Weight Mediated Effects of Antidepressant Medications: A Narrative Review

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Abstract

Antidepressant medications are the first-line treatment option for moderate to severe major depressive disorder (MDD). However, most antidepressants have numerous documented adverse events including cardiometabolic effects and weight-gain, which are major public health concerns. Antidepressant agents provide varying risk of associated weight-gain, including significant within class differences. Some agents, such as mirtazapine, show significant levels of weight gain, while others, such as bupropion, demonstrate weight loss effects. Current findings suggest the role of histamine and serotonin off-target appetite promoting pathways in adverse weight-gain effects. Therefore, controlling for undesired weight effects is an important consideration for the selection of antidepressants.

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Introduction

Major depressive disorder (MDD) is a major public health concern given its significant contributions to medical morbidity and mortality risk. It is a chronic and disabling disease, affecting approximately 264 million individuals worldwide, with a lifetime prevalence of 17% [1,2]. By 2030, MDD is projected to be the leading cause of disease burden worldwide, affecting approximately 23% of the global population [3,4]. Antidepressant medications are the most common treatment for MDD. Thus, they are one of the most commonly prescribed drug classes worldwide [5,6].

Following the therapeutic success of the phenothiazine amines as long-lasting anti-histaminergic drugs, Häfliger and Schinder modified the chemical properties of the phenothiazine ring to develop imipramine [7,8]. By the end of 1957, imipramine was released as the first clinically efficacious tricyclic antidepressant (TCA) [9]. In the same year, clinical trials of iproniazid, originally brought to market to treat tuberculosis, were found to serendipitously treat MDD due to its effects as a monoamine oxidase inhibitor (MAOI) [10]. Later, in an effort to reduce the adverse effects associated with TCAs and MAOIs, agents targeting serotonin were developed, leading to the subsequent development of selective serotonin reuptake inhibitors (SSRIs) [11]. Present-day MDD treatment guidelines recommend antidepressants as a first-line treatment option for moderate to severe MDD [12]. While noteworthy improvements have been achieved for tolerability, all antidepressants still have significant adverse effects and balancing the antidepressant benefits with these adverse effects remains a significant challenge.

In a recent meta-analysis, Ciprani et al., (2018) compared the efficacy and tolerability of 21 antidepressant medications. They found that although efficacy rates were similar for all 21 drugs, discontinuation was significantly greater for the antidepressant groups compared to placebo [13]. Data collected from long-term users of antidepressants demonstrated that 65.3% of

patients experienced adverse effects of weight-gain [14], which is relevant given that obesity is two-to-three times more common in individuals with mental illness compared to the general population [15]. Weight-gain may occur during both acute and maintenance antidepressant treatment [16], such that body weight and other associated metabolic parameters (i.e., insulin resistance) may significantly influence antidepressant compliance. Indeed, weight-gain has been shown to be a significant cause of treatment discontinuation within two months of treatment onset [17]. As such, tolerability and associated adverse effects should be strongly considered during antidepressant selection [18]. Herein, the current review will synthesize extant literature for antidepressant treatment of MDD and associated effects on weight for the following antidepressant drug classes: SSRIs, SNRIs, MAOIs, TCAs, noradrenergic and specific serotonergic antidepressants (NaSSAs), norepinephrine-dopamine reuptake inhibitors (NDRIs) and multimodal antidepressants.

Mechanisms of Action

Pharmacological differences across antidepressants may directly translate to differential vulnerability to weight-gain and/or metabolic disruption. For example, activity of antidepressant-specific receptors, such as histaminergic H1 receptor, and serotonin 5-HT_{2C} receptor antagonism, may be causative of metabolic risks, primarily through increasing appetite and suppressing satiety [19]. Thus, it is appropriate to discuss the distinct mechanisms of action for the major classes of first-line antidepressants.

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (TCAs) can act as serotonin, noradrenaline and dopamine reuptake inhibitors depending on the specific agent, as well as moderate antagonists of the histamine H1 and muscarinic acetylcholine receptors [20–22]. The structure of tertiary amine TCAs (e.g., amitriptyline) suggest its efficiency in serotonin reuptake inhibition. However, their metabolites generate a selective noradrenergic action. This results in a mixed effect on both serotonin and noradrenaline receptors [23]. The clinical effects of TCAs vary based on their metabolism in the body and the resulting mechanism of action [23]. The mechanisms of action for TCAs are non-selective and these contribute to adverse weight-gain effects [17]. Despite this, TCAs remain effective in the treatment of MDD [24].

Monoamine oxidase inhibitors (MAOIs)

Monoamine oxidase inhibitors (MAOI) exert their effects by selectively inhibiting monoamine oxidase-A (MAO-A) and/or monoamine oxidase-B (MAO-B) enzymes, which catalyze the oxidative deamination of monoamines [25]. Inhibiting this process allows for greater availability and concentration of monoamines for dopamine, serotonin, and norepinephrine. MAOIs can be classified by specificity for monoamine oxidase (MAO) enzymes (MAO-A, MAO-B, or both), affinity for inhibition sites (reversible or irreversible), or by chemical structure (hydrazine or non-hydrazine) [26–28]. Non-specific, irreversible MAOIs are reported to be associated with adverse effects, drug-drug interactions, and toxicities such as hepatotoxicity [25]. However, MAOIs may effectively treat depressive symptoms in individuals with treatment-resistant MDD, specifically patients that have not received sufficient symptom relief from SSRIs and TCAs [29].

Selective serotonin reuptake inhibitor (SSRI)

Serotonin, a monoamine neurotransmitter, has been identified as an important treatment target for many psychiatric disorders [30]. A number of antidepressants, including SSRIs, modify serotonin levels in the central nervous system (CNS) [31]. Mechanistically, serotonin is released from the raphé nuclei into the presynaptic terminal where it acts on presynaptic serotonin receptors and is metabolized by MAO. Serotonin's interaction with its receptors induces a negative feedback loop to inhibit further release from the synaptic bouton [32]. This increases the extracellular synaptic concentration of serotonin, thus improving the antidepressant effects [33]. Ultimately, the serotonergic system presents an important treatment target in depressed individuals.

Some SSRIs may differ slightly from this general mechanism of action. One such example is fluoxetine. Mechanistically, fluoxetine targets serotonin reuptake, 5-HT_{2C} and 5-HT_{2A} receptors in the serotonergic system. However, fluoxetine treatment has also been shown to increase norepinephrine and dopamine levels in the prefrontal cortex of the brain, while decreasing serotonin reuptake in the presynaptic terminal [34]. As such, fluoxetine has a higher level of dopaminergic and adrenergic activity compared to more selective SSRIs, such as citalopram [35].

Serotonin and norepinephrine reuptake inhibitor (SNRI)

Along with serotonin, norepinephrine also serves as an important treatment target for many psychiatric disorders [17]. Norepinephrine is projected from the locus coeruleus to the

frontal cortex and the limbic system. Postmortem studies on subjects diagnosed with MDD demonstrate decreased norepinephrine transporter binding in the locus coeruleus. Moreover, neuroimaging studies demonstrate abnormal norepinephrine metabolism in the limbic and paralimbic structures of the prefrontal cortex in depressed patients. SNRI use has been shown to normalize abnormal metabolism in the amygdala and prefrontal cortex [36]. SNRIs bind to serotonin and norepinephrine transporters with a range of potencies and binding affinity ratios. They inhibit the reuptake of both serotonin and norepinephrine, and unlike SSRIs, produce an ascending dose-response curve [37].

Some variability exists in the mechanism of action for some SNRIs. For example, due to its higher affinity toward the serotonin channel than the norepinephrine transporter, venlafaxine closely resembles an SSRI. That is, it will first inhibit the serotonin transporter and with a dose increase, subsequently inhibit the norepinephrine transporter. A higher dose produces greater adverse effects due to higher uptake and blockade of the norepinephrine transporter [38]. Therefore, there exists a dose-concentration relationship between venlafaxine and its function as an SNRI [37]. Likewise, desvenlafaxine has a similar potency for the serotonin and norepinephrine transport systems [39]. However, compared to other SSRIs and SNRIs, it has a relatively low binding affinity for the serotonin and norepinephrine receptors and therefore, has a low risk of adverse drug-drug interactions [37]. Another SNRI, duloxetine, has high, but balanced, affinity for both the serotonin and norepinephrine neurotransmitters [40]. It is not a potent inhibitor of the dopaminergic, adrenergic, or histaminergic receptors [41].

Multimodal antidepressants

Multimodal antidepressants demonstrate affinity for selective serotonin receptors and the serotonin transporter, resulting in enhanced antidepressant safety, tolerability, and efficacy [24]. For example, vortioxetine's multimodal mechanism of action targets the 5-HT_3, 5-HT_7, 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} serotonergic receptors, and inhibits the serotonin receptor transporter [42,43]. Extant findings illustrate that the antidepressant effects of vortioxetine are the result of interactions with multiple systems and receptors including, serotonin, norepinephrine, dopamine, acetylcholine, histamine, and glutamate [43–45]. Another multimodal antidepressant, vilazodone, operates as an inhibitor of the serotonin receptor and a partial agonist of 5-HT_{1A}. It also lacks binding affinity for dopaminergic or noradrenergic receptors [46]. Similarly, trazodone is a partial agonist of the 5-HT_{1A} receptor, however is a potent agonist of the 5-HT_{2A} [47].

Levomilnacipran demonstrates affinity for both serotonergic and noradrenergic receptors as it is a potent inhibitor of both the serotonin and norepinephrine receptors [48]. In essence, multimodal antidepressants demonstrate high specificity for receptors to produce greater antidepressant efficacy, safety, and tolerability.

Norepinephrine and Dopamine Reuptake Inhibitors (NDRIs)

Norepinephrine and dopamine reuptake inhibitors (NDRIs) lack affinity for serotonin receptors. Instead, they selectively inhibit dopamine and norepinephrine reuptake pumps to increase dopamine and norepinephrine neurotransmission [17]. Extant literature has demonstrated the role of dopamine and norepinephrine in MDD pathophysiology. In particular, dopamine and norepinephrine impact hedonic drive, cognitive function, energy, and motivation [49]. For example, bupropion is an NDRI that shows therapeutic potential for MDD. Contrave, a combination of bupropion and naltrexone, demonstrates antidepressant efficacy by increasing norepinephrine and dopamine neurotransmission [17]. Thus, NDRIs demonstrate antidepressant efficacy by modulating dopamine and norepinephrine neurotransmission, with no affinity for serotonin receptors.

Proposed Mechanisms of Treatment-Emergent Weight-Gain

Pharmacological antidepressant therapies modulate neurochemical activity to alleviate depressive symptoms. However, these neurochemical changes may also result in adverse effects, such as weight gain. The following will discuss central and peripheral mechanisms for antidepressant-related weight changes. A summary of the mechanisms of actions for treatment emergent weight-gain are provided in **Figure 1**.

Antihistamine and anticholinergic effects

Off-target antihistamine and anticholinergic effects are likely very important for weight-gain effects, and affinity for the histaminergic H1 receptor is shown to best predict weight-gain [35,50]. In particular, drugs demonstrating a high affinity for H1 receptor blockade are associated with low satiety and increased carbohydrate craving. This leads to an increase in caloric intake, and subsequent weight-gain [51]. Moreover, the blockade of anticholinergic sites is associated with increased appetite, further facilitating weight-gain effects [52]. TCAs demonstrate these effects as they are antagonists of the histamine and muscarinic acetylcholine receptors [20–22].

Serotonin

Serotonin is the most commonly targeted neurotransmitter in the treatment of depressive disorders. Treatment with antidepressants that modulate serotonin can produce either weight-loss or weight-gain effects. For example, acute serotonin reuptake inhibition helps regulate appetite and produces an anorexigenic effect. However, weight-gain occurs when decreased serotonin reuptake produces an increase in extracellular synaptic serotonin concentration, resulting in the blockade of serotonin receptors [51]. In summary, acute reuptake inhibition results in reduced impulsivity and therefore reduced food intake, along with enhanced satiation through stimulation of metabolism and sympathetic activity [30]. Contrarily, prolonged inhibition (≥12 months) results in weight gain due to carbohydrate cravings [17,51]. Therefore, drugs inhibiting serotonin reuptake produce varying weight loss and weight-gain effects depending on length of treatment.

Norepinephrine

Norepinephrine has been shown to regulate mood and weight [17]. Combined serotonin and norepinephrine reuptake inhibition appears to have a small weight-loss effect during acute use, followed by weight-gain with prolonged use. However, relative to serotonin reuptake inhibition alone, this leads to greater weight-loss effects and smaller weight-gain effects [35]. This is because, in response to norepinephrine, beta-3 adrenoceptors in adipose tissue convert fat into heat and energy. Consequently, noradrenergic effects promote weight neutrality or weight loss [51].

Dopamine

Dopamine plays a critical role in reward and eating behaviour. Dopaminergic neurotransmission modulates the hypothalamic melanocortin system, which regulates homeostatic energy balance. Antidepressants that increase dopamine neurotransmission also upregulate the hypothalamic melanocortin system. Typically, a reduced dopaminergic tone is observed in individuals with obesity, and reversal of this reduced tone may facilitate weight loss [17]. Contrarily, in a sample of healthy participants, reduced dopaminergic striatal response was associated with increase in weight and obesity [53,54]. Therefore, dopamine receptor stimulation can produce weight-loss or weight-gain effects, where an increase in dopaminergic neurotransmission is associated with weight loss, and reduced neurotransmission is associated with weight gain.

Peripheral effects

Peripheral effects produce weight change through components in peripheral circulation that provide feedback for neural circuits involved in satiety and hunger. Changes in concentrations of certain substances, such as glucose, has been associated with changes in eating behaviour [55]. For example, MAOI use (i.e. phenelzine) may lead to hypoglycemia in some patients. In particular, a significantly lower xylose return is observed in the urine of phenelzine treatment-responders compared to treatment-nonresponders [56]. This decline in blood glucose levels may produce hunger-stimulating effects, thereby increasing caloric intake [55–57]. However, some peripheral changes may induce weight-change without an increase in caloric intake, suggesting that the weight-gain may be a result of aberrant metabolic processes as opposed to increased appetite and food intake [58]. For example, phenelzine use is also associated with altered development of adipose tissue, specifically during the process of adipocyte differentiation. This has important implications on weight, as adipose tissue acts as a calorie reservoir, playing a critical role in the homeostatic regulation of systematic energy. This leads to weight-gain without increased food intake [59]. Consequently, current findings suggest that treatment-related weight-gain may be related to drug-induced cellular changes through effects on peripheral systems.

High Risk Agents for Antidepressant Induced Weight-Gain

Differences exist within all antidepressant drug classes in relation to associated weight-change. For example, in an acute treatment trial, 4.3% of patients treated with SSRIs experienced at least 7% weight-change following 4-12 weeks of treatment [60]. A recent meta-analysis found that, although initially correlated with weight-loss, for some SSRIs, this effect disappears following four months of use. [61]. Herein, the acute and long-term weight change implications of antidepressant classes are discussed below. If a consensus amongst data types (i.e., meta-analysis or long-term randomized control trial) report significant weight-gain (>7%) and ≥1.5kg weight-change in acute and/or long-term treatment, the antidepressant is classified as a high-risk agent. Moreover, if consensus amongst data types report significant weight-gain (>7%) and +0.5-1.4kg weight-change, the agent is classified as a moderate-risk agent for weight-gain. Similarly, if consensus findings report weight-loss or weight-neutral effects in acute and long-term treatment, the antidepressant is classified as a low-risk agent. Additionally, classification is supported by expert opinion. A summary of findings are presented in **Table 1**.

Tricyclic antidepressants (TCAs)

Amitriptyline and Nortriptyline

Among the TCAs, amitriptyline and its metabolite, nortriptyline, have the greatest documented weight-gain effects. A review of contemporary antidepressant drugs found TCAs to be frequently associated with weight-gain during both acute and long-term exposure [35,61]. For example, a meta-analysis by Serretti et al., (2000) explored changes in weight gain with short- (4-12 weeks) and long-term (>12 weeks) exposure to amitriptyline and nortriptyline. They found that short-term exposure to amitriptyline and nortriptyline was associated with +1.52 kg and +2.00 kg, respectively, while long-term exposure to the drugs led to +2.24 kg and +1.24 kg weight-gain, respectively [35]. Similarly, a systematic review and meta-analysis comparing 54 commonly prescribed drugs found that amitriptyline was associated with an average weight-gain of +1.8 kg [62]. Additionally, a narrative review reported a +0.4-7.3 kg weight gain in patients using amitriptyline and +0.3-4.1 kg weight gain in patients using nortriptyline [63].

Moreover, a longitudinal investigation by Berken et al., (1984) followed patients who were treated for depression with the TCAs amitriptyline, nortriptyline, and imipramine over a six-month period. A consistent increase in weight over the duration of treatment (+0.6-1.3 kg/month) was evident, followed by weight-loss subsequent to treatment discontinuation. The largest total weight change was generated by amitriptyline, while imipramine was found to generate the smallest weight change [64]. However, all three of the TCAs resulted in weight-gain, evidencing their overall adverse weight-change effects. More recent findings have shown TCAs predispose individuals to metabolic syndrome independent of depressive symptom severity [65]. Therefore, amitriptyline and nortriptyline should be considered a high-risk for adverse weight-gain.

Monoamine oxidase inhibitors (MAOIs)

Phenelzine

Phenelzine is an irreversible non-specific hydrazine MAOI and has been shown to cause severe adverse weight change [55,56]. For example, in a study investigating both the short- (3 week) and long-term (6 months) adverse effects of phenelzine, 42.8% of participants (n=14) reported a mean long-term weight gain of +9.1 kg [66]. Similarly, a preclinical trial found that phenelzine alters the development of adipose tissue during the process of adipocyte differentiation [59]. Consequently, current findings suggest that phenelzine-related weight-gain may be related to drug-induced cellular changes when non-specific MAOIs exert effects on

peripheral systems. Meta-analysis data comport with earlier findings that suggest phenelzine presents a high risk of weight-gain [67]. As such, weight-change effects of phenelzine require monitoring.

Selective serotonin reuptake inhibitor (SSRI)

Citalopram

Citalopram is one of the most widely prescribed SSRI antidepressants [68]. Data reporting weight change during acute and maintenance treatment found significant weight gain (+1.69kg) ≥4 months following treatment [35]. Similarly, an electronic chart review reported 13% of patients (n=5215) prescribed citalopram reported >7% weight-gain compared to baseline after a nine-month follow-up [69]. In a retrospective-cohort trial, patients experienced an average weight-gain of +2.68 kg (n=1137) after 24 months of citalopram treatment [70].

Moreover, in a smaller, cross-sectional study investigating cardiometabolic implications of antidepressant drugs found citalopram to result in significant weight-gain (>7%) in 31.6% of patients (n=19) [71]. As such, citalopram has shown a high risk of adverse weight gain among other SSRIs [63]. These results were in line with previous findings illustrating long-term weight-gain (>7%) in patients prescribed citalopram [35,72]. Overall, findings suggest severe long-term weight-gain associated with citalopram and weight monitoring is recommended.

Paroxetine

Paroxetine is prescribed as a treatment for numerous psychiatric illnesses, including MDD, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), as well as anxiety and panic disorders. Compared to other SSRIs, paroxetine has shown significant patient reported weight increase. In particular, paroxetine is associated with adverse weight change (+2.73 kg) following long-term use (≥4 months) [35]. Approximately 13% of patients prescribed paroxetine report >7% weight-gain after a nine-month follow-up [69]. Moreover, a retrospective cohort study observed a mean weight gain of +2.49 kg in patients prescribed paroxetine at a two year follow-up [70,73]. In a cross-sectional study, paroxetine was associated with weight-gain of 7% or more compared to baseline in over 50% of participants, and a weight gain of 20% or greater in 10% of patients (n= 80) [71]. Thus, paroxetine appears to have adverse weight-change effects following prolonged use that require monitoring.

Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs)

Mirtazapine

Mirtazapine is a NaSSA primarily prescribed in the treatment of MDD. It has been shown to be associated with adverse weight-gain in both acute (+1.74kg; 4-12 weeks) and long-term (+2.59kg; ≥ 4 months) use [35]. Approximately 22% of patients prescribed mirtazapine report >7% weight-gain at nine months [69]. Similarly, in a 10-year assessment of antidepressant use and incident weight-gain, mirtazapine was associated with the greatest risk of adverse weight-gain (rate ratio[RR]: 1.50; 95% CI [1.45-1.56]) [68].

Furthermore, a retrospective-cohort analysis found patients (n=36) treated with mirtazapine experienced a mean +7.35kg weight-change after 24 months [70]. Moreover, a cross-sectional study assessing weight-gain in patients using novel antidepressants found that the use of mirtazapine was associated with weight-gain in 88% of participants (n=17). In particular, 76.5% of participants experienced a ≥7% increase in weight, while 17.6% reported a 20% or more weight-gain compared to baseline following an average of 13.5 months of mirtazapine use [71]. Overall, the combined activity of mirtazapine on histaminergic and serotonergic receptors results in a high risk for weight gain in both short- and long-term use.

Moderate Risk Agents for Antidepressant Induced Weight-Gain

Selective serotonin reuptake inhibitor (SSRI)

Sertraline

Sertraline has been implicated in eating behaviours in preclinical trials and is a commonly prescribed first-line SSRI treatment for MDD and OCD [74,75]. During acute treatment (4-12 weeks), there is a small weight-loss (-0.87 kg) effect observed [35]. Similarly, another study reported an average 6.5% reduction ($p < 0.01$) in the BMI of obese patients following six months of combined cognitive behavioural therapy (CBT) and sertraline treatment. Furthermore, combination therapy with CBT led to the best weight-loss results [30]. However, no effect on weight-change is observed following long-term maintenance treatment [35]. Sertraline, along with fluoxetine, was associated with the lowest weight change amongst SSRIs [76].

In contrast, newer findings show a moderate increase in weight following long-term use in patients prescribed sertraline. An electronic chart review found predicted and observed weight change to be +1.0kg at nine months [69]. Similarly, findings from a cross-sectional study found a weight gain of ≥7% in 20% (n=80) of patients and a retrospective cohort study found a weight increase of +4.76 kg following long-term use (24 months) [70,71]. Consequently, sertraline may

be associated with weight-neutral or weight-loss effects during acute treatment, however, the majority of findings illustrate moderate weight-gain effects following long-term maintenance treatment.

Escitalopram

Escitalopram is shown to have fewer comparative weight implications than the racemic enantiomer, citalopram. Preliminary analysis of data indicated weight-loss (-0.33kg) during acute treatment and no effect on weight during long-term maintenance treatment [35]. Similarly, Uher et al., (2011) found stable weight associated with escitalopram use, as indicated by less than 3% of individuals in the escitalopram treatment group experienced significant weight change (≥2 kg) following a six-month treatment [77].

In contrast, a double-blind placebo-controlled trial comparing the antidepressant effects of escitalopram and duloxetine found an average weight-gain of +1.83 kg (n=274) at eight months [78]. Indeed, a medical record review of 19,244 adult patients prescribed antidepressants for at least three months found a similar weight-change profile for escitalopram and citalopram. At nine months, the observed weight-gain for patients prescribed escitalopram (n=758) was 1.1kg [69]. Thus, findings illustrate moderate implications of weight-gain during long-term and maintenance treatment with a low-risk of weight-change during acute treatment.

Serotonin and norepinephrine reuptake inhibitor (SNRI)

Duloxetine

Duloxetine is used for the treatment of MDD, and is also approved for use in the treatment of chronic pain [79]. Meta-analysis data reports weight-loss (-0.55kg) during acute treatment and no effect on body weight during a maintenance period [35]. In contrast, Blumenthal et al. (2014) reported a mean weight-change of +0.5kg (n=326) at nine months [69]. Similarly, a retrospective cohort study observed a mean weight change of +1.63kg at 24 months in patients (n=37) prescribed duloxetine [70]. Other studies have also demonstrated positive associations between weight-gain and duloxetine prescription, with a gradual increase over time (+0.61 kg; 8 months) [68,71,78]. As such, extant findings suggest that duloxetine has a moderate risk of weight-gain during long-term treatment.

Low Risk Agents for Antidepressant Induced Weight-Gain

Tricyclic antidepressants (TCAs)

Imipramine

Imipramine presents a low risk of weight-gain and has the lowest implications of weight change in patients amongst the other TCAs. In a comprehensive review and meta-analysis, imipramine demonstrated no significant acute (4-12 weeks) or long-term (≥8 months) effect on body weight [35]. Moreover, imipramine was found to exhibit the smallest weight change compared to amitriptyline and nortriptyline [64]. Similarly, in a long-term treatment trial of imipramine, observed no significant weight-change between imipramine-treated and placebo-treated patients in the long-term treatment of MDD [80].

Monoamine oxidase inhibitors (MAOIs)

Tranylcypromine

Tranylcypromine is an older generation, non-specific irreversible MAOI [81]. A review and meta-analysis of tranylcypromine found that tranylcypromine use in patients with depression was associated with a low risk of weight gain [67]. Minimal weight-gain effects have been reported (between 0.0 – 4.1kg) by patients prescribed tranylcypromine [58,82,83].

In a chart review of 198 patients between the ages of 19 and 64, no patients reported severe weight-gain over the course of treatment, with severe weight-gain defined as an increase of at least 6.8kg or causing distress to a level that causes the patient to discontinue the treatment [58]. Taken together, these findings suggest that in the context of MAOI use, tranylcypromine may be a more favourable MAOI than phenelzine when patient weight-gain is of concern, especially for patients who experience overeating as a symptom of depression [63].

Moclobemide

Moclobemide is a new-generation, reversible inhibitor of MAO-A with a strong affinity for the MAO-A enzyme and little affinity for MAO-B [25]. After six weeks of moclobemide treatment for MDD, patients who had experienced symptoms of weight-gain or appetite increase during the depressive episode had a significant weight-loss [84]. A double-blind clinical trial comparing eight weeks of treatment on moclobemide versus imipramine found that patients taking moclobemide lost an average of 0.1 kg following treatment [85]. Overall, moclobemide demonstrates limited effects on body weight [86]. Therefore, current findings suggest that moclobemide is associated with minimal weight-loss or is a weight-neutral antidepressant.

Selective serotonin reuptake inhibitor (SSRI)

Fluoxetine

Fluoxetine is prescribed for the treatment of MDD, OCD, and bulimia nervosa. Studies investigating the weight changes associated with fluoxetine have been largely inconclusive; however, extant literature is implicative of its generally weight-neutral effects [38]. Fluoxetine is shown to effect weight change over only an acute period. That is, acute weight loss (-0.94kg) has been observed in patients prescribed fluoxetine compared to placebo-controls over the course of 4 to 12 weeks [35]. In a retrospective study, patients administered fluoxetine (n = 80) had no documented weight change following treatment [87]. Similarly, Michelson et al., (1999) demonstrated that generalized acute treatments of fluoxetine may provide neutral or weight-loss effects, while long-term treatment results in moderate weight-gain [88].

Moreover, a review of medical health records found the least long-term weight change in patients using fluoxetine when compared to other SSRIs. Predicted and observed weight change was +0.8kg and +0.7kg at nine months, respectively [69]. Extant literature suggests that fluoxetine trends towards weight-loss. This was evident based on the weight neutrality of fluoxetine in acute clinical trials [35,63]. Therefore, current literature suggests that long-term fluoxetine use may require weight monitoring, however, acute exposure results in generally weight neutral effects.

Serotonin and norepinephrine reuptake inhibitor (SNRI)

Venlafaxine

Venlafaxine closely resembles an SSRI as it is a more potent inhibitor of the serotonin channel than the norepinephrine transporter [38]. In a comprehensive review of antidepressants and weight change, Serretti and Mandelli found small acute weight-loss (-0.50 kg) in venlafaxine users [35]. Similarly, venlafaxine was associated with below average weight-gain in a 10 year cohort study [68].

However, long-term and maintenance period weight-change is inconclusive. A few studies suggest that there is an observed increase in weight over long-term treatment [69,89]. A cross-sectional study observed severe weight-gain (>7%) in over 50% of psychiatric outpatients (n = 49) prescribed venlafaxine. Similarly, a patient chart review (n=944) observed 13% of patients with >7% weight-gain at nine months. Meanwhile, a clinical trial investigating the long-term weight changes associated with second generation antidepressants reported insufficient data

to estimate long-term weight-change in venlafaxine patients [70]. Overall, extant clinical findings suggest weight-neutral acute effects and moderate long-term weight increase in patients prescribed venlafaxine. However, long-term effects remain inconclusive and short-term findings suggest venlafaxine has a minimal effect on body weight.

Levomilnacipran

Levomilnacipran is an SNRI with a higher affinity for norepinephrine receptors than serotonin. A systematic review investigating the efficacy and safety profile of levomilnacipran found that no short- or long-term trials were associated with significant weight-gain [48]. For example, in a three-phase, 48-week open-label trial, the mean change in body weight was -0.6 kg. Moreover, 10% of participants experienced at least a 7% increase in weight, while 17% of participants experienced a 7% decrease in weight or greater [90]. Thus, current findings suggest levomilnacipran to have favourable weight-gain effects. However, the available literature for levomilnacipran is limited and future studies should continue to investigate the adverse effects associated with levomilnacipran.

Desvenlafaxine

Although desvenlafaxine presents very similar pharmacological effects as venlafaxine, it is considered a more weight-neutral SNRI. For example, Tourian et al. (2010) pooled data from nine short-term (n=1,834) and one long term (n=594) double-blind, placebo control trial assessing the effects of desvenlafaxine in participants with MDD. They found that desvenlafaxine was not associated with any clinically significant changes in weight with either acute or prolonged use [91].

Moreover, a pooled, post hoc analysis by McIntyre et al. (2015) assessed the effect of baseline BMI on desvenlafaxine efficacy and weight change associated with 50mg or 100mg of desvenlafaxine in adults with MDD. Results demonstrated that short-term use of desvenlafaxine was associated with a statistically significant decrease in weight (<1kg) in participants of all BMI subgroups using both 50mg/day or 100mg/day of desvenlafaxine (both $P<0.0001$). No significant long-term changes in weight were observed [92]. Therefore, current findings suggest slight decrease or weight-neutral effects of desvenlafaxine during both acute and long-term exposure. As such, it should be considered a weight-positive antidepressant.

Multimodal Antidepressants

Vortioxetine

Vortioxetine is a multimodal antidepressant that is approved for the treatment of MDD and has robust effects in many clinically significant domains of depressive symptomatology [93]. Current clinical trials show low incidence of weight change in patients prescribed vortioxetine [94]. A study investigating the safety and tolerability of vortioxetine found no significant weight-gain following long-term treatment. There were no observed dose effects and weight change was similar for both placebo and vortioxetine patients from baseline to week 6-8 post-treatment. Weight gain incidence in the long-term open-label extension studies for vortioxetine was reported as 3.8% for the 5-10mg group and 4.4% for the 15-20mg group. The mean weight-gain was +0.8kg (n = 1297) and +0.7 kg (n = 1105), respectively, at the conclusion of the trial [95]. As such, preliminary results suggest that vortioxetine presents a viable first-line antidepressant option with minimal weight-altering implications.

Vilazodone

Similar to vortioxetine, vilazodone is a second-generation antidepressant that appears to have weight neutral effects. In a one-year open label study investigating the tolerability of vilazodone, Robinson et al. found minimal weight-gain following treatment (mean weight-change= +1.7 kg). Only 9.5% of participants reported weight-gain at the conclusion of the study [96]. Overall, extant literature has shown similar adverse events between placebo and vilazodone groups with no significant weight-altering effects [97,98].

Trazodone

Trazodone is a weight-neutral antidepressant with similar pharmacological properties as vilazodone. Extant findings on the tolerability and safety of trazodone have found no or minimal weight-gain [19,47,99]. Some studies also demonstrated an association between trazodone and mild weight loss. For example, a randomized double-blind placebo control study compared the weight change effects of amitriptyline and trazodone in a sample of 272 depressed participants. Results indicated that trazodone produced a slight weight loss in overweight participants [100]. Moreover, a narrative review of medications and their weight gain effects also associated trazodone with slight weight loss effects [63]. Therefore, trazodone demonstrates minimal weight gain or weight loss, making it well suited for patients with weight-related concerns.

Norepinephrine and Dopamine Reuptake Inhibitors (NDRIs)

Bupropion

Bupropion is the only agent that has been shown to cause significant weight loss and is considered optimal from a metabolic perspective. Contrave, a drug composed of bupropion and naltrexone, it is used as a treatment for chronic weight management in obese individuals [101]. Bupropion/naltrexone combination therapy also demonstrated significant efficacy in reducing depressive symptoms in a sample of 25 overweight/obese female participants with MDD. Open-label bupropion/naltrexone therapy combined with dietary and behavioural counselling, was also associated with weight loss 12 (-4.0%, $P<0.001$) and 24 (-5.3%, $P<0.001$) weeks following the start of the experiment [102]. Moreover, a 44-week double blind randomized placebo control trial by Croft et al. (2002) observed the weight of 210 patients with major depressive disorder being treated with bupropion sustained-release (SR). They found that mean weight loss varied based on baseline body weight, where a higher baseline body weight indicated greater weight loss following treatment with bupropion-SR. The greatest mean weight loss (2.4 kg) was observed in individuals with a body mass index (BMI) greater than 30 kg/m^2, whereas individuals with a BMI lower than 22 kg/m^2 displayed a modest loss of 0.1 kg [103]. Therefore, the weight-loss effects of bupropion make it particularly well suited for individuals that are obese with depression or normal-weight patients that are concerned about weight-gain.

Conclusion

In conclusion, close monitoring of weight-change should be prioritized during pharmacological treatment of mood disorders. A large number of antidepressants, which are currently the first-line treatment for MDD, have significant weight change implications. Weight-gain is a known risk factor for obesity, CVD, diabetes mellitus, and premature mortality. Consequently, weight-neutral treatments should be the focus of future antidepressant developments. Clinical trials suggest that ketamine and vortioxetine may be efficacious options for the treatment of MDD with minimal effects on weight [94,104] . Currently, there are no metabolic monitoring guidelines for antidepressants (as compared to antipsychotics that have well established guidelines) and given the high risk of weight change effects with some agents, we should adopt similar monitoring guidelines for antidepressants balanced with resource utilization. Some second-generation antipsychotics are used for MDD augmentation and we should be mindful of the adverse effects of other agents for depression beyond the focus of this review.

Risk for Drug-Induced Weight Gain			
	High	Medium	Low
Antidepressants	Amitriptyline Citalopram Mirtazapine Nortriptyline Trimipramine Paroxetine Phenelzine	Escitalopram* Sertraline* Duloxetine	Moclobemide Vortioxetine Tranylcypromine Venlafaxine Bupropion (associated with weight-loss) Levomilnacipran Vilazodone Desvenlafaxine Fluoxetine * Imipramine

Table 1: Summary of commonly prescribed antidepressants and the associated risk for adverse cardiometabolic effects

[*acute results demonstrate weight-loss/no weight-gain]

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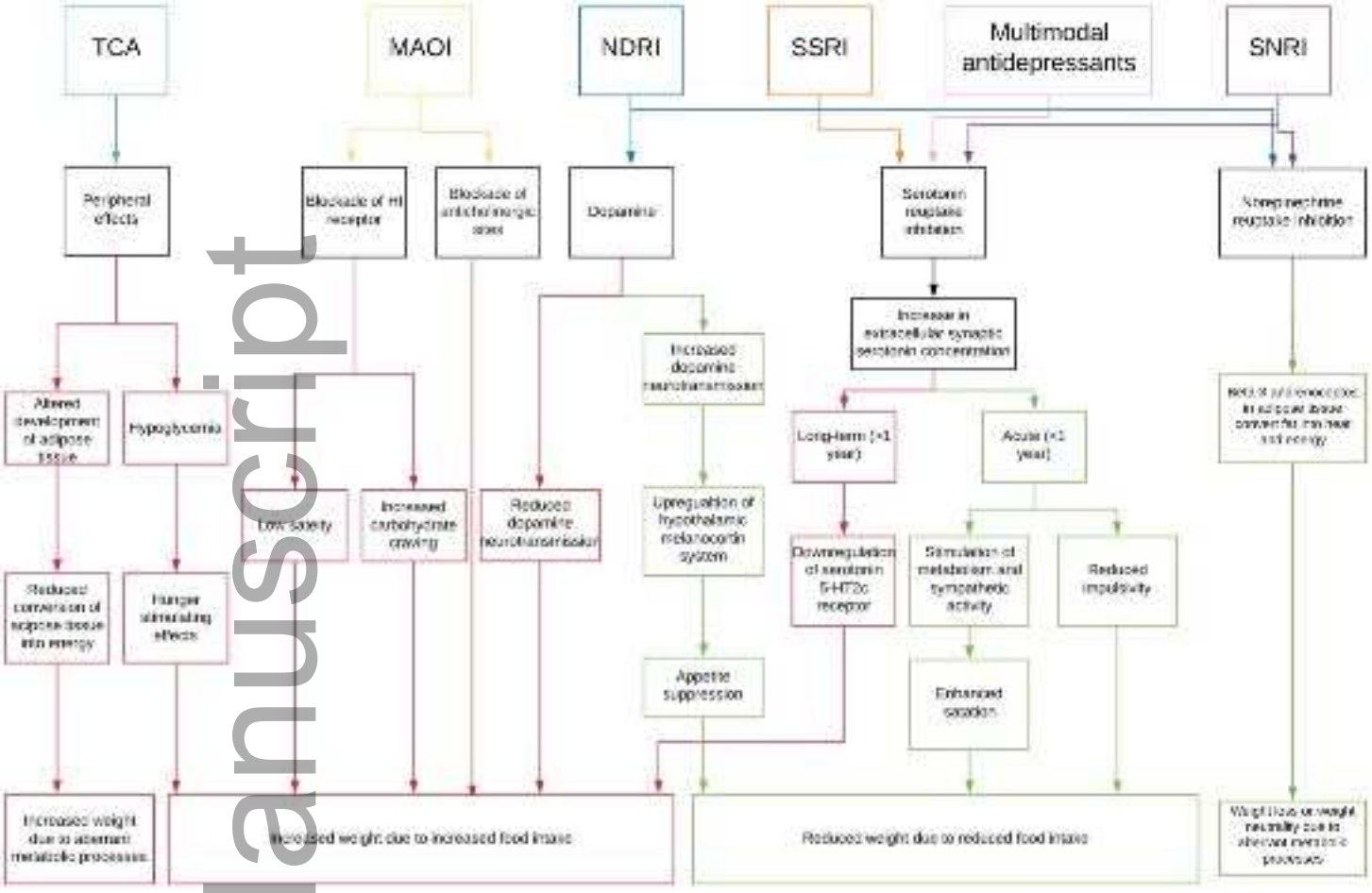

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