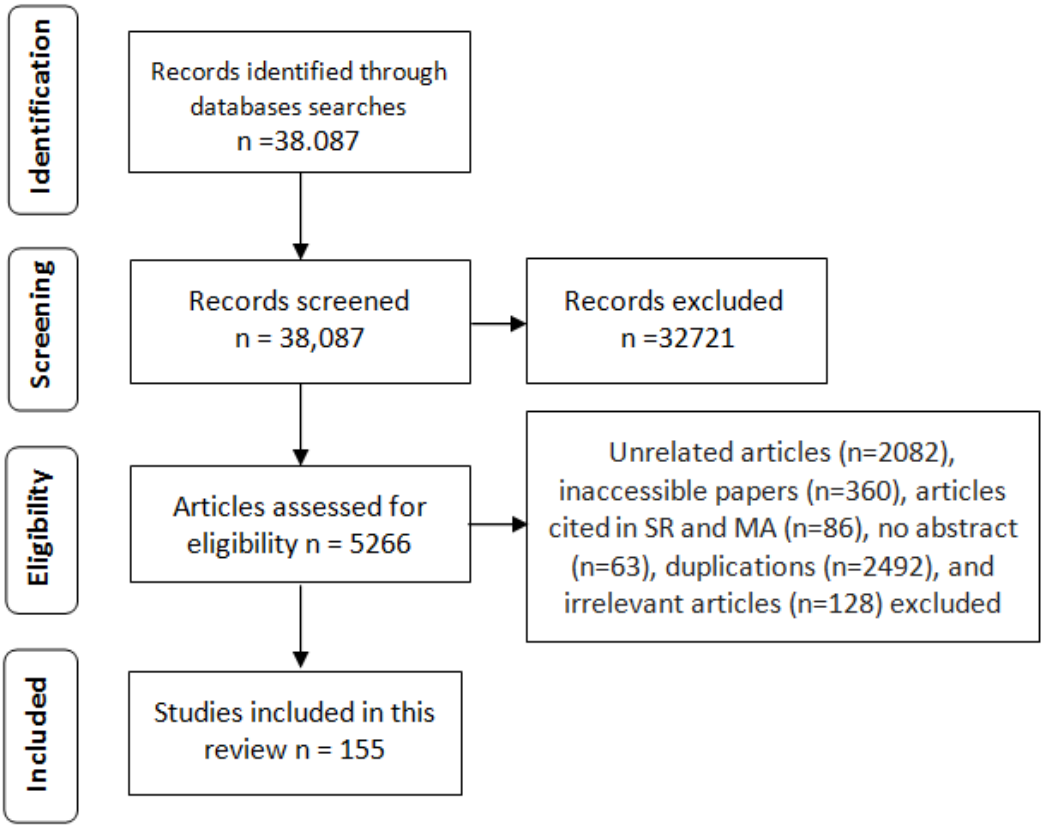

Fig. 1. Prisma diagram summarizing the flow of search results (SR=systematic review & MA=meta-analysis)

was higher for adolescent girls aged 13 and over, and those on multiple antipsychotics [47]. Jerrell and McIntyre (2008) observed similar trends, with overall rates of 20% in antipsychotic-exposed cohort compared with 9% in the general population [48]. Patel et al. determined that 53% of 95 inpatient children on atypical antipsychotics were overweight; however, the authors suggested that the high prevalence of obesity may also be due to geographical and ethnic differences. The lack of a non-psychiatric comparison group makes the interpretation of weight gain difficult in this study [49]. Adolescent girls on multiple antipsychotics had greater weight gain [47-49]. Correll et al. reported weight gain and obesity, hyperlipidemia, insulin resistance, and hypertension matching features of metabolic syndrome in children and adolescents exposed first time to atypical antipsychotics [50].

Briefly speaking, the weight gain could be prevented if metformin is given adjunctively with antipsychotic medications in this particularly vulnerable population, i.e., young age with psychosis [51]. Sample size limits many current pediatric weight control interventions proven to be effective in research trials because these trials excluded participants with psychiatric co-morbidities [52]. Thus, it is important that clinicians treating overweight and obese children and adolescents with psychiatric disorder assess individual, familial, and contextual variables specific to weight in order to prioritize treatment objectives, i.e., opting for a psychotropic drug associated with minimal or no weight gain (a full paper on therapeutic challenges of weight management in psychiatric population including children and adolescents is forthcoming soon).

The prevalence of pediatric obesity is on the rise in both developed and developing countries. Overweight children and adolescents are at an increased risk of developing medical and psychiatric co-morbidities and behavioral

difficulties, and antipsychotic-induced weight-gain further contribute significantly to the public health concerns of obesity [52]. Children and adolescents are known to be at a higher risk for weight-gain associated with antipsychotic treatment [53]. Initial BMI also contribute to weight gain or loss in this population. A recent study looked at antipsychotic-induced weight-gain in a pediatric sample with no previous exposure to antipsychotics and found rapid, substantial weight-gain [50]. Children and adolescents between the ages of 4 and 18 were treated with aripiprazole, olanzapine, quetiapine, or risperidone for 12 weeks and results showed an average weight-gain between 4.4 and 8.5 kg depending on the given antipsychotic drug. The highest and lowest weight gain was observed in patients on olanzapine and aripiprazole, respectively [50]. In a systematic review of the literature, De Hert and colleagues found that children and adolescents (<18 years) with varying diagnoses treated with SGAs developed greatest weight gain with olanzapine and the least with ziprasidone, and younger drug-naïve patients with autistic disorders were highly vulnerable to the greatest weight-gain [54]. Similarly, drug-naïve adolescents with psychosis treated with SGAs found having a significant shift in all parameters toward metabolic syndrome including weight gain except blood pressure [55]. Here the clinical pearl is that clinicians should use antipsychotic with minimal weight gain or weight-neutral in young adolescents with significant psychiatric conditions for preventing weight gain. At the same time, mental health practitioners should take into account the other identified predictive risk factors for weight gain in children and adolescent population [6,7,13,15,56] (Table 1).

ADHD occurs most commonly in children and adolescents, and about 2/3 of its residual symptoms including impairments persist in adults (adult ADHD) and also co-occurs mostly with a variety of other psychiatric disorders [57,58]. Therefore, its treatment becomes very complex and multidimensional. However, almost all psychostimulants tend to produce weight loss in children, adolescents and adults with ADHD (Table 2) but antipsychotic medications, antidepressants and mood stabilizers including lithium when prescribed for the management of its co-occurring psychiatric conditions are definitely associated with weight gain.

3.1.2 Weight gain in adults

Weight gain is a common occurrence in adult population. The prevalence of weight gain or obesity induced by psychotropic medications in adults with major psychiatric disorders is reported to range between 6% and 55% [83-85]. Most studies found the largest weight gain or obesity linked to olanzapine use in patients with schizophrenia and other psychoses [86,87] and the weight gain is considered one of the most commonly reported adverse effects, besides metabolic changes and sexual dysfunctions [88]. Both clozapine and olanzapine with or without antidepressants are associated with the largest weight gain evidenced in several studies [86,87,89]. The association between olanzapine and weight gain, and clozapine with metabolic syndrome is consistent with the findings of a head-to-head meta-analysis concerning adult schizophrenia population [90] and these findings are also replicated by other studies [91]. Leucht and colleagues found that olanzapine, followed by zotepine and clozapine were associated with the highest weight gain in patients with schizophrenia. Leucht et al. suggested that more longitudinal studies of adequate duration are required to assess the distribution and pattern of antipsychotic-related weight gain in adult population with psychoses [91]. Conversely, aripiprazole and ziprasidone have been linked with the lowest weight gain and dyslipidaemia in adult patients with schizophrenia [92,93].Young people with first-episode psychosis (FEP) commencing antipsychotic medications can experience weight gain and obesity, hyperlipidemia, insulin resistance, hypertension and metabolic syndrome, which often develop rapidly within first 12 weeks of antipsychotic medications [94]. Overall, among second generation antipsychotics (SGAs) clozapine and olanzapine are linked to the greatest weight gain and glucose dysregulation in patients with psychoses; iloperidone, paliperidone, quetiapine, and risperidone have a medium risk; and aripiprazole, asenapine, lurasidone, and ziprasidone have a low risk. Young, drug–naïve patients are highly vulnerable to weight gain due to second generation of antipsychotics. Concerning second generation antidepressants (SGAntideps) used in mood disorders, paroxetine and mirtazapine are associated with minimal weight gain, and bupropion causes modest weight loss, and other SGAntideps are mostly weight-neutral with individual variations [89].

Table 2. Psychotropic drugs (psychostimulants) and weight gain variations

Psychiatric medications	CNS stimulants	Weight change	Dosage (mg),	Remark with indications
Psychostimulants				
Methylphenidate	CNS stimulant	Loss/ Neutral	5 mg BD(children> 6 yrs), 5 mg TID in adults, up to 60 mg/day	No weight loss with therapeutic doses? Used in ADHD, ADD, narcolepsy and resistant depression; tabs to be taken before breakfast & lunch to avoid insomnia at night.
Amphetamine	CNS stimulant & abuse heavily	Loss/ Neutral	5-10 mg (>6 yrs of age, 30 mg/day in adults	With therapeutic doses no weight loss? Used in ADHD, narcolepsy and obesity and is a drug of abuse
Dextroamphetamine	CNS stimulant & abuse heavily	Loss/ Neutral	5 to 10 (>6 yrs children) to 60 mg in adults in divided doses	ADHD, narcolepsy, obesity and resistant depression, and optimal dose is 60mg/day
Lisdexamfetamine	CNS stimulant & Abuse of drug, C-II	Loss/ neutral	30 mg (children) to BD (adults),	Prodrug to dextroamphetamine used in ADHD and binge eating disorder and night eating syndrome [56] ; Up to 70mg/day in adults
Atomoxetine	NRI	Loss	40-100 mg (in adults) & Children wt. (<70 kg) 0.5mg to1.4 mg/kg/day	Norepinephrine reuptake inhibitor (NRI), non-stimulant used in ADHD, depression, fibromyalgia and social anxiety disorder
Adrafinil	CNS stimulant	Loss/ neutral	150 to 300 mg, potent stimulant start with low doses	Anorexic& precursor to modafinil; nootropic, over-the-counter (OTC) drug used in elderly to enhance cognition, wakefulness, attention and decreases fatigue and tiredness
Modafinil	CNS stimulant	Loss	100 to 200 mg/day in adults in the morning, anorexic.	Anorexia; only used in persons >17 years for wakefulness in obstructive sleep apnea (OSA), narcolepsy, or shift work sleep disorder and depression. Schedule IV substance. Acts on gamma-aminobutyric acid (GABA)
Armodafinil	CNS stimulant	Loss	150 to 250 mg/day in adults in the morning, anorexic	Used for wakefulness in persons with OSA, narcolepsy, or shift work sleep disorder& depression. Schedule IV substance.

+=mild to moderate weight gain, ++=moderate to marked weight gain; Adolescents and young adults with ADHD often have comorbid psychosis, bipolar disorders, drug abuse, and violent behavior are also treated with antipsychotic drugs that lead to increase in weight (wt.). CNS=central nervous system

FGA used in patients with schizophrenia were reported to reduce BMI, lower waist/height ratio, android fat mass index, and peripheral insulin resistance. Conversely, SGAs were associated with increased BMI, increased abdominal fat and lowering of insulin resistance [95]. Thus, SGAs are associated with increased weight gain compared to FGAs. The results of a couple of meta-analyses evidenced that prolonged exposure (> 38 weeks) to most antipsychotics with exception to amisulpride, aripiprazole and ziprasidone was associated with moderate weight gain. Interestingly, antipsychotic-naive patients showed pronounced weight gain [1,96]. Notably paliperidone probably needing longer exposure is not associated with weight gain among adult patients with schizophrenia [97] and this finding is not supported by other study [22]. Like ziprasidone, aripiprazole is seldom associated with weight loss or gain in patients with psychoses. Lurasidone either monotherapy or adjunctive with mood stabilizers such as lithium, approved for the treatment of bipolar depression and schizophrenia is reported to cause sleepiness and milder weight gain compared to quetiapine [81,98]. Importantly, schizophrenic patients on lurasidone tend to think better cognitively and take part in everyday life compared to placebo or extended-release quetiapine [98]. According to one study, the antipsychotic medications associated with the greatest weight gain in psychiatric patients are olanzapine and clozapine, but the moderate and the least weight gain are associated with quetiapine, risperidone, paliperidone and aripiprazole and ziprasidone, respectively [22]. Typical antipsychotic molindone does not increase weight gain in patients with schizophrenia [99].

Asenapine a relatively newer antipsychotic is associated both with increase in weight gain, up to 0.9 kg weight in adult patients with bipolar disorder and schizophrenia in the first three weeks of treatment and negligible weight gain after three weeks. Thus, asenapine may be less problematic drug concerning metabolic effects [100,101]. Furthermore 19% and 31% patients with mania managed by asenapine and olanzapine developed weight gain, respectively [102]. Asenapine is also reported to reduce weight by 6.6% in a patient with schizophrenia treated with olanzapine [103]. Olanzapine and clozapine are reported to link with food craving and binge eating and, hence, these medications increase the largest weight gain in adult patients with schizophrenia and related disorders [104]. Using 3-year observational data concerning amisulpride, clozapine, olanzapine, quetiapine, risperidone, and oral and depot FGAs, Bushe and colleagues (2012) reported that the mean weight gain was lowest with amisulpride (FGA, 1.8 kg) and highest with olanzapine (4.2 kg). The weight change for all antipsychotics was variable but most rapid during the first 6 months, then very slow weight change over three years period without plateau [105]. The proportion losing ≥7% of their baseline bodyweight was highest with quetiapine (10%) and lowest with depot FGAs (5%). Furthermore, between 7% and 15% of patients moved into an overweight or obese BMI category (≥25). Most antipsychotics were associated with significant (≥7%) weight gain but few led to weight loss from baseline [105]. Overall the results concerning weight gain and loss attributed to FGAs and SGAs in adult population with major psychoses are inconsistent in the literature may be due to methodological differences and underlying predictive risk factors.

3.1.3 Elderly population

Elderly population is vulnerable to lose weight because of aging and accompanying multiple physical and psychological conditions including dementias. According to World Health Organization (WHO), groups of dementia make a public health priority [106] as millions of people especially females suffer from such degenerative diseases of the brain. When elderly psychiatric population either with dementia or carry-on psychoses (residual psychosis) are exposed to psychiatric medications tends not to develop weight gain. However aripiprazole is reported to reduce the weight compared with olanzapine which conversely induced weight gain [39]. According to some researchers, unintentional weight loss is common in patients with dementia attributed to cognitive impairment, poor disease outcome, aging, and other co-occurring physical diseases [107]. Ironically elderly patients with dementias who already have weight loss due to medical diseases, poor dietary habits and inaccessibility to functional foods need adequate weight gain, and this could be achieved by using small doses of olanzapine only for short-term period. In similar context, SGAs especially aripiprazole in small doses is effective and safe in the treatment of behavioral and psychological symptoms associated with dementia, delirium and other psychiatric disorders without producing extrapyramidal symptoms, sedation or weight gain [108,109]. When the use of SGAs is contraindicated in older obese patients with

dementia psychosis or delirium, in that case non-pharmacological approaches such as functional analysis-based interventions, music therapy and analgesics need to be prescribed to high risk elderly patients who are already on multiple medications taking for various diseases [110].

Elderly patients with dementia and carry-on psychotic disorders (residual psychosis) with weigh gain or obesity may benefit from acetylcholinesterase inhibitors (ACIs) such as donepezil and memantine (it is not an ACI but having glutamatergic and dopaminergic effects) that may reduce weight as evidenced in a retrospective controlled cohort study [32] and systematic review [111]. Notably, a proportion of 29.3% of patients given aforesaid ACIs lost weight compared to chronic patients given other medications (22.8%) [32,36]. Females are reported to gain weight (12/2,259, 0.53%) when given memantine and, hence, it is wise not to use memantine (but its use is not contraindicated) in female patients with moderate to severe dementia [35]. Similarly, natural plant-derived ACIs such as galanthamine, quercetin and timosaponin AIII would be better option for the management of male as well as female patients with dementia [112].

3.2 Weight Gain in Specific Conditions

3.2.1 Mood disorders

Mood disorders are common mental health conditions in three age categories affecting about 2% to 5% of population [38-41,113-115]. Mood disorders often present with mania or depression or mixed picture requiring antidepressants as mainstay of treatment. Sometimes antide-pressants are combined with antipsychotic medications and mood stabilizers for the management of patients with bipolar disorders especially manic phases and psychotic depression. Mood disorders are typically chronic conditions involving recurrent episodes with shorter periodicity throughout a patient's life trajectory. In order to reduce the chance of relapse, long-term treatment with antide-pressants is mandatory. Unfortunately, many patients discontinue medication due to their long-term side effects, and one of which is weight-gain [116]. Among individuals with bipolar disorder, Fagiolini and colleagues (2002) found that 68% of the patients were overweight or obese at entry into the study; 32% of the individuals in the study were finally classified as obese as participants tend to weight loss after treatment. Additionally, the number of previous depressive episodes experienced by an individual patient predicted overweight or obesity at study entry [117]. Thus, weight-gain is prevalent in patients with affective disorders, although weight gain or obesity is likely to result from both the effects of the illness as well as treatment with psychotropic drugs. For example, asenapine atypical antipsychotic is reported to increase mild weight gain in patients treated for bipolar I disorder (mania) and schizophrenia [100,101]. Polypharmacy is common in psychiatric practice. Antidepressants, mood stabilizers and antipsychotic drugs are simultaneously prescribed to patients with schizophrenia, schizoaffective disorder, post-psychotic depression, bipolar disorders and other psychoses resulting in weight gain and obesity, which in turn lead to multiple physical conditions and potentially serious clinical consequences [118]. Gao et al. reported subjective and objective reporting of weight gain in patients with schizophrenia and bipolar disorder who were treated with SGAs. Self-awareness (subjective) of weight gain was lower in patients with schizophrenia (likely to have more overweight) compared to bipolar patients, and, hence, objective evaluation of SGAs related weight change in patients with schizophrenia and bipolar disorders should be a routine practice [119]. Patients with bipolar disorder (and schizophrenia) manifest cognitive dysfunction, which is a predictor of weight gain [3]. Clinical wisdom also suggests that patients with schizophrenia and related psychoses develop severe cognitive impairment that weakens their judgment about subjective weight gain. In a study, van Winkel et al. reported that the diagnosis of schizoaffective disorder predicted higher risk for metabolic changes including weight gain, also attributed to higher BMI related to their inherent vulnerability to metabolic disturbances [4].

Lithium carbonate is especially recommended in the management of patients with bipolar I and II and associated with greatest weight gain, up to 10 kg or more in 20% of patients [25,120]. Addition of antipsychotic drugs (SGAs) in bipolar patients further aggravates weight gain especially when patients are receiving lithium carbonate or other mood stabilizer with weight gain propensity [121] such as sodium valproate. Overall individual psychiatric disorders such as depression, anxiety disorders, schizophrenia and schizoaffective disorders, bipolar disorders and

other psychoses and dementia are important parameters to explain the metabolic changes including weight gain in the shadow of psychiatric medications especially traditional antidepressants (amitriptyline), SSRIs, SGAs, lithium and other mood stabilizers [122-124].Patients with bipolar disorder tend to gain weight especially when they are exposed to synthetic antidepressants (FG and SG Antideps), or natural antidepressants, mood stabilizers (lithium, valproate or divalproex) and antipsychotic medications (Tables 3, 4, 5 & 6). Patients with mood disorders certainly need weight management by using appropriate intervention programs (a full paper on therapeutic challenges of weight management in psychiatric population is forthcoming soon).

3.2.2 Schizophrenia

Antipsychotic drugs-FGAs and SGAs-are the main treatment of patients with first episode of psychosis, schizophrenia, and other psychotic disorders and are associated with variable degree of weight gain or minimal weight loss [1,95,96,105]. Long sustained exposure of patients with psychosis to antipsychotics mostly results in weight gain. In such patients with weight gain, switching to antipsychotic associated with less weight gain possibly is of no value. According to some researchers, it is an over-rated idea [1,130]. Antidepressants and mood stabilizers when combined with antipsychotic drugs in patients with schizophrenia and bipolar disorders greatly increase weight gain possibly through synergistic effect that causes multiple potentially negative consequences [118]. In a comparative study, placebo was associated with a mean weight reduction of 0.74 kg, molindone reduced the mean weight by 0.39 kg, and thioridazine increased mean weight by 3.19 kg, clozapine increased weight gain by 4.45 kg, olanzapine increased weight gain by4.1 kg, and 2.92 kg, 2.1 kg and 0.04 kg weight increases with sertindole, risperidone and ziprasidone, respectively. Ziprasidone is also known to produce weight loss [81,131]. Several studies evidenced that typical and atypical antipsychotics tend to produce weight gain or loss in patients with schizophrenia [8,20,81,91,131]. Evidently typical and atypical antipsychotics along with adjunctive use of antidepressants and mood stabilizers tend to produce mostly weight gain in patients with schizophrenia and other psychoses on longterm basis. Conversely patients of psychoses with initial high BMI treated with aforesaid psychotropics initially loss weight [132]. Thus, almost all antipsychotics [1] given to patients for prolonged time tend to produce a variable degree of weight gain mostly in younger patients with psychotic conditions especially schizophrenia and schizoaffective disorders.

3.2.3 Special note on schizophrenia and pregnancy

Pregnancy is a prerogative of women. However women with schizophrenia and other psychotic conditions when get pregnant tend to receive more often less prenatal care and have poorer mental health and parenting difficulties. All these factors lead to many health risks for mothers as well as infants [133,134]. In a prospective comparative study, McKenna et al. followed pregnant women taking atypical antipsychotics, i.e., olanzapine, risperidone, quetiapine, and clozapine and found a greater BMI in the mothers along with therapeutic abortions and lower birth weight in the infants [135]. Furthermore, psychotropic medications induced weight-gain and increased BMI pose many other health risks for pregnant women with pre- and postpartum psychotic disorders including gestational diabetes mellitus, pre-eclampsia, and caesarean delivery. This is also true for obese women without psychiatric disorders. Concerning this issue, Boney et al. found that children exposed to maternal obesity during the course of pregnancy were more likely to have metabolic syndrome. In addition, pregnancies in obese women are more likely to result in stillbirth and neonatal deaths than pregnancies in women of normal weight [136]. Furthermore, maternal obesity during pregnancy adversely affects the perinatal outcome and long-term maternal and child health [137]. In a related study, it was found that women exposed to SGAs began pregnancy with higher BMIs than controls. However, both exposed and unexposed groups experienced similar weight gain during pregnancy [138]. In our view, the weight gain in mentally sound pregnant women is mainly due to fetal development and other metabolic/humoral changes but in mentally unsound women both aforesaid factors operate plus psychotropic drug prescribing in inducing weight gain. Overall, weight-gain or obesity as a result of antipsychotic medication or otherwise can pose additional risks to pregnant women resulting in diverse negative health consequences for the mothers and their infants.

Table 3. Psychotropic drugs (antidepressants) and weight gain variations

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Antidepressants				
Amitriptyline	TCA	Yes +	50-150QD	Moderate wt. gain; chronic use with wt. gain & cardiac side-effects; QD=daily, up to 300 mg in admitted patients
Nortriptyline	TCA	Yes++	3-150QHS	Mild wt. gain, -do-; used in depression, QHS=every bedtime
Protriptyline	TCA	Yes +	5-10 TID	Used in depression
Clomipramine	TCA	Yes+	75-250 divided TID	Mild wt. gain –do-, used in OCD
Desipramine	TCA	Yes+	25-300	Mild wt. gain-do-; QHS=every bedtime
Imipramine	TCA	Yes++	75-200QHS	Moderate wt. gain (3-4 kg wt. gain) -do-used in depression, anxiety and bulimia; inpatients=100-300QHS
Trimipramine	TCA	Yes+	50-150QHS	Moderate wt. gain, used in depression
Doxepin	TCA	Yes+	25-150 QHS	Mild wt. gain, -do-, used in depression and nerve pains
Maprotiline	TCA	Yes+	25-75TID	Mild wt. gain and used in depression
Phenelzine,	MAOI	+/neutral, 15–20 kg wt. gain	15-30TID	Interactions with food having tyramine, used in chronic atypical depression
Tranylcipramine	MAOI	+/neutral	10-20TID	Interactions with food having tyramine, used in chronic atypical depression and anxiety disorders
Isocarboxazid	MAOI	+/neutral	10-30BID	Interactions with food having tyramine, used in chronic atypical depression
Selegiline	MAOI	+/neutral	6-12 QD	In atypical depression, QD=daily
Citalopram	SSRI	+/Neutral	20-60QD	Mild wt. gain(1 to 1.5 kg over 12-month);used in depression, OCD and anxiety disorders
Fluoxetine	SSRI	+/Loss	20-80QAM	Initial wt. loss, 0.35-2–2.5kg; gain on longterm use in depression, anxiety, eating disorders, OCD and premenstrual dysphoric disorder; QAM = every morning
Fluvoxamine	SSRI	Neutral	50-300QD	Used in depression and obsessive compulsive disorder (OCD)
Paroxetine	SSRI	Yes+++	10-50QD	Longterm use++wt. gain (>7%),>other SSRIs; used in depression, anxiety disorders [89]

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Escitalopram	SSRI	Neutral	10-20QD	Mild wt. gain; used in depression, anxiety and OCD
Sertraline	SSRI	+/Neutral	50-200QD	Longterm use mild wt. gain>control group, used in depression and OCD
Desvenlafaxine	SNRI	Neutral	50-400QD	+in NE effects and -appetite linked to wt. loss
Duloxetine	SNRI	+/Neutral	20-60 QD	Duloxetine is linked with insignificant +wt. gain, used in depression, anxiety, and neuropathic pains
Venlafaxine	SNRI	Neutral/-	25-75BID	OR TID with food; used in major depression and anxiety disorders,
levomilnacipran	SNRI	Yes/No		-055kg
Mirtazapine	SGAntidep	Yes++	15-45QHS	+Appetite & wt. gain due to - in NE effects. Doses >15 mg/day more NE effects & results in - appetite and wt. loss. QHS=every night
Bupropion	DNRI	Loss	100-200BID	No effect on 5-HT and H-1 receptors, wt. loss (4.6%) /3–4.4 kg, used in depression & smoking addiction & obesity [89]
Vilazodone	SMs(atypical)	Yes++	10-40QD/daily	Moderate wt. gain, used in depression, QD=daily
Trazadone	SMs(atypical)	Yes++	150-400BID	Moderate wt. gain, used in depression, avoid use of nefazodone (50-300BID) that causes liver toxicity
Vortioxetine	SSRI	+/- due to many reasons	5 to 20 mg/day	Antidepressant used in depression; serotonin receptor modulator and stimulator

+=mild to moderate weight gain, ++=moderate to marked weight gain; SMs=Serotonin Modulators; MAOIs=Monoamine oxidase inhibitors; TCAs=Weight gain (average 1-3 kg) in 10-20% of population (FGAntideps)

Table 4. Psychotropic drugs (natural antidepressants) and weight gain 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	300 mg 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 [125,126].
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 dis. (800 to 1000 mg/day).
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 persons loss weight, Saffron stigmas used in persons with underweight, depression, cancers Alzheimer's dis. MD, & Parkinsonism and other diseases (PMS) [127,128].
5-HTP	Help in 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 comes 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 [129].
Ginkgo biloba	Nootropic	Wt. +/-	40 to 240 mg divided doses	Used (its standardized extract of 24% flavone glycosides and 6% terpene lactones) in elderly with cognitive impairment, anxiety, schizophrenia, TD, and wt. 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 5. Psychotropic drugs (mood stabilizers) and weight gain variations

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Mood stabilizers & anticonvulsants				
Lamotrigine	AE	+/neutral	200 to 400 mg/ day	*Used in depression &bipolar disorder seizures, schizophrenia, schizoaffective disorder, with or without valproate, and conditions with pain.
Gabapentin	AE	+/neutral	900 to 1800 mg	Also used as mood stabilizer, anxiolytic, and pain reliever, dose may be increased
Lithium	-	Yes++	1200-1800 QD	Lithium-induced hypothyroidism ++wt. gain plus its independent effect; acute mania; patient needs monitoring; (level=1 to 1.5 meq/L) [25-27,120]
Topiramate	AE	Loss	200 to 300 mg/ day	Used in seizure disorder and migraine headache prophylaxis [30]
Valproic acid/ sodium valproate	AE	Yes++	250-500TID	Weight gain like divalproex, used in bipolar, neuropathic pain and seizure disorder
Divalproex	AE	Yes++	60 mg/kg/day	Wt. gain of 6 kg and up to 14kg in >70% and 8-59% of patients, respectively
Carbamazepine	AE	Yes+	200-1200BID	1600QD(max. dose/day), wt. gain mild to moderate,
Oxcarbazepine	AE	Yes+	300 to 1200 mg BD	Anti-seizure drug, also used in bipolar disorder (add-on)
Levetiracetam	AE/mood stabilizer		500 to 1500 mg Daily	Used in seizures, bipolar disorder, Tourette syndrome, anxiety disorder, and Alzheimer's disease.
Phenobarbitone (anticonvulsant)	AE,		60 to 80 mg/ day	Used in seizures in children and adults, sleep and anxiety, and has a great potential for abuse
Tiagabine	AE			Also used in anxiety and panic disorders

*+=mild to moderate weight gain, ++=moderate to marked weight gain; AE=antiepileptic; *Potentially fatal immune reactions (hemophagocytic lymphohistiocytosis) to lamotrigine draw FDA black box warning;*

Table 6. Psychotropic drugs (antipsychotics) and weight gain variations

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Antipsychotics				
Chlorpromazine	FGA#	Yes++/Neutral	10-300TID	Wt. gain, observe sedation and EPS, rarely used now
Haloperidol	FGA	Yes+/Neutral	0.5-5B/TID	Mild wt. gain, observe for EPS, used in schizophrenia and delirium tremens
Benperidol	FGA	Yes+	0.25-1.5 mg/day in divided doses	Used especially in antisocial hypersexual behavior. Most potent butyrophenone.
Thioridazine	FGA	Yes+	50-300B/TID	Wt. gain, observe for cardiac effects
Loxapine	FGA,	No wt. change	10-125BID	Dibenzoxazepine class; Wt.-neutral or loss, rarely used in schizophrenia
Amoxapine	SGA	Neutral	200 to 300 mg/ day	Wt.-neutral or loss, rarely used nowadays and is used as antidepressant (act on 5HT and D2 receptors [139].
Molindone	FGA	Yes-	50 to 75 mgQD & max. dose 225 mg/D	Wt. loss [131,140].
Trifluoperazine	FGA	Yes+	1-10BID	Traditional neuroleptics, used rarely.
Perphenazine	FGA	Yes+	4-8TID	Wt. gain or neutral rarely used nowadays
Fluphenazine	FGA	Yes+	1-10TID	Wt. gain or neutral rarely used nowadays
Thiothixene	FGA	Yes+	2-10B/TID	Wt. gain or neutral rarely used nowadays
Pimozide	FGA	+/-	1 to 20 mg QD, usual dose 8/10 mg QD	Antipsychotic, class diphenylbutylpipredine, schizophrenia, Tourette syndrome and tic disorder, delusional disorders
Aripiprazole*	SGA	+/Neutral	10 to 15 mgQD	Mild wt. gain, +appetite or –satiety, 0.5–0.9 kg>placebo, used in schizophrenia, bipolar disorder [141].
Clozapine	SGA	Yes+++	25-900QD	*+appetite or –satiety, 2.4 to 31.3 kg, 1.7 kg/m, >10% gain from baseline, used in resistant schizophrenia
Lurasidone	SGA	+/Neutral	40-160QD	+appetite or –satiety, QD=daily
Iloperidone	SGA	+/1.5–2.1 kg	6-12BID	+appetite or –satiety, similar to risperidone
Olanzapine	SGA	4.2–7.4 kg, Average gain of 12 kg,	10 to 15 mgQD	+appetite or -satiety, and wt. gain up to 90% of patients, average weight gain 2.3 kg/m, used in schizophrenia**,** schizoaffective disorder**,** bipolar disorder**,** and dementia**s** and obsessive compulsive

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Quetiapine	SGA	++4.1to 5.6 kg, 1.8 kg/m	25-375BID	Wt. gain due to +appetite or –satiety, used in schizophrenia, depression, and insomnia (low dose)
Paliperidone	SGA	+/neutral	6-12QAM	+appetite or -satiety, needs long exposure to pts.
Risperidone	SGA	Yes++	2-4BID	Wt. gain, +appetite/–satiety, 0.3–2.6 kg, average wt. gain 1.0 kg/ month, LA=long acting (25-50 mg/2wkly) IM.
Asenapine	SGA	0.9 kg wt. gain	5-10BID	In first 3-month of treatment of schizophrenia & BPD
Ziprasidone	SGA	+/- or Neutral	20-80BID	Mild wt. gain, 0.8 kg/month

*+=mild to moderate weight gain, ++=moderate to marked weight gain; *acts on multiple receptors-dopamine, serotonin, norepinephrine, histamine-1; FGAs- amisulpride, brexpiprazole, cariprazine, sertindole, chlorpromazine, thioridazine, haloperidol, loxapine, molindole, perphenazine and others now used rarely; however they slightly -/+ wt. in psychiatric population compared with SGAs*

3.2.4 Anxiety disorders

Anxiety disorders are second common conditions observed in patients with different age groups in psychiatric practice, and often these disorders co-occur with depression. Common anxiety conditions include obsessive-compulsive disorder, generalized anxiety disorder, post-traumatic stress disorder, several types of phobias, and panic disorders with or without agoraphobia or depression. Patients with anxiety disorders are often managed by anxiolytics, first and second generation of antidepressants, antipsychotic drugs with low doses (off-level use) and various psychotherapies with variable outcome [142-145]. Most anxiolytics usually do not produce weight gain. However like in other psychiatric disorders, antidepressants and antipsychotic medications are associated with weight gain in all age groups of patients with anxiety disorders (Tables 3, 4, 6 & 7).These results should be interpreted in light of a study that reported some psychiatric disorders comorbid with overweight and obesity were mood disorders, anxiety states, alcohol and other drug abuse and several personality disorders [146]. In such clinical scenarios of comorbid obesity or overweight or underweight, psychotropic medications with weight loss trend will be beneficial in reducing weight gain. Most anxiolytics given for short period are not associated with weight gain or loss; however, anxiolytics have an addictive potential and, hence, need to be used cautiously in clinical settings (Table 7).

3.2.5 Dementia

Elderly population with aging process mostly develops reduction in weight and cognitive changes precursor to dementia. People in their midlife (<65 years) with high BMI (>30) are associated with increased incidence of dementia and cardiovascular ailments compared to normal weight persons (BMI 20-25). Late life (>65years) underweight persons, i.e., BMI <20 were reported to develop higher risk of dementia. Conversely persons with overweight, i.e., BMI >25-30 were not associated with increased incidence of dementia. Rather being obese reduced the risk of dementia compared with normal BMI control group, which is called 'obesity paradox' [147]. BMI may influence or be disturbed by the brain structures and functions involved in dementia processes [148]. The adipose tissue associated with BMI changes reduces over the lifespan and impact brain processes including cognitive functioning, judgment and intelligence. As a result, mild cognitive impairment to mild, moderate or severe dementia ensues over a period of time. Lower BMIs accompanied by greater rates of weight decline during the years preceding dementia herald the development of dementia and pathological processes such as production and deposition of amyloid proteins. Risk of dementia is increased, however, by a high BMI during mid-life or in the 5-10 years preceding dementia onset [148]. There are reports of deaths in elderly patients taking first and second generation antipsychotic medications or mood stabilizers (valproic acid and its derivatives) and antidepressants [149,150]. FDA black box warning concerning these medications resulted in their restricted use and reduced adverse events including falls, metabolic alterations and extrapyramidal symptoms in elderly patients with dementia [151,152]. Overall psychotropic drugs associated with minimal weight gain or being weight-neutral should be used in patients with dementia. Several acetylcholinesterase inhibitors-synthetic and natural, and most are associated with weight loss (Table 8) can be used in patients with mild, moderate and severe dementia [153-156]. To control psychological and behavioral symptoms including violent episodes of dementia, the doses of antipsychotics, or antidepressants or stabilizers need to be half of adult dose and given for short-term with continuous monitoring for weight change, metabolic and cardiac effects.

4. DISCUSSION

This narrative review described psychotropic medications induced weight gain in three age categories, i.e., children and adolescents, adults and elderly, and specific diagnoses including schizophrenia, mood disorders, anxiety disorders, ADHD and dementia. The age and psychiatric diagnoses are reported to be the important predictive risk factors of weight gain in patients receiving psychotropic drugs [1-7,20]. Psychotropic medications are common denominators of weight gain when focusing on age and psychiatric diagnoses [7-21], and evidently all antipsychotics are associated mostly with weight gain in patients with major diagnoses [1]. In addition, in-depth knowledge of predictive risk factors of weight gain is important from the perspective of tailoring therapeutic strategies directed towards amenable and modifiable risk factors of weight gain or obesity in mentally ill patients as well as physically ill or healthy

Table 7. Psychotropic drugs (anti-anxiety) and weight gain variations

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Sedative-hypnotics				
Diazepam,	BZD, Sedative class	Neutral	2-10B?TID	Anxiolytics, used for short-period during detoxification from alcohol or other addictive drugs (30-90QD), insomnia, restless legs syndrome, and in seizures
Lorazepam,	BZD	Neutral	0.5-2B/TID	WT. –neutral
Oxazepam,	BZD	Neutral	10-30TID	WT. –neutral
Temazepam,	BZD	Neutral		WT. –neutral
Alprazolam,	BZD	Neutral	0.25-0.5TID	WT. –neutral
Clobazam,	BZD	Neutral		WT. –neutral
Clorazepate,	BZD	Neutral	7.5-30B?TID	WT. –neutral
Estazolam	BZD	Neutral		WT. –neutral
chlordiazepoxide	BZD	Neutral	5-25TID	WT.–neutral
Clonazepam	BZD	Neutral	0.25B?TID	WT.–neutral
Hydroxyzine	Antihistamine as anxiolytic		50-100QID	Used in anxiety, antiemetic, itches, and opioid potentiator
Eszopiclone	NBZD class	Neutral	1 to 3 mg	Non-benzodiazepines sedative- classes cyclopyrrolone and pyrazolopyrimidine; bedtime
Zopiclone	NBZD class	Neutral	3.5 to 7.5 mg	Mainly for insomnia at bedtime
Zolpidem	NBZD class	Neutral	5 to 10 mg QD	Mainly for insomnia at bedtime
Zaleplon	NBZD class	Neutral	5 to 10 mgQD	Mainly for insomnia at bedtime
Buspirone	Anti-anxiety	Neutral	7.5-30BID	Used in GAD, and add-on with antidepressants in depression
Propranolol	Beta-blocker	Yes	10 to 40 mgQD	Used in acute anxiety, panics, migraine and hypertension

+=mild to moderate weight gain, ++=moderate to marked weight gain, GDA=generalized anxiety disorders

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

Psychiatric medications	Class	Weight changes	Dosage (mg), adult dosage	Remark with indications
Synthetic ACIs				
Donepezil	ACIs	Anorectic agents, Wt. loss	5 to 10mg to 20mg QD	Synthetic, reduce wt., and used in early mild to moderate to severe Alzheimer disease (AD) for improving cognition [153].
Galantamine	ACIs	Wt. loss	16 to 24 mg QD	Synthetic, reduce wt., and used in early mild to moderate AD improving cognition [154].
Rivastigmine	ACIs	Wt. loss	3 to 6 mg QD	Synthetic, reduce wt., and used in early AD for improving cognition; Parkinson Dementia
Memantine*	Glutamatergic & DA effect	Wt. gain/loss	5 to 20 mg QD	Used in moderate to severe dementia
Natural ACIs@				
Galanthamine** (Reminyl®)	NACIs	Anorectic agents/wt. loss	16 to 24 mg/day, max. dose	Tried in nerve pains, poliomyelitis, facial paralysis and schizophrenia. Better option for treating dementia (AD) with initial overweight [155]. Maximum dose: 16 to 24 mg/day [157].
Quercetin#	NACIs	+/-	25 to 50 mg QD	Used in many physical diseases and in 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 [158,159].

*+=mild to moderate weight gain, ++=moderate to marked weight gain; (N)ACIs= (natural)Acetylcholinesterase inhibitors; *memantine is not ACI; ** NACI*

population [1-21,62,69,104]. Therefore, we have further updated the risk factors underpinning weight gain in this narrative review [6-7].

Evidently young patients with major psychiatric disorders are most vulnerable to develop overweight or obesity when exposed to psychotropic drugs specifically first and second generation of antipsychotics and antidepressants and mood stabilizers[10,22,26,41,47-55,62,84, 86-98,118-132,145]. There are some inconsistent results; some traditional and atypical antipsychotics are associated with weight loss (negligible weight gain) irrespective of age and diagnoses, and these are ziprasidone [81,131], asenapine [103,100,101], molindone [99] and lurasidone [81,98]. Similarly some traditional and second generation of antidepressants are reported to decrease weight in patients with major depression and bipolar disorders [29-30, 89].Similar trend goes with some mood stabilizers such as topiramate, most natural antidepressants and SNRIs such as venlafaxine and DNRI such as bupropion used in major depression, bipolar disorders, schizoaffective disorder, and depression (melancholia) in elderly population [29,30,89,155]. Concerning older adults and elderly population with carry-on major psychoses (residual psychosis) including schizophrenia and mood disorders and dementia psychosis, antipsychotic drugs are prescribed to them resulting in weight gain and premature death [149,150]. This happens because geriatric population suffers from various comorbid physical diseases and disabilities along with effects of aging and prescribed multiple drugs causing natural weight loss [107]. In addition, elderly patients with dementia without any behavioral disturbances are mainly managed by acetylcholinesterase inhibitors that further decrease their weight due to their anorexic effect [153-156]. Overall mentally ill adolescent, young adult, elderly patients exposed to psychotropic drugs for long time are likely to develop overweight or obesity in order of decreasing frequency and severity but metabolic disturbances, physical comorbidities and adverse events including premature death in increasing frequency in same age categories.

According to this review, children and adults with ADHD mainly managed by psychostimulant medications tend to lose weight [7,160-162] (See Table 2). These patients may infrequently require antipsychotic drugs for the management of impulsive violent episodes linked with mental subnormality or other co-occurring psychiatric disorders for short time with minimal or without gaining weight. Like ADHD, children with autistic spectrum disorders require multidimensional interventions including antipsychotic medications and antidepressants and non-pharmacological approaches and antipsychotic medications tend to increase weight gain in patients with autistic disorders [54,163]. The patients with age below 18 also manifest symptoms suggestive of various anxiety disorders including obsessive compulsive disorder (OCD) and treated by first and second generation of antidepressants, antipsychotics and benzodiazepines, and develop mild to moderate weight gain with the first two groups of medications [142-145]. Benzodiazepines and hypnotics used mainly for very short period in sleep disorders are not associated with weigh gain; however, these medications have great potential for abuse and addiction and need to be cautiously prescribed in clinical settings [7,164]. In nutshell, age below 25 and various diagnoses specifically major psychiatric conditions including first episode psychosis, schizophrenia, schizo-affective disorder, depression and bipolar disorder I and II treated by psychotropics are linked with the greatest weight gain.

Evidently, there are a myriad of predictive risk factors underpinning weigh gain and age and psychiatric diagnoses are two of them [1-21,37, 59-72,104]. The weight gain in the background of psychotropic medications is mediated by biological, psychological, social, cultural and environmental risk factors. Thus weigh gain in psychiatric population is heterogeneous and multidimensional in nature. The contribution of each risk factor to weight gain in psychiatric patients managed by psychotropic drugs is variable. This review calls for precise assessment of variance concerning individual risk factor of weight gain in psychiatric population exposed to psychotropic medications using sophisticated research methods and measurement tools.

This narrative review has some limitations. The most important of them are selection and publication biases. Another caveat is that this is not a comprehensive and systematic review of weight gain in light of age and psychiatric diagnoses. This review has multiple strengths. This is the first review of psychotropics-induced weight gain with a focus on age and psychiatric diagnoses in Saudi Arabia. This review updated the predictive risk factors of weight gain associated with psychotropic prescribing in mentally ill patients 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

In summary, young age and major psychiatric disorders are contributors to overweight and obesity in light of psychotropic prescribing of antipsychotics, antidepressants and mood stabilizers. Elderly people with significant psychosis including severe depression and dementia with behavioral problems requiring antipsychotic medications and antidepressants are likely to gain minimal weight gain, but concurrent prescribing of antidementia acetylcholinesterase inhibitors and other drugs for comorbid physical diseases most likely tend to nullify the weight gain. Evidently, a large number of predictors of weight gain operating simultaneously in psychiatric population make it very difficult to inform which of the predictor contribute most to the weight gain.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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