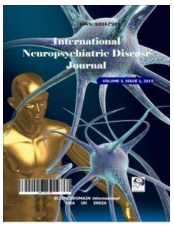

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# Clinical and Biological Perspectives of Non-antipsychotic Psychotropic Medications and Weight Gain

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***Authors' contributions***

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

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## ABSTRACT

**Background:** Non-antipsychotic medications are frequently used in psychiatric patients with a variety of disorders. However, there is limited research concerning weight gain and metabolic changes in mentally ill population.
**Objective:** This review aimed to critically describe non-antipsychotic psychotropic (NAP) medications and their impact on weight in the psychiatric population. Also, the biological and psychosocial mechanisms of weight gain or loss attributed to NAP and antipsychotic medications are also described in this paper. Methods: Electronic searches (2000-2018) of PubMed, Medline,

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and Google Scholar were conducted using Boolean operators and keywords. Large numbers of articles were retrieved, and two independent reviewers retained 85 articles published in English peer-reviewed journals.

**Results:** Only a few non-antipsychotic psychotropic medications prescribed to psychiatric population produce overweight and some metabolic changes, but most of them cause minimal weight gain, or they are weight-neutral and weight-loss. Variable results are reported concerning biological mechanisms attributed to genetics, individual vulnerability, diagnosis and pharmacology of antipsychotic and non-antipsychotic psychotropic medications.

**Conclusion:** Unlike antipsychotic medications, non-antipsychotic psychotropic drugs cause the least weight gain mediated by multiple mechanisms, but mostly without meeting salient features of metabolic syndrome. Further studies are needed to explore metabolic changes and underlying mechanisms concerning psychotropic drugs given chiefly to mentally ill patients around the world.

*Keywords: Psychotropic medications; weight gain; the biology of weight gain; metabolic changes.*

## 1. INTRODUCTION

Weight gain in psychiatric population is a public health problem. There are a large number of risk factors and predictors of weight gain, obesity and metabolic syndrome in patients with severe mental illnesses (SMIs) including bipolar disorders and major depression, drug-induced psychosis, and psychosis associated with medical conditions managed by antipsychotic medications [1]. Non-antipsychotic psychotropic (NAP) drugs tend to cause weight gain or loss in patients with SMI, anxiety disorders, bipolar disorders, major depressive episode and other related disorders but least likely to produce metabolic changes, physical, psychological, and social consequences including premature death. NAP medications are prescribed to millions of mentally ill patients around the world. Schizophrenia affects approximately 1% of world adult population [2]. Depression affects about 2.7% to 5.2% of child and adolescent population [3,4]. The prevalence of the pediatric bipolar disorder is 1.8% in participants up to 21 years of age [5]; indeed some of these participants might have developed bipolar depression/mania earlier than 21 years of age. Bipolar disorder is also increasingly common in youth (between the ages of 15 to 24 years) [6]. There are many other mental disorders such as anxiety disorders, autistic spectrum disorders, bipolar I & II and major depression, schizoaffective disorders, delusional disorders, addictive disorders and dementia and others including physical disorders comorbid with various psychiatric disorders are managed by NAP medications, which are often combined with antipsychotic medications. Overall, NAP drugs are prescribed to larger patients of all age groups including children and adolescents, youths, adults and elderly, and are liable to cause weight gain or loss.

The standard weight, weight gain, and grades of obesity are good guide to assess and monitor the increasing weight in mentally ill patients given antipsychotics [1] and NAP medications. The average body weight varies between 57.7 kg to 87.7 kg. The overweight Asian adult population constitutes 24.2%, out of 2.82 billion. The overweight adult population of North America is 73.9%, out of 263 million. The adult population globally is 4.63 billion with an average weight of 62 kg, and overweight population constitutes 34.7% of the total population [7]. The weight gain is defined as a mean weight gain of 1.9 kg to 20.1 kg. Body mass index (BMI, formula = weight in kg/square of height in meters), a simple weight measurement tool for both adult genders is used to classify normal weight (BMI= 18.5 to 24.9) overweight (BMI = 25 to 29.9) and obesity (BMI 30 to 39.9). Patients with a BMI above 40 are considered extremely obese [8]. Abdominal obesity is defined as waist circumference >102 cm in men or >88 cm in women [9]. Overweight and obesity, in general, are associated with cardiovascular diseases, diabetes, musculoskeletal disorders, cancers, neurological diseases including stroke, disabilities, impairment of social and body functioning, several psychological conditions and premature mortality [9]. Similarly, potential adverse consequences are found in a psychiatric population having overweight and obesity induced by psychotropic drugs especially antipsychotics, antidepressants and mood stabilizers.

Generally speaking huge data concerning weight gain or loss by NAP drugs are available in the Western world. In Saudi context, Alsanosy (2017) described metabolic syndrome caused by antipsychotic medications [10] and Alfadda developed clinical guidelines for the management of obesity in the adult population

[11] but without any reference to mentally ill people. However, no data are available regarding weight gain or loss induced by NAP medications. Therefore, this review aimed to critically describe NAP medications causing weight gain or loss in psychiatric population, from children to elderly patients, along with underlying biological mechanism of actions and effects concerning NAP and antipsychotic medications. The significance of this review is that it will bridge the knowledge gap of mental health professionals, physicians, and paramedical staff who routinely deal with NAP medications. This critical review also may guide them for choosing appropriate NAP medication during consulting a patient with severe mental illness (SMI) and other less severe disorders such as anxiety disorders. We have submitted our paper concerning antipsychotic medications and weight gain and, hence, our focus is now on NAP medications and weight gain or loss in clinical population.

## 2. METHODS

### 2.1 Search

Boolean operators were used to search specific data (from 2000 to 2018) on non-antipsychotic psychotropic medications associated with weight gain, overweight, obesity and weight-neutral or weight-loss. 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 using keywords such as psychotropic medications AND weight gain OR overweight OR obesity OR biological mechanisms OR psychiatric disorders OR severe mental illness. Additional searches were made using keywords such as weight gain OR overweight OR obesity AND tricyclic antidepressants OR selective serotonin receptor inhibitors OR monoamine oxidase inhibitors OR serotonin-norepinephrine reuptake inhibitors OR mood stabilizers OR benzodiazepines OR psychostimulants OR cholinesterase Inhibitors OR natural antidepressants for retrieving pertinent articles published in peer-reviewed scientific journals. In addition, case reports, case series, editorials, cross-sectional and case controlled studies, observational studies, randomized clinical trials (RCTs), systematic reviews and meta-analysis, which focused on psychotropic medications induced weight gain, overweight, obesity and weight-neutral and weight-loss and underlying mechanisms of antipsychotic and NAP drugs were considered in this review. The searches and keywords were modified whenever needed and compatible with databases.

## 3. RESULTS

### 3.1 Search Results

A large number of articles (n=32,542) were retrieved. A quick screening by a single author excluded 29,357 articles that did focus only on weight gain associated with typical and atypical antipsychotics. Then two authors (NAQ and DSD) independently reviewed the available data (n= 3185) for extracting relevant articles. Consequently, unrelated articles (n=1224), inaccessible papers because of high price tag (n=304), articles cited in systematic reviews and meta-analysis (n=312), no abstract available (n=72), duplications (n=1125), and irrelevant information (n=45) were excluded from this study. The remaining were 103 articles, which were screened further for eligibility, and those articles which did not focus on NAP medications concerning weight gain, overweight, and weight loss were excluded (n=18). Thus, the total articles included in this narrative review were 85 (Fig. 1).

### 3.2 Tricyclics, MAOI, SSRIs and Weight Gain

Antidepressants are commonly used in psychiatric patients along with many physical conditions comorbid with mental health problems. First generation antidepressants are used in diverse mental disorders including anxiety disorders. Tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, imipramine, desipramine, maprotiline and monoamine oxidase inhibitors (MAOIs) such as selegiline, rasagiline, isocarboxazid, phenelzine, tranylcipramine and moclobemide cause some weight gain in clinical population with therapeutic doses; the latter are used in atypical depression and have interaction with certain foods containing tyramine [12-14]. Mirtazapine (tetracyclic, atypical antidepressant) causes weight gain during first 4 weeks of treatment with dose titration and then sustained in depressed patients presenting with prominent insomnia [12,13]. Bupropion is chemically unrelated to tricyclic, tetracyclic (mirtazapine) and selective serotonin reuptake inhibitors (SSRIs) but closely resembles that of diethylpropion. Bupropion use is reported to cause weight loss in patients with depression [13,14]. Unlike SSRIs, nefazodone

and bupropion are less likely to produce weight gain [12]. Bupropion is also used in nicotine addiction [15] and sexual dysfunctions induced by SSRIs with good outcome [16]. Most antidepressants including mirtazapine, vilazodone and vortioxetine are linked with sexual dysfunctions. Bupropion has one major disadvantage of inducing seizures attributable to variations in doses, root of administration, and individual vulnerability [17,18]. Patients with atypical unipolar depression characterized by hyperphagia and oversleep develop overweight, and TCAs and MAOIs prescribing to such patients results in additional overweight [19,20] (Fig. 2). In sum, almost all traditional antidepressants produce weight gain in depressed patients with a risk to cause cardiac effects but bupropion a new generation antidepressant tends to induce weight loss.

Selective serotonin reuptake inhibitors are second generation antidepressants that have nearly replaced the use of traditional antidepressants. Most SSRIs including sertraline, citalopram, escitalopram, fluoxetine and fluvoxamine are least likely to cause weight gain among health users with depression and anxiety disorders. Conversely, paroxetine (SSRI) causes weight gain with therapeutic doses in patients with major depression during initial and long-term treatment; however, weight loss is also reported in some patients. Citalopram with initial low doses tend to cause weight loss (rarely small weight gain) due to its appetite suppressant effect, nausea and diarrhea [12-14]. Furthermore weight gain sometimes produces depression in some people with high BMI and treatment of depression lead to weight loss in such patients [21]. Sertraline induces weight gain by fluid retention and increased appetite. Paroxetine sedative effect impacting mobility or physical activity leads to weight gain. Notably not all patients taking SSRIs tend to gain weight but some of them loss weight. In fact weight gain or loss also varies with gender, individual vulnerability [12-14,21] initial BMI, culture, dietary habits and other life style factors (Fig. 2). According to a study, SSRIs induce paradoxical weight gain based on the interaction of 5-hydroxytriptamine (5HT) with multiple receptors and subtle pharmacologic differences within the group of antidepressants and in addition, both the neurobiology of depression and recovery from it might be a major contributing factor to individual response to these drugs, weight gain or loss [22]. The mechanism underlying SSRIs related weight gain is mediated by hypothalamic–pituitary–adrenal (HPA) axis activation, and is disturbed in stressful conditions, obesity and metabolic syndrome. The HPA axis disturbance is reported to be the best understood shared pathophysiological pathway underpinning major depression [20].

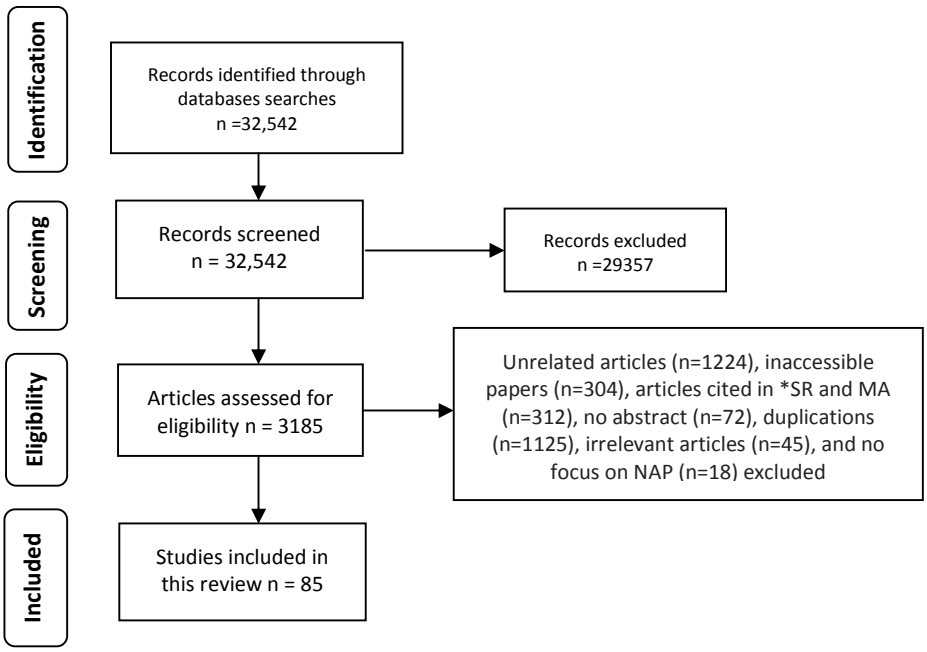


**Fig. 1. Prisma diagram summarizing the search results (*SR=systematic review & MA=meta-analysis)**

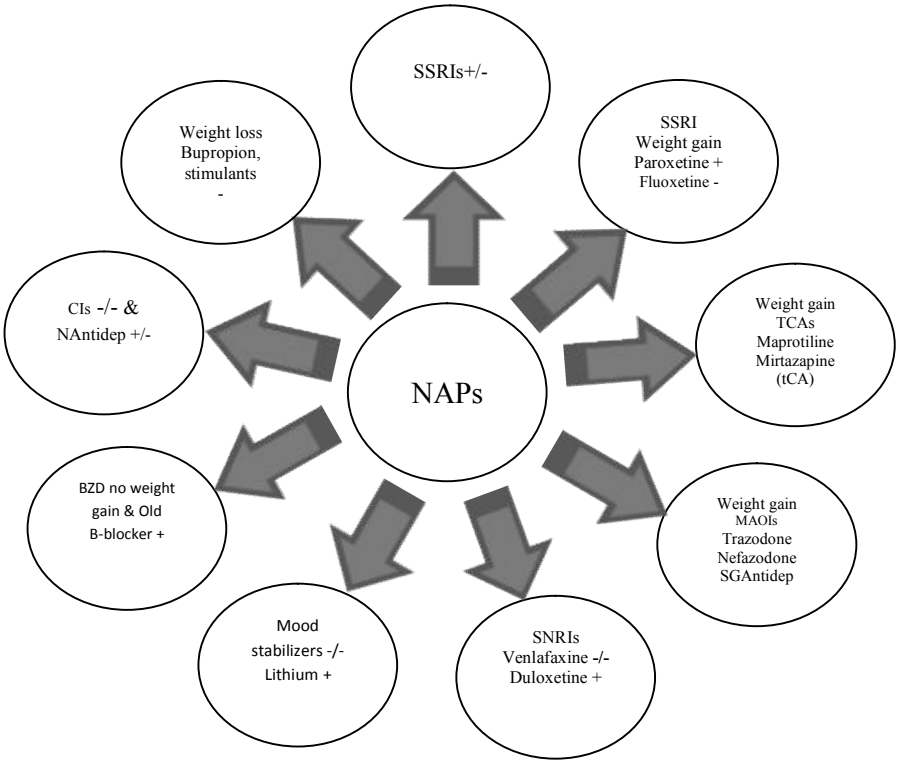


**Fig. 2. Shows NAP drug and weight gain or loss (+/-), weight-neutral (-/-), weight gain (+) and weight loss (-), and CIs=Cholinesterase Inhibitors)**

### 3.2.1 Antidepressants and timeline of weight gain

First generation of antidepressants (FGAntideps-TCAs & MAOIs) mostly cause weight gain in patients with depression and anxiety disorders on short- and long-term basis. Second generation of antidepressants (SGAntideps, SSRIs) use has been associated with weight gain or loss during acute treatment but long-term risk of weight gain [12-14,20,22]. The long-term effect of SSRI treatment on bodyweight is contentious because of multiple confounding factors and research methods. According to Lee and colleagues (2016) increasing exposure to antidepressants might be a contributory factor to the rapidly growing obesity [20]. Another study reported that amitriptyline, mirtazapine, and paroxetine cause a greater risk for weight gain during longterm treatment [14]. On the contrary, both fluoxetine and bupropion causes weight loss, the former in acute phase. Other antidepressants have neither transient nor negligible effect on body weight in the shortterm treatment. Each antidepressant may vary greatly depending on an individual's characteristics but weight gain may become evident on longterm use [14]. Overall use of most antidepressants (SSRIs) in patients with depression and anxiety disorders are associated with unwanted weight-gain on longterm basis.

Furthermore, studies have found that most antidepressants variably lead to an increase of weight in about 24% to 100% of patients, with a mean weight-gain of 0.57 to 1.37 kg per month of treatment [12,23]. Lithium carbonate therapy used in bipolar I & II patients switching between mania and depression is also associated with significant weight-gain, with some studies reporting a gain of over 10 kg in 20% of patients [24]. In nutshell, most of the antidepressants from all classes are associated with weight gain on longterm treatment and only few links to initial weight loss (fluoxetine) in patients with mood and anxiety disorders (Fig. 2). Arguably patients with initial overweight and obesity (initial high BMI) determine whether or not they will loss or gain weight while receiving antidepressants (Tables 1 & 2).

**Table 1. Antidepressants and weight changes in clinical population**

| Medications | Wt. gain | Wt. loss | Remarks |
|---|---|---|---|
| Paroxetine | Yes | No | More wt. gain than sertraline and fluoxetine |
| Sertraline | Minimal | No | SSRI, wt. gain more than control groups |
| Venlafaxine | No | No | SNRI Extended Release (SGAntidep) |
| Desvenlafaxine | No | No | SNRI |
| levomilnacipran | Yes? | Yes | SNRI, -0.55 kg |
| Duloxetine | Yes, 0.61 kg | No | SNRI, no significant weight gain |
| Bupropion | No | Yes, 3–4.4 kg | DNRI (SGAntidep) |
| Fluoxetine | Yes | Initially yes | Initial weight loss, 0.35 kg and 2–2.5 kg gain on long-term use |
| Citalopram | 1 to 1.5 kg | No | Over 12 months |
| Escitalopram | Yes, 1.83 kg | No | SSRI |
| Vortioxetine | No | No | SSRI |
| Fluvoxamine | No | No | SSRI |
| Trazodone | Yes | No | SGAntidep (SSRIs) |
| Nefazodone | Yes | | SGAntidep (SSRIs) |
| Vilazodone | Yes | No | SGAntidep (SSRIs) |
| Mirtazapine | Yes | No | SGAntidep, More weight gain compared with Fluoxetine, paroxetine and citalopram |
| Imipramine* | 3-4 kg weight gain | No | TCA, chronic effect (weight gain) with cardiac side effects |
| Amitriptyline* | Minimal | No | TCA, chronic effect (weight gain) with cardiac side effects |
| Nortriptyline* | Minimal but >amitriptyline | No | TCA, chronic effect (weight gain) with cardiac side effects |
| Tranylcypromine | 15–20 kg weight gain | No | MAOI |

**Weight gain (average 1-3 kg) in 10-20% of population (FGAntideps), SNRI = Serotonin Norepinephrine Reuptake Inhibitors, DNRI = dopamine norepinephrine reuptake inhibitor, Mostly weight gain is associated with therapeutic doses of antidepressants*

### 3.3 Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

This class of antidepressants is mainly used in depression and depression with anxiety symptoms (mixed state) with good outcome. SNRIs probably cause lesser longterm weight gain compared to SSRIs. Venlafaxine (SNRI) is reported neither to cause weight gain nor weight loss but duloxetine (SNRI) tends to produce low weight gain. These findings suggest a lesser iatrogenic weight gain side effect profile of SNRIs compared to SSRIs and atypical antipsychotic medications [13,25]. Desvenlafaxine and levomilnacipran are other two newer SNRIs, and individual SNRIs are recommended mainly for the treatment of depression, anxiety disorders and panic attack, and cause no weight gain. In a review, Deardorff and Grossberg (1914) found no significant weight gain with levomilnacipran, vilazodone and vortioxetine [26]. In an open label study with 48 weeks extension period, levomilnacipran was found to reduce weight (mean= -0.55 Kg) and one patient discontinued study due to weight gain [27]. In summary, most SNRIs are weight neutral except duloxetine that causes weight gain (Tables 1-2).

### 3.4 Mood Stabilizers and Weight Gain

Mood stabilizers most commonly used as an adjunctive in bipolar disorder, schizophrenia, neurological disorders such as seizure disorders, and pain disorders. Lithium is one of them which standalone causes maximum weight gain and other adverse effects on longterm treatment such as hypothyroidism and toxic manifestations with higher doses including coma and death [28]. Lithium also induces polyuria and polydipsia, which are due to its blockade of antidiuretic hormone. Lithium related weight gain partially attributed to intake of high calorie fluids in response of polydipsia. Weight gain interferes in compliance to lithium in patients with mood disorders. Other studies also reported that lithium causes weight gain of over 20 pounds

**Table 2. Antidepressant classes and weight changes**

| Antidepressant Classes | Medications | Weight change |
|---|---|---|
| Selective serotonin reuptake inhibitors (SSRIs)# | Sertraline, citalopram, escitalopram, paroxetine, Fluoxetine, vortioxetine, fluvoxamine | Paroxetine causes weight gain but others minimal Weight gain |
| Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)# | Venlafaxine, desvenlafaxine, duloxetine | Duloxetine is associated with mild weight gain but others are weight neutral |
| Dopamine Norepinephrine reuptake inhibitors (DNRIs) | Bupropion | Weight loss |
| Serotonin Modulators# | Trazodone, nefazodone*, vilazodone | All are weight neutral |
| Tricyclic antidepressants (TCAs)** | Amitriptyline, nortriptyline, imipramine, doxepin | All induce weight gain |
| Monoamine oxidase inhibitors (MAOIs)** | Phenelzine, tranylcipramine | Weight gain/neutral |
| Atypical# | Mirtazapine | Mirtazapine is linked with weight gain |

**Causes hepatotoxicity withdrawn from the market, #SGAntidep, **FGAntidep linked with cardiac effects, and MAOIs interactions with food containing tyramine*

**Table 3. Mood stabilizers and weight changes in clinical population**

| Medications | Wt. gain | Wt. loss | Remarks |
|---|---|---|---|
| Valproic acid | Yes | No | Weight gain like divalproex |
| Divalproex | Yes, 6 kg and up to 14kg | No | In >70% and 8-59% of patients, respectively |
| Lamotrigine | Yes, 0.6 kg | Yes, 2 kg | Neutral drug |
| Carbamazepine | Yes | No | Up to 15 kg |
| Oxcarbamazepine | Yes | No | 15% children became obese |
| Lithium | Yes 6.3 kg to 10kg or more | No | Used in bipolar 1 disorder |
| Topiramate | No | Yes | |
| Felbamate, | No | Yes | Antiepileptic |
| Asenapine | During initial treatment but negligible (0.9 kg) on longterm | Yes | Antipsychotic, bipolar disorders, schizophrenia spectrum disorders |

among 20% of patients with bipolar disorders [13,28]. Lamotrigine, a mood stabilizer and antiepileptic prescribed for bipolar patients with depression causes weight loss. Weight gain may be due to bipolar disorder itself and increase appetite and disturbed individual metabolism. Notably, after treatment when patient improves, this weight gain decreases. Divalproex (derivative of valproic acid) prescribed for patients with bipolar, migraine and seizure disorder is associated with weight gain [13,29]. In a naturalistic study, surprisingly patients with bipolar disorders on mood stabilizer with add-on atypical antipsychotics did not develop weight gain compared to the control group not received antipsychotics medication. Instead female sex, young age, low-baseline BMI, and euphoric episodes were associated with clinically significant weight gain [30]. Evidence suggest that not all psychotropic drugs lead to weight-gain: SSRIs (fluoxetine, appetite suppression and initial titration with low doses) causes weight loss during the first few weeks of use [31]; antiepileptic felbamate causes weight loss in about 75% of patients with intractable epilepsy [32]; and topiramate [33] tend to cause weight loss. Asenapine an antipsychotic and mood stabilizer has mixed results regarding weight gain (negligible to 0.9 kg; 19% vs. 31% [with olanzapine]) in patients with bipolar disorder I and schizophrenia and weight loss in 6.6% of patient treated with olanzapine during initial phase of treatment [34-36]. Like carbamazepine and valproate, oxcarbamazepine tend to cause significant weight gain in about 15.4% of children [37]. In summary, like patients with schizophrenia and mood disorders, most patients with seizures and behavioral problems, chronic pains and migraine receiving mood stabilizers tend to lose weight with exceptions to both valproic acid and lithium linked to weigh gain (Table 3). The detailed description of mood stabilizers and their mechanisms of action along with psychotropic effects are available here [38,39].

### 3.5 Benzodiazepines and Weight Changes

Benzodiazepines (BZDs) are commonly used in clinical psychiatric practice especially in anxiety spectrum disorders, and lifetime prevalence use is up to 75% [40]. Benzodiazepines such as chlordiazepoxide, diazepam, alprazolam, clobazam, clonazepam, clorazepate, and triazolam are used for anxiety disorders and non-benzodiazepine such as eszopiclone, zopiclone, zolpidem, zaleplon are used for insomnia in psychiatric practice; none of them is associated with weight gain (Table 4). However these drugs have a great potential for causing abuse and withdrawal syndrome [41]. Therefore, newer drugs were developed for the management of depression and comorbid sleep disturbances which are agomelatine, ramelteon, and tasimelteon and suvorexant with safe clinical profile [41]. Unlike other BZP, lorazepam, temazepam and oxazepam (quick acting BZPs) are metabolized by phase II conjugation which is preserved in chronic liver disease making them first choice sedatives in psychiatric patients with impaired liver functions. Another anti-anxiety medication is buspirone that also does not induce weights gain [42]. Sometimes patients with anxiety disorders mainly manifesting cardiovascular symptoms such as palpitations are prescribed old generation of beta blockers (atenolol & metoprolol) which are reported to cause weight gain. However, weight gain is not reported with newer beta blockers such as carvedilol in diabetic and hypertensive patients [43]. This finding is not supported by other research in which a number of drugs including

newer beta blockers used in patients with hypertension are liable to increase weight gain [44]. Overall, all benzodiazepines and non-benzodiazepines hypnotics are not associated with weight gain or metabolic syndrome but have liability to cause potential abuse, falls in elderly, rebound anxiety and discontinuation syndrome [41,45] and, hence, need to be cautiously prescribed to psychiatric population.

### 3.6 Psychostimulants and Weight Changes

Psychostimulants, Schedule II controlled substances associated with addiction liability, are reported to cause weight loss. Psychostimulants such as methylphenidate, mixed amphetamine salts, amphetamines, atomoxetine (long-acting with reduced potential for abuse), modafinil, and armodanafil are used mainly in children with ADHD and sleep disorders such as narcolepsy tend to cause appetite suppressant (anorectic effect) and weight loss. The appetite suppressant and weight loss does not occur at recommended therapeutic doses of these psychostimulants [42,46]; however, this claim is strongly contested by some researchers. Pemoline, another psychostimulant that also induces weight loss, is not used presently because of its fatal hepatotoxic effect. Another CNS stimulant lisdexamfetamine (prodrug of d-amphetamine) associated with weight loss is prescribed to patients with binge eating disorder and ADHD but has very low potential for abuse, and contraindicated in patients with cardiac disease [47]. However, use of psychostimulant in children with ADHD tends to reduce the risk of developing substance use disorder (SUD) in adults. Patients with ADHD taking psychostimulants are at a greater risk to develop SUD and violence predicted by co-morbid antisocial personality disorder, bipolar disorder, an eating disorder, severe ADHD and dropout of school [48]. Adults with ADHD treated with psychostimulant also are vulnerable to develop SUD and psychosis [46,48]. At symptom level, methamphetamine (strong stimulant) addiction is associated with more positive symptoms of psychosis than cocaine (stimulant) combined with methamphetamine [49] and certainly both drugs used for recreational purpose and cause weight loss are not categorized under psychotropic medications. Overall, all psychostimulants causes weight loss but have more disadvantages than advantages and, hence, should not be used among those patients with ADHD characterized by high risk factors for developing SUD and other psychiatric disorders. However psychostimulants may be tried in psychiatric patients with overweight or obesity induced by psychotropic drugs including antipsychotic medications (Table 4).

### 3.7 Cholinesterase Inhibitors and Weight Changes

Acetylcholinesterase inhibitors (ACIs) such as donepezil, galantamine, rivastigmine act on CNS and used in Alzheimer's disease (AD) and other dementias may cause weight loss because of anorectic side effect as found in a retrospective controlled cohort study [50]. A proportion of 29.3% of patients given aforesaid ACIs lost weight compared to chronic patients given other medications (22.8%) [50]. Tacrine, other centrally acting ACI is withdrawn from the market due to hepatotoxicity and bad taste. Memantine with glutamatergic (NMDA receptor) and dopaminergic effects used in moderate to severe dementia is weight-loss medication as reported in a single patient with schizophrenia having overweight due to antipsychotic medication [51] but weight-gain is also reported with memantine (in females; 12/2,259, 0.53%) [52]. Cholinesterase inhibitors (CIs) are reported to have variable symptomatic therapeutic effects, and induce nausea, vomiting, anorexia and weight loss, insomnia, and urinary tract infection [53,54]. In another systematic review, patients of Chinese decent with AD, vascular and mixed dementias reported cognitive benefit with rivastigmine, galantamine and donepezil; however, anxiety, mood and psychotic symptoms were not affected, and in some cases worsened [55]. It is speculated that anorexia and weight loss as an adverse effect of these medications may be used for reducing weight gain in psychiatric patients treated by psychotropic drugs. In the same context, natural plant-derived CIs such as galanthamine, quercetin and timosaponin AIII with good safety profile would be better option for the treatment of dementias [56]. In summary, ACIs (Table 4) that increase brain level of acetylcholine at the synapses are used in mild, moderate and severe AD with cognitive improvement; however, they have a variety of adverse effects including cardiac needing electrocardiogram [53] and wider details of ACIs are available here [53,56,57].

**Table 4. Summary of psychotropic drugs and weight gain/loss**

| Psychiatric medications | Weight changes | Remark |
|---|---|---|
| **Antidepressants** | | |
| Amitriptyline | Yes + | TCA, more weight gain than other TCAs |
| Bupropion | Loss | DNRIs, no effect on serotonin and histamine-1 receptor, little weight gain or even weight loss (4.6%) in short- and long-term studies |
| Citalopram | Minimal/ Neutral | SSRIs |
| Clomipramine | Yes+ | TCA |
| Desipramine | Yes+ | TCA |
| Desvenlafaxine | Neutral | SNRIs, increase in NE effects and decreased appetite causes of weight loss |
| Doxepin | Yes+ | TCA |
| Duloxetine | Neutral/minimal | SNRIs |
| Fluoxetine, | Loss | SSRIs |
| Fluvoxamine | Neutral | SSRIs |
| Imipramine | Yes+ | TCA, more weight gain than other TCAs |
| Mirtazapine | Yes++ | Increased appetite and weight gain due to decrease in NE effects. Doses more than 15mg/day increase NE effects and hence results in decrease in appetite and weight loss. |
| Nortriptyline | Yes+ | TCA |
| Paroxetine | Yes+ | SSRIs, Initial doses weight loss, long-term use extreme weight gain>7% |
| Escitalopram | Neutral | SSRIs |
| Sertraline | Neutral | SSRIs, long-term use mild weight gain |
| Venlafaxine | Neutral | SNRIs |
| Trazadone | Yes++ | SGAntidep |
| **Mood stabilizers** | | |
| Lamotrigine | +/Neutral | Used in the treatment of depression |
| Lithium | Yes+ | Lithium induced hypothyroidism increase weight gain besides independent effect of Li |
| Topiramate | Loss | |
| Valproic acid | Yes++ | |
| Carbamazepine | Yes+ | |
| Oxcarbamazepine | Yes+ | |

| Psychiatric medications | Weight changes | Remark |
|---|---|---|
| **Sedative-hypnotics (BZD and Non-BZD)** | | |
| Lorazepam, Oxazepam,Temazepam , and others | Neutral | Benzodiazepines sedatives |
| Eszopiclone, zopiclone, zolpidem, and zaleplon | Neutral | These are non-benzodiazepines sedatives |
| Buspirone | Neutral | |
| **Psychostimulants** | | |
| Methylphenidate | loss | With therapeutic doses no weight loss |
| Amphetamines | Loss | With therapeutic doses no weight loss |
| Atomoxetine | Loss | |
| modafinil, and armodanafil | Loss | |
| Synthetic acetylcholinesterase inhibitors | | |
| Donepezil, galantamine, rivastigmine, memantine | Anorectic effect | Reduce weight |
| Natural acetylcholinesterase inhibitors | | |
| Galanthamine, quercetin and timosaponin AIII, | Anorectic agents | Better option for treating dementia with initial overweight but research evidence is needed |
| Natural antidepressants | | |
| St. John's Wort | Weight loss/neutral | Some reports suggest its appetite suppressant side effect and weight loss through increasing brain serotonin level |
| S-adenosylmethionine-SAMe | Weight +/- | Speculative! On longterm intake weight gain? |
| Omega 3 fatty acids | Weight loss | Causes fat loss |
| Saffron | Weight+/- | Obese persons loss weight |
| 5-HTP | Weight loss | Decreases carbohydrate and starch intake and early stomach fullness. Increases brain serotonin |
| DHEA | Weight loss | |
| Gingko biloba | Weight +/- | |

*+=mild to moderate weight gain, ++=moderate to marked weight gain,*Act on multiple receptors-dopamine, serotonin, norepinephrine, histamine-1, SAMe= S-adenosylmethionine, 5-HTP = 5 hydroxytryptophan, DHEA = Dehydroepiandrosterone, Most of these drugs produce weight gain or loss when patient are given their therapeutic optimal doses*

### 3.8 Natural Antidepressants

St. John's Wort is not approved by the Food and Drug Administration (FDA) to treat depression in the U.S., but remains a popular treatment for depression in Europe. SAMe, omega-3 fatty acids, saffron, 5-HTP, DHEA, and Gingko biloba are briefly described elsewhere [58,59]. In a double blind placebo controlled study involving overweight healthy participants, combination of citrus aurantium extract, caffeine, and St. John's Wort resulted in weight reduction and fat loss compared to control group [60]. Gingko biloba produced weight gain in 22/1192 users (1.9%) [61]. The natural antidepressants with low level of research evidence have mixed results surrounding weight gain or loss, and this may be because of two reasons: overweight patients with depression tend to improve and their weight often decreases, and secondly these medical herbs are concocted with vitamins and other medical plants making it hard to predict precisely which of the component of supplement is accounted for weight loss or gain (Table 4).

### 3.9 Psychotropic Drugs and Biology of Weight Gain

The underlying mechanisms of weight-gain or loss concerning psychotropic drugs including antipsychotic medications remain a complex paradigm and need continuous research. The second generation antipsychotics (SGAs) are most liable to induce weight gain in patients with SMI [62]. The strongest correlate of body weight gain discovered so far is the relative receptor affinity of the atypical antipsychotics for histamine H1, auto/hetero receptor H3 (control of hunger), 5-HT2C, noradrenaline, muscarinic acetylcholine, glutamatergic and dopamine D2 receptors and their sub-type receptors [63,64]. In the past, some of the adverse effects of atypical antipsychotic treatment shown to be associated with the antagonism of monoamine receptors; recent experimental data, however, indicate that metabolic effects (e.g. hypertriglyceridemia, impaired glucose-insulin homeostasis) may not be related to these mechanisms [65]. New theories of the mechanisms underlying antipsychotic-associated weight-gain focus on peptide hormonal regulators of metabolic control including leptin, ghrelin, and adiponectin [66]. Jin and colleagues found that the weight gain associated with antipsychotic medications was directly related to changes in leptin, and there were no added antipsychotic effects on leptin signaling. However, longterm studies on ghrelin showed increased levels in patients on atypical antipsychotics that typically produce weight gain. Thus, it appears that ghrelin and other peptide hormones including leptin may be useful predictors of weight gain in patients who are receiving atypical antipsychotic treatments [66]. Recently, Erzin and colleagues found no significant differences concerning adiponectin, irisin, and leptin levels in patients with schizophrenia on antipsychotic medications compared to normal control group [67]. Furthermore variable results (high leptin levels but no differences regarding ghrelin or adiponectin) were reported in patients with schizophrenia compared to normal controls [68]. Ferritin an inflammatory marker and resistin a metabolic marker but not leptin were found higher in antipsychotic-naïve patients with first episode psychosis (FEP) compared to healthy controls. Seven months post-treatment with SGAs, BMI, leptin and C-peptides (metabolic markers) were higher but lower level of adiponectin found in FEP patients compared to healthy controls [69]. The inconsistent results may be attributed to a variety of reasons including individual sociodemographic features and environment (stresses), research method, acute or longterm treatment by antipsychotic medications, their doses, typical or atypical forms and types of psychoses under treatment. Recently Grimm et al (2017) proposed that altered reward anticipation related to dopaminergic dysregulation (mesolimbic system and blocked by FGAs & SGAs) may explain uncontrolled increased eating behavior, metabolic changes, psychopathology and obesity in individuals with schizophrenia [70] that substantiates the results of other researchers [71].

Individual genetic factors may also contribute to the pool of weight gain in mentally ill patients. Evidently genetic factors, i.e., common allele of pro-melanin concentrating hormone (PMCH rs7973796) may be associated with a greater BMI in olanzapine-treated patients [72]. Furthermore, several studies reported an association between weight gain and various other genes related to single nucleotide-polymorphism (SNP: T allele, C allele, HTR2C gene, C825T/GNB3) [72-75]. Some researches provided serotonin-related genetic factors in antipsychotic-induced weight gain concerning the promoter region polymorphism [759 T/C (rs3813929)] in the HTR2C gene (on the X chromosome) [73-75]. The results related to T allele are inconsistent regarding weight gain or loss. Notably twin and candidate gene studies

have suggested a role of genetic factors in overall risk of antipsychotic induced weight gain. A recent genome-wide association study performed on a Han Chinese sample suggested a possible role of rs1097714 and rs10977154 variants of the protein tyrosine phosphatase receptor type D (PTPRD) gene and antipsychotic induced weigh gain [76]. Antipsychotic drugs given to patients with schizophrenia and other psychoses are associated with increased body fat mediated by 5-hydroxytryptamine 2C receptor (5-HT2C). A genetic polymorphism of the promoter region of this receptor in terms of the −759T variant allele significantly associated with less weight gain than in those without this allele who were more likely to have substantial (>7%) weight gain [77]. Furthermore candidate gene studies have produced significant findings concerning adrenergic α2a (ADRα2a) receptor, leptin, guanine nucleotide binding protein (GNB3) and synaptomal-associated protein 25kDa (SNAP25) genes [77]. Review results from genome-wide association and linkage studies pointed to several chromosomal regions, i.e., 12q24, promelanin concentrating hormone (PMCH), polycystic kidney and hepatic disease 1 (PKHD1), peptidylglycine α-amidating monooxygenase (PAM) [72,78]. Further latest details about genetic factors (variants rs9939609 and rs7185735) concerning weight gain induced by SGAs are available here [79]. In experimental models, Manu et al (2015) reported that the second-generation antipsychotic olanzapine stimulates the orexigenic hypothalamic structures responsible for energy homeostasis [80]. In sum, antipsychotic medications evoke multiple mechanisms underlying weigh gain in patients with psychoses, and inconsistent results call for further studies.

Tricyclic antidepressants have been shown to increase appetite and carbohydrate cravings and, hence, induce weight gain. Additionally, depression and antidepressant related sedation tend to decrease energy expenditure that also may contribute to weigh gain [13]. In case of lithium carbonate therapy, research has shown an insulin-like effect on carbohydrate metabolism, altered fat cell metabolism, and depressed thyroid functions leading to weight gain [12,23,24]. There is extensive literature on biopsychosocial mechanisms underlying weight gain-induced by psychotropic drugs and their description is beyond this review. Notably, it is very difficult to reduce overweight derived from the use of antipsychotic [81] and NAP medications in psychiatric population; however, weight is manageable if priori proper treatment strategies (choice of drug combined with counseling) and life style changes (exercise and low calorie diet) are adopted and directed towards patients with psychoses (Table 5).

**Table 5. Mechanisms of weight gain by psychotropic drugs**

| Medications | Mechanism | Remarks |
|---|---|---|
| Olanzapine | Increase in calorie intake, Slowing of metabolism, Action on multiple receptors, neurotransmitters and neurocircuits, 5-$HT_{2C}$ blocking property | Resting energy expenditure. Pharmacodynamics is complex and broad involving affinity to serotonin 5-HT2C and dopamine D2 receptors |
| Clozapine | Acts on δ-opioid receptors, 5-$HT_{2C}$ blocking property | Mice knocked off 5$HT_{2C}$ become obese |
| Quetiapine | 5-$HT_{2C}$blocking property | H1 antagonist action also. |
| Mirtazapine | 5-$HT_{2C}$ blocking property | Antidepressant, H1 antagonist action also. |
| TCAs | Through alpha adrenoceptors | Weight gain, psychotropic with low affinity to these receptors such as SSRIs causes little or no weight gain |
| Psychotropic | Blocking Histamine H1 receptor, The induction of leptin secretion | SGAs induce weight gain by antagonizing H1 receptors at hypothalamus |
| Psychotropic drugs & genetic, psychosocial and cultural factors | 5HT2C receptor, SNP genes, & others including individual vulnerabilities, gender, lifestyles, dietary habits, socioeconomic position, environment, ethnicity, and diagnosis. | Complex mechanisms with variable results need further research |

## 4. DISCUSSION

This review critically describes weight gain or loss with non-antipsychotic medications used in psychiatric population and underlying biological mechanisms related to all psychotropic medications including antipsychotic medications. Weight gain induced by antipsychotic medications is quite consistent and robust, and associated with multiple adverse consequences in all groups of patients with SMIs including bipolar disorders [1]. Few antipsychotics produce the lowest weight gain, which are lurasidone, iloperidone, paliperidone and asenapine [13,82,83]. Unlike non-antipsychotic psychotropic medications such as TCAs, MAOIs, SSRIs, mood stabilizers, BZDs, SNRIs, DNRIs, ACIs and natural antidepressants, the weight gain induced by antipsychotic drugs is potentially problematic and associated with metabolic syndrome [1,10] and, hence, antipsychotic medications with better clinical profile need to be developed in future.

Concerning non-antipsychotic psychotropic (NAP) medications and weight, four epidemiological trends emerged; overweight, minimal weight gain, weight neutral, and weight loss. Overweight is caused by TCAs (Imipramine), MAOIs (tranylcipramine), SSRIs (paroxetine), tetracyclic (mirtazapine), mood stabilizers (valproic acid, divalproex, lithium and carbamazepine) [12-14]. Minimal weight gain is produced by most SSRIs (sertraline, citalopram, and escitalopram), SGAntidep (trazodone and nefazodone), mood stabilizer and antipsychotic (asenapine) and SNRI (duloxetine) [13,25,27,33]. Some psychotropic medications such as BZDs, psychostimulants, SNRIs (venlafaxine and desvenlafaxine), neither cause nor reduce weight (neutral) in patients with depression, anxiety and other disorders [13,25-27,41,42,46-48]. However, most psychostimulants given to ADHD patients with overweight certainly decrease weight [46-48]. Some NAP medications are reported to decrease weight gain, which are bupropion (DNRI & SGAntidep), fluvoxamine (SSRI), felbamate and topiramate (mood stabilizers and antiepileptics), fluoxetine (early part of treatment, SSRI), synthetic and natural cholinesterase inhibitors (donepezil, rivastigmine, galantamine, memantine, and galanthamine, quercetin and timosaponin AIII) and natural antidepressants (DHEA, 5-HTP, Omega 3 fatty acids) [13-15,31-33,50,60]. Non-antipsychotic psychotropic medications especially paroxetine (SSRI) during 16 weeks of treatment causes metabolic changes (in weight, BMI, waist circumference, fasting glucose, total cholesterol, LDL and triglyceride) compared to other SSRIs (fluoxetine, sertraline, citalopram and escitalopram) among adult female patients with first episode of generalized anxiety disorder [84]. Other SSRIs and psychotropic drugs including traditional and newer antidepressants (SNRIs & DNRIs), mood stabilizers, psychostimulants, BZDs, cholinesterase inhibitors and natural antidepressants tend to produce minor or no abnormalities in metabolic profile [84] though these drugs are used most commonly around the world. The propensity of individual psychiatric disorders such as depression, anxiety disorders, schizophrenia and schizoaffective disorders, bipolar disorders and other psychoses and aging needs to be considered in order to explain the metabolic changes induced by non-antipsychotic psychotropic medications especially traditional antidepressants (amitriptyline), SSRIs and mood stabilizers [84-86]. Metabolic syndrome is not common with NAPs drugs; however, frequently associated with new generation of antipsychotic medications [1,10,84]. Arguably SSRIs and other antidepressants causing partial cardiometabolic changes need not to be or prescribed cautiously among psychiatric patients with compromised cardiac functioning. In sum, research on metabolic changes caused by SSRI and other antidepressants in patients with anxiety disorders, depression, bipolar disorders and psychosis is limited and the results are quite variable, and, hence, this review calls for further research.

Despite extensive research, the biology of weight gain or loss caused by psychotropic medications is poorly understood. Atypical antipsychotic medications act on many receptors; histamine H1, receptor H3, 5-HT2C, noradrenaline, muscarinic acetylcholine, glutamate and dopamine D2 and their sub-type receptors that mediate the weight gain and metabolic changes [63,64]. Furthermore, antipsychotic-associated weight gain is also mediated via peptide hormonal regulators (including leptin, ghrelin, and adiponectin) of metabolism. These are predictors of weight gain in psychiatric population receiving secondary generation of antipsychotics [66] and these findings are not supported by recent controlled studies [67,68]. However, antipsychotic (SGAs) induced weight gain is most likely produced by peptide hormone especially leptin. In another controlled study of SGAs induced weight gain, ferritin (an inflammatory marker) and resistin (a metabolic

marker) but not leptin were found to be higher in antipsychotic-naïve patients with first episode psychosis (FEP) compared to healthy controls. Furthermore, seven months post-treatment, BMI, leptin and C-peptide (metabolic markers) were higher but lower level of adiponectin were found in FEP patients compared to healthy controls [69]. Altered reward anticipation reflecting mesolimbic dopaminergic dysregulation and use of antipsychotic drugs may explain uncontrolled eating behavior, metabolic effects, psychopathology and obesity in patients with schizophrenia [70] results consistent with other researchers [71]. In sum, biology of weight gain induced by psychotropic drugs involves pharmacology of medications, individual genetic endowment, environmental factors, diagnosis, and other unknown factors. Individual factors and single nucleotide polymorphism contribute considerably to the mechanism of weight gain by psychotropic medications in psychiatric patients. Individual genetic endowment involving single nucleotide polymorphism (SNP: T allele, C allele, HTR2C gene, C825T/GNB3, allele of PMCH rs7973796, 5-HT2C) and diagnosis itself are underlying mechanisms of weight gain induced by psychotropic drugs [72-75]. There are many other genes involved in genetic mechanisms underlying weight gain induced by antipsychotics and antidepressants medications. These multiple genes concern variants rs9939609 and rs7185735 [79] adrenergic α2a (ADRα2a) receptor, the leptin, guanine nucleotide binding protein (GNB3) and synaptomal-associated protein 25kDa (SNAP25). In addition, several chromosomal regions are also involved; 12q24, promelanin concentrating hormone (PMCH), polycystic kidney and hepatic disease 1 (PKHD1), and peptidylglycine α-amidating monooxygenase (PAM) [87] and rs1097714 and rs10977154 variants of the protein tyrosine phosphatase, receptor type D (PTPRD) [76,88]. The GNB3 C825T polymorphisms is associated with BMI, waist circumference, total cholesterol, triglyceride, low-density lipoprotein and leptin levels among bipolar patients treated with valproate [89]. Overall, weight gain concerning antipsychotic and antidepressants and mood stabilizers especially valproate involve multiple CNS receptors genes, SNP genes, and individual psychosocial, cultural, environmental and genetic characteristics along with disease features in patients with mental disorders of variable grades of severity. Nonetheless, further researches are required to provide consistent results concerning non-antipsychotic and antipsychotic psychotropic drugs induced weight gain or loss in psychiatric population.

This review has some limitations. This is not comprehensive and systematic. The selection and publication biases are obvious. The strength is that it is the first review from Saudi Arabia. This will possibly bridge the knowledge gap of mental health professionals concerning weight gain or loss and its underlying mechanisms caused by psychotropic medications including antipsychotics frequently used in patients with mental illnesses around the world.

## 5. CONCLUSION

In summary, non-antipsychotic psychotropic drugs tend to increase or decrease weight in patients with mental illnesses including mood disorders and anxiety disorders. Multiple biopsychosocial and cultural mechanisms mediate this weight gain or loss effect including of antipsychotic medications. Although most non-antipsychotic psychotropic medications do not cause overweight, some traditional antidepressants, mirtazapine, paroxetine, valproate, and lithium with therapeutic doses cause high BMI in vulnerable patients and metabolic changes not meeting criteria of metabolic syndrome. In light of this review, psychotropic medications linked with weight loss need to be prescribed for patients with severe mental illnesses liable to develop overweight and obesity. Unlike other psychotropic drugs, an antipsychotic induced metabolic syndrome is well established, and, therefore, further studies need to be conducted in mentally ill patients receiving non-antipsychotic psychotropic medications.

## 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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