Antidepressants and Unintentional Weight Gain

By Sophia Yoon

Abstract

Antidepressants remain among the most widely prescribed medications for major depressive disorder and related conditions, yet their therapeutic benefits are often followed up with unwanted metabolic side effects. A growing body of research indicates that selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) can lead to significant weight gain, raising concerns about long-term adherence and patient health outcomes. This article examines the pharmacological effects of these drug classes, focusing on how their actions on serotonin, norepinephrine, and other neurotransmitter systems can alter appetite, metabolism, and energy balance. Emphasis is given to the role of serotonin in satiety and carbohydrate craving, and the action of norepinephrine in affecting metabolic rate. The biochemistry of depression itself is also considered, since changes in neurotransmitter signaling from disease converge on drug effects in complex fashion. Contemporary clinical research highlights genetic factors of weight gain risk both between and within antidepressant classes, with some drugs, such as bupropion, emerging as weight-neutral alternatives. The discussion summarizes these findings in the perspective of clinical practice, both the challenge patients have in balancing mental health treatment with physical health and the imperative of individualized prescribing. Lastly, the findings underscore the ongoing need for both the creation of antidepressants that do not sacrifice efficacy for adverse metabolic consequences and for clinicians to closely monitor and assist patients in managing both mood and metabolic health.

Key Words: Major Depressive Disorder (MDD), weight gain, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, neurotransmitters, serotonin signaling, norepinephrine, noradrenaline, bupropion

Introduction

Psychiatric diseases affect various age demographics globally, regardless of age, gender, and socioeconomic status. According to the World Health Organization (WHO) nearly one in eight people worldwide, over 970 million people, live with a mental disorder, with anxiety and depression being the most common (2022). In the United States alone, it is estimated that more than one in five adults lives with a mental illness (NIMH, 2023). The conditions patients experience are not only emotionally disruptive but can also lead to long-term physical conditions if not treated properly. The persistence and prevalence of mental health disorders emphasize the need for effective medical intervention, especially in forms suitable for long-term use. Among psychiatric conditions, Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) are especially common, affecting 6.8 million adults in the US and often treated with medications associated with weight gain (Anxiety and Depression Association of America, 2025). MDD is characterized by persistent sadness, fatigue, loss of interest, changes in appetite or sleep, and impaired concentration(American Psychiatric Association [APA], 2013).

Neurobiologically, MDD is associated with irregular signaling of serotonin, norepinephrine, and dopamine, neurotransmitters involved in mood regulation, energy, and reward (Malhi & Mann, 2018). GAD, marked by excessive and uncontrollable worry about everyday situations, is also linked to disruptions in similar neurotransmitter pathways, as well as hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis (Stahl, 2021). Pharmacological treatments are often necessary for moderate to severe cases of both disorders as therapy alone.

Medications used to treat mood and anxiety disorders are among the most commonly prescribed psychotropic drugs, including. These include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs), and newer agents like vortioxetine and bupropion. They work by extending the availability of key neurotransmitters in the synaptic cleft, which helps revive emotional and cognitive function (Stahl, 2021). While these medications can transform patients' lives by greatly enhancing their quality of life, long-term use is often complicated by weight gain, a side effect reported in varying degrees across nearly all classes (Seretti & Mandelli, 2010).

Antipsychotics, though more commonly prescribed for schizophrenia and bipolar disorder, are sometimes in combination therapy for depression and anxiety. These include typical antipsychotics (first-generation) like haloperidol, and atypical antipsychotics (second-generation) such as olanzapine, clozapine, and risperidone. While highly effective in managing psychotic symptoms, the second-generation antipsychotics are more prone to create side effects of weight gain and metabolic syndrome. However, because antipsychotic medications are used to treat more severe psychiatric conditions compared to antidepressants, their side effects, such as weight gain, are overlooked as a secondary concern, as managing the primary illness takes priority. And thus the usages of antipsychotic medications in non-psychotic disorders such as MDD are a matter of clinical debate (Allison et al., 1999; Baptista et al., 2002).

As it is shown in the complex interplay between psychiatric medications, neurotransmitter systems, and metabolic regulation, it is critical to examine which drugs are most associated with weight gain and how these effects manifest at the cellular and biochemical level. Understanding these mechanisms can help inform treatment decisions and guide the development of more metabolically safe options. Specifically, targeting either weight-neutral or weight-reducing alternatives, or incorporating behavioral and dietary interventions alongside pharmacotherapy might allow clinicians to enhance the efficiency and tolerability. The goal of this paper is threefold: One, to identify the drug classes most associated with weight gain in the treatment of mood and anxiety disorders. Two, to explain how these drugs biologically induce weight gain on a cellular and molecular level. Three, to emphasize the importance of safer, weight-neutral alternatives in psychiatric care. By recognizing the biochemical mechanisms of drug-induced weight gain, the medical world could optimize treatment strategies to protect both the mental and physical health of the patients.

Main Body: weight gain and its effects and psychiatric medications that induce it

Weight gain isn't a trivial side effect. From a biological perspective, it reflects a border disruption of metabolic and hormonal homeostasis. On a psychological level, it can lead to reduced medication adherence, worsening self-esteem, and even symptom relapse as a result. The side effect of weight gain is concerning for patients with mood and anxiety disorders because they may already struggle with body image or disordered eating. Research has shown

that weight gain contributes to increased risk for obesity, type 2 diabetes, cardiovascular disease, and early mortality (De Hert et al., 2011). Furthermore, the experience of weight gain can be psychologically draining— potentially reinforcing the very depressive symptoms that the medication is intended to mitigate. For example, a patient gaining weight may experience low self-esteem and turn to emotional eating as a coping strategy, creating an endless cycle of weight gain and mood symptoms in a vicious cycle (Zimmermann et al., 2003).

This issue is made more complex by the variability in weight-related effects among different antidepressants and antipsychotics, as well as the variability due the uniqueness of each patient. For example, SSRIs like paroxetine are associated with significant weight gain, while fluoxetine or sertraline show more moderate or neutral effects (Fava, 2000; Serretti & Mandelli, 2010). Among antipsychotics, olanzapine and clozapine are among the most obesogenic, with weight gains exceeding 4–5 kg (8.8 lbs-11.0 lbs) within just 10–12 weeks of treatment in some studies (Allison et al., 1999). In contrast, Bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI), is one of the few antidepressants shown to promote weight loss, making it a viable alternative in patients concerned about metabolic side effects (Anderson et al., 2002).

SSRIs: Selective Serotonin Reuptake Inhibitors

Selective Serotonin reuptake inhibitors, in short, SSRIs, are the most commonly prescribed class of antidepressants and are considered first-line pharmacological treatments for Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD). They function by selectively inhibiting the serotonin transporter (SERT), thereby increasing synaptic concentrations of serotonin (also known as 5-HT) in the central nervous system (Fig 1). In patients with MDD, lower levels of circulating serotonin have been evident, contributing to dysregulated mood and appetite (Katzman et al., 2022). Serotonin regulates mood, appetite, and satiety through its action in areas of the brain such as the hypothalamus. By preventing reuptake, SSRIs aim to normalize serotonergic signaling and alleviate depressive symptoms.

Despite their effectiveness, SSRIs are frequently associated with weight gain during long-term use. This adverse effect is thought to be multifactorial. First, we must consider the role of serotonin, which plays an important role in appetite regulation. Chronic SSRI treatment can cause 5-HT_1A autoreceptors to become less sensitive, which allows serotonin neurons to fire more consistently. Because serotonin also helps regulate hunger and satiety, these changes may alter appetite signals in the brain and contribute to weight gain (Commons et al., 2019). Whether such desensitization occurs in hypothalamic neurons involved in satiety control remains to be established. In addition to effects on appetite, SSRIs may also influence metabolism more broadly by altering insulin sensitivity and lipid processing, which could further contribute to weight gain (Chiba et al., 2021).

Paroxetine (Paxil) is one of the SSRIs most strongly associated with weight gain. A systematic review by Fava (2020) found that around 25% of patients treated with paroxetine for more than six months experienced significant weight gain (>7% of baseline body weight). In contrast, other SSRIs like fluoxetine or sertraline show more moderate effects, although weight gain can vary significantly across individuals, with some patients experiencing early weight loss followed by delayed gain (Chiba et al., 2021). These inconsistencies highlight the need for long-term monitoring in clinical practice.

SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, are another major class of antidepressants that target both the serotonin and norepinephrine transporters (SERT and NET). Norepinephrine is involved in attention, arousal, and the regulation of energy expenditure and metabolism through adrenergic pathways in both the brain and peripheral tissues. Like serotonin, reduced norepinephrine transmission is implicated in depressive symptoms (Delgado, 2000).

Therefore, by increasing extracellular levels of both neurotransmitters, SNRIs provide simultaneous treatment for depression and anxiety disorders. However, the additional targeting of norepinephrine can result in the production of distinct metabolic consequences. For instance, norepinephrine can increase energy expenditure (thermogenesis) and break down fat stores (lipolysis) through β-adrenergic receptor activation. These effects may either counteract or amplify the appetite-increasing effects of serotonin reuptake inhibition, influencing whether weight gain occurs (Hainer et al., 2006).

Compared to SSRIs, SNRIs are usually associated with a lower number of cases of weight gain. Duloxetine has been shown to have a relatively weight-neutral effect, with some clinical studies reporting minimal to no significant weight changes during short-term treatment (Wise, Mace, Krause, & Nelson, 2006). Venlafaxine shows a similar profile, although weight gain may occur after extended use. The process behind these differences is still under investigation, but it is likely that norepinephrine's role in inducing energy expenditure provides partial protection against weight accumulation.

TCAs: Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) represent an older class of antidepressants that are now reserved for cases that are treatment-resistant due to their unfavorable side effect profile. Studies show a substantial decline in TCA use for depression, with some reports indicating they were used in only 2% of patients with depression in 2001, compared to 47% in 1987 A MEPS-based study through 2015 reported that amitriptyline comprised ~2.0% of antidepressant monotherapy prescriptions, indicating TCAs remained a small minority of depression monotherapy by 2015. It is important to note that more recent prescription-count databases still record substantial absolute numbers of TCA prescriptions (often for pain, insomnia, or low-dose uses), but those counts do not directly measure the percentage of *patients diagnosed with depression* receiving TCAs. TCAs function by blocking the reuptake of both serotonin and norepinephrine, but they also antagonize various other receptors, including histamine (H1), muscarinic acetylcholine, and α-adrenergic receptors. These off-target effects can contribute dramatically to weight gain and other adverse effects such as sedation and anticholinergic symptoms (such as dry mouth, constipation, blurred vision, and urinary retention), which in the long term limit their clinical use.

One of the most prominently studied TCAs, amitriptyline, is associated with substantial weight gain. According to clinical data, about 25% of people taking amitriptyline report weight gain, often due to increased appetite and slower metabolism (Hers, 2022). The predominant reason behind this weight gain is believed to be H1 histamine receptor antagonism in the hypothalamus that enhances appetite and reduces satiety. In addition, muscarinic M3 receptor antagonism has been associated with impaired insulin secretion and signaling, which leads to glucose dysregulation, imbalances in blood sugar levels, and an increased risk of metabolic syndrome (Grajales et al., 2019).

The severity of weight gain caused by TCAs is normally greater than that of SSRIs and SNRIs, making them a less favorable option for patients at risk of obesity or type 2 diabetes. Moreover, TCAs are associated with sharp cardiotoxicity (damage to the heart or impairment of heart function that can lead to irregular heartbeats, reduced heart function, or other cardiovascular problems), especially in overdose scenarios, further limiting their utility. Due to these risks, TCAs like amitriptyline are now rarely prescribed unless newer agents with more moderate side effects fail to produce adequate results.

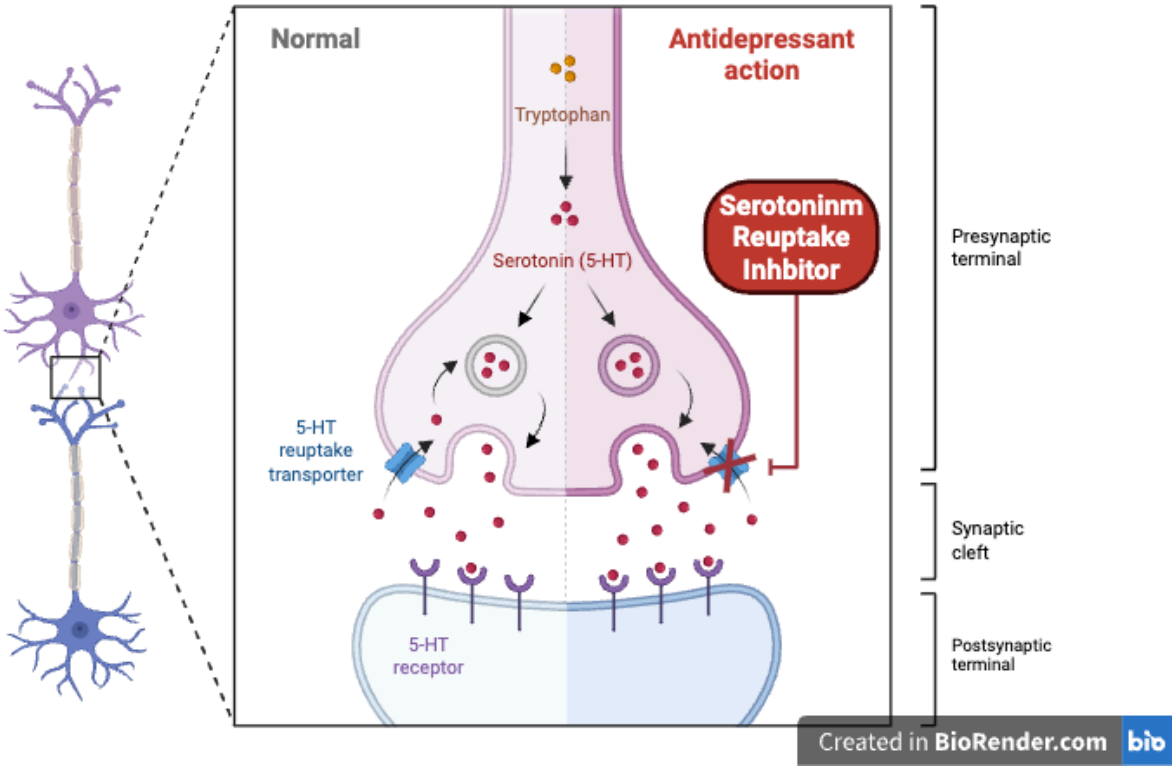

Fig. 1 | **Serotonin-related Antidepressants Mechanism of Action (SSRIs, SNRIs, TCAs)** | The figure on the left side (normal) illustrates that Serotonin (5-HT) is made from tryptophan inside the neuron. When released into the synaptic left, serotonin binds to receptors, passing along the signal. Normally, extra Serotonin is removed from the cleft by a 5-HT reuptake transporter. The figure on the right side (antidepressant action) illustrates that SSRIs, SNRIs, and TCAs block this serotonin reuptake transporter. And as a result, more serotonin remains in the synaptic cleft for longer, causing the increased serotonin signaling. That leads to improvement in mood and relief of depression.

NaSSAs (Noradrenergic and Specific Serotonergic Antidepressants)

NaSSAs, such as mirtazapine, amplify serotonin and norepinephrine release by antagonizing α_2-adrenergic autoreceptors, and also block histamine H_1 receptors, which is a unique pharmaceutical profile (Watanabe et al., 2010). This histamine H_1 antagonism contributes to mirtazapine's sedative and appetite-stimulating effects, making it beneficial for depressed patients with comorbid insomnia or weight loss, yet it also increases the risk of weight gain and daytime drowsiness.

Mirtazapine is greatly associated with significant weight gain. A pooled analysis of randomized U.S. clinical trials found that approximately 7.5% of adult patients experienced weight gain of ≥ 7% of baseline body weight, compared with none in the placebo group. In pediatric data, 49% of mirtazapine-treated youth gained ≥ 7% body weight (FDA label, 2020). From a mechanistic aspect, its strong H_1 antagonism is implicated in appetite stimulation and subsequent metabolic effects, including dyslipidemia - abnormal blood lipid levels that can increase cardiovascular risk (Lechner et al., 2023).

MAOIs (Monoamine Oxidase Inhibitors)

MAOIssuch as phenelzine, isocarboxazid, and tranylcypromine raise synaptic levels of serotonin, norepinephrine, and dopamine through irreversibly inhibiting the monoamine oxidase enzyme (MAO-A and MAO-B), which are responsible for breaking down monoamine neurotransmitters through oxidative deamination (Fig. 2). MAO-A mainly breaks down serotonin and norepinephrine, whereas MAO-B primarily affects dopamine and various trace amines. By inhibiting these enzymes, MAOIs halt the breakdown of serotonin, norepinephrine, and dopamine, leading to higher levels of these neurotransmitters in the presynaptic neuron, which are then released into the synaptic cleft. This increased availability boosts the activation of postsynaptic receptors, enhancing mood, motivation, and energy in individuals suffering from depression. The overall rise in monoamine signaling accounts for both the effectiveness of MAOIs and the risks of serious interactions, such as hypertensive crises from consuming tyramine-rich foods or serotonin syndrome when taken with other serotonergic substances. Although they are effective, especially for the patients who are resistant to typical treatments, they are now infrequently prescribed due to serious dietary restrictions such as avoidance of aged cheese, cured meats, fermented foods, and alcoholic beverages, etc. since MAOIs prevent the degradation of tyramine, a compound present in specific food items. If patients on MAOIs eat foods rich in tyramine, it can result in a critical increase in blood pressure referred to as a hypertensive crisis. This condition may lead to intense headaches, elevated heart rates, and potentially stroke. In addition, hypertensive risk is similar to tricyclic antidepressants (TCAs).

Weight gain is a notable side effect, especially with phenelzine, which has been most notably related with this issue. In one review, 68% of phenelzine-treated patients gained weight, with mean gains of 9.1 kg (20.1 lbs) and 6.8 kg (15 lbs) in different subgroups. The phenomenon is believed to result from MAOIs' overall increase in serotonin, norepinephrine, and dopamine, which modifies the hypothalamic control of hunger and fullness. Long-term elevations in serotonin are associated with cravings for carbohydrates, while alterations in dopamine and norepinephrine signaling can interfere with metabolic rate and energy equilibrium. These physiological processes provide insight into the considerable weight gain seen with phenelzine and like medications (Wharton, 2018).

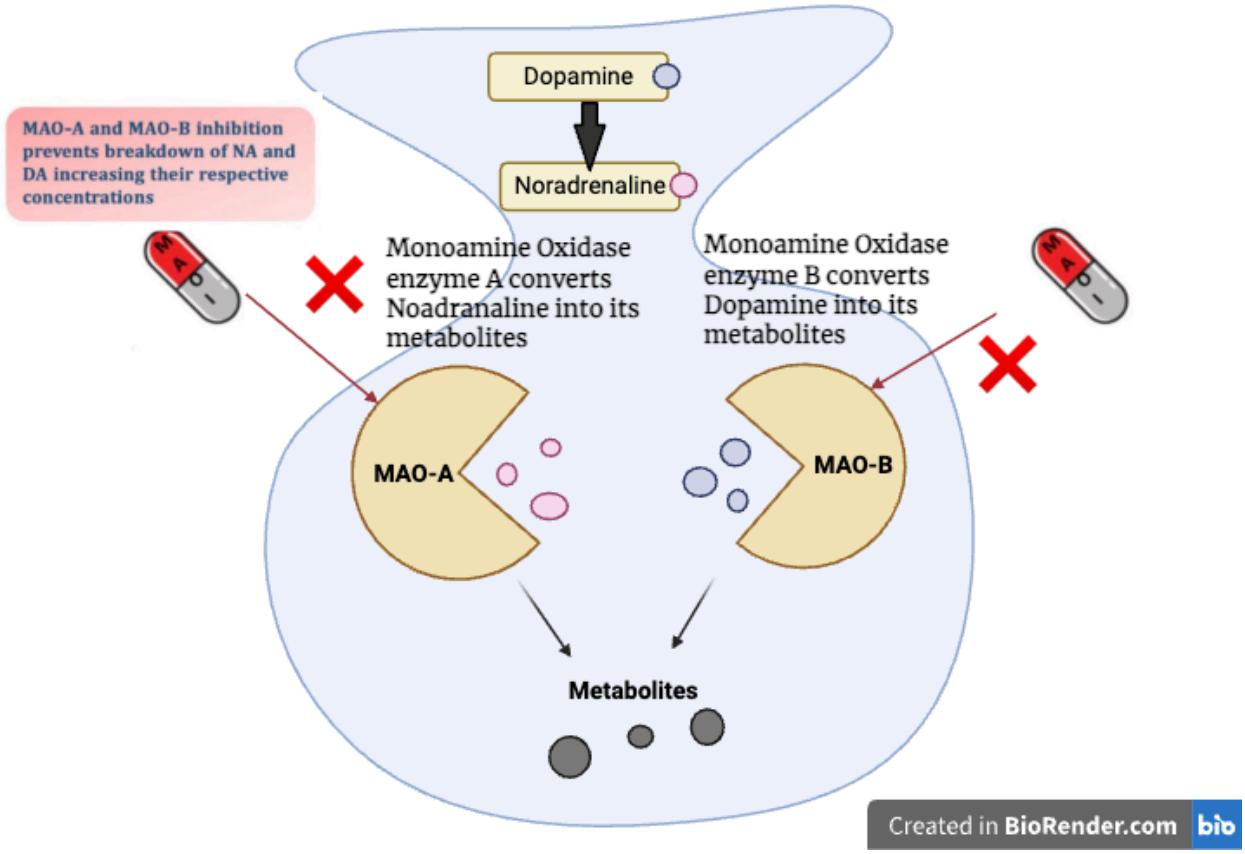

Fig. 2 | **Effect of MAOI on Neurotransmitters (Dopamine and Noradrenaline)** | a.The figure on the left illustrates the production of Dopamine, showing Tyrosine Uptake by the tyrosine transporter. Then Tyrosine Hydroxylase converts into dopamine and it is then converted into dopamine. Stored dopamine can be released into synapse when needed; dopamine can also be converted into noradrenaline. b.The figure on the right illustrates the metabolism of dopamine, which dopamine and noradrenaline are broken down by monomaine oxidases (MAOs). However, in this figure, MAOIs are blocking both MAO-A and MAO-B and this prevents the breakdown of dopamine and noradrenaline, causing higher concentrations of these neurotransmitters inside the neuron. Higher dopamine and noradrenaline concentrations lead to elevated mood. (Rege, S., 2021)

Bupropion

Bupropion acts as a norepinephrine–dopamine reuptake inhibitor (NDRI), distinguishing it by its minimal impact on serotonin systems. By preventing the reuptake transporters for norepinephrine and dopamine, bupropion elevates the synaptic levels of these neurotransmitters, improving reward pathways and energy regulation while minimizing numerous side effects related to serotonin. Clinically, bupropion is notable for its weight-neutral to weight-loss profile. This difference in mechanism appears to play a central role in its weight-neutral to weight-loss profile, which sets it apart from many first-line antidepressants like SSRIs and SNRIs.

In contrast to SSRIs or SNRIs, bupropion mainly focuses dopamine and norepinephrine activity, particularly in brain regions like the nucleus accumbens and prefrontal cortex, which are associated with motivation, reward processing, and energy regulation, not hypothalamus where Serotonin Inhibitors usually act upon. This dopaminergic activity causes a reduction in food-related reward sensitivity, decreases cravings, and reduces emotional eating. Additionally, increased norepinephrine levels can affect the energy level, which is linked to greater sympathetic activity.

Clinically, bupropion is one of the few antidepressants associated with weight reduction rather than gain. In a randomized controlled trial, patients taking extended-release bupropion (400 mg/day) lost an average of 3.7% of body weight over 48 weeks (Anderson et al., 2002). Meta-analyses have confirmed this finding, supporting bupropion's use in patients who are overweight, at risk for metabolic syndrome, or concerned about weight-related side effects of antidepressant treatment (Patel et al., 2016).

Antipsychotics

Although not antidepressants, second-generation antipsychotics are sometimes used adjunctively in depression treatment. "Second-generation" or "atypical" antipsychotics differ from first-generation drugs in that, in addition to mainly blocking dopamine D_2 receptors, they also target serotonin receptors. This action decreases the likelihood of movement-related side effects and expands their therapeutic applications. They are well-known for causing substantial weight gain, with some patients gaining 20–22 kg (approximately 44–48 lbs) within the first year (Harvard Health Blog, 2022). However, it is important to understand that weight gain is not always a primary clinical concern, as these drugs are usually prescribed in cases of severe psychiatric illness where mitigating symptoms is critical . In such scenarios, the therapeutic benefits often outweigh the metabolic risks, especially when paired with lifestyle interventions and ongoing medical monitoring.

Drug Class	Primary Mechanism	Example Drugs	Weight Gain Risk	Other Notable Side Effects
SSRIs	Block serotonin reuptake	Fluoxetine, Sertraline	Moderate	GI upset, sexual dysfunction
SNRIs	Block serotonin + norepinephrine reuptake	Venlafaxine, Duloxetine	Low–moderate	Insomnia, Hypertension
TCAs	Block serotonin + norepinephrine reuptake (non-selective)	Amitriptyline, Nortriptyline	High	Sedation, anticholinergic effects
NASSAs	Increase the release of norepinephrine and serotonin by blocking α2 receptors, and direct serotonin activity mainly toward the 5-HT1A pathway by blocking other serotonin receptors.	Mirtazapine	High	Sedation, increased appetite, weight gain (due to H1 blockade)
MAOIs	Inhibit monoamine oxidase (prevent NT breakdown)	Phenelzine, Tranylcypromine	Variable	Food interactions (tyramine), hypertension
NDRIs (weight-neutral)	Block norepinephrine + dopamine reuptake	Bupropion	Low/Neutral	Insomnia, dry mouth

Table.1 | **Table Summary of Different Antidepressant** | Summary of various kinds of antidepressants and their primary mechanism, examples, weight gain risk, and other notable side effects

Discussion and Conclusion

Summary of findings:

The relationship between antidepressant drugs and weight gain has emerged as one of the most clinically relevant and concerning side effects in modern society. As shown in multiple recent studies, many commonly prescribed medications, such as SSRIs and SNRIs, and those less commonly prescribed such as TCAs and MAOIs, have been implicated in causing significant weight gain in some patients (Mayo Clinic, 2024; Healthline, 2019). Though SSRIs and TCAs are frequently highlighted for their metabolic side effects, MAOIs such as phenelzine may also contribute to weight gain, albeit potentially to a lesser degree than TCAs (Cantú & Korek, 1988; Mayo Clinic, 2024). Weight gain poses risks that go beyond physical health, which includes heightened body dissatisfaction, decreased self-esteem, and reduced treatment adherence due to the fear of experiencing side effects. These can all impair mental health outcomes, creating an ironic situation where medication intended to support mood ends up undermining recovery. This complex interplay highlights the necessity for therapeutic options that effectively treat mood disorders without compromising on patients' metabolic stability.

Future Directions in Drug Development:

One promising direction for less side effects for these treatments is to develop and widely adopt the usages of weight-neutral antidepressants. The NDRI class, particularly bupropion, is highlighted for its favorable metabolic profile that provides therapeutic relief without the risk of weight gain. In reality, certain patients may even notice slight weight loss while taking bupropion, setting it apart from the majority of other antidepressants. This weight-neutrality is believed to result from bupropion's lack of significant impact on serotonin signaling. Unlike SSRIs and SNRIs, which increase synaptic serotonin and are often associated with changes in appetite and metabolism, bupropion acts primarily on dopamine and norepinephrine pathways. It shows minimal to no activity at serotonin transporters or receptors, which may explain its lower likelihood of causing weight gain (Stahl, 2004). Clinicians need to exercise caution when prescribing bupropion, given its contraindication in individuals with eating disorders like anorexia nervosa or bulimia nervosa, where electrolyte imbalances together with bupropion's potential to decrease the seizure threshold can greatly elevate the risk of seizures. Therefore, thorough patient selection and screening are crucial prior to starting treatment.

The future of effective and metabolically safe treatment for patients may lie in personalized medicine. Currently, the selection of antidepressant follows a trial-and-error approach that often leads to avoidable side effects. Integrating genetic and metabolic profiling into prescribing decisions prior to trial could help predict which patients are at higher risk for weight gain, and therefore moving more towards weight-neutral options. Moreover, the field lacks biochemical markers for depression; and clinical diagnoses are heavily symptom-based. Identifying molecular or neuroimaging biomarkers could be treated by enabling the therapies to be more precision-targeted, therefore reducing both inefficiency and negative side effects.

Clinical Implications:

Clinicians must exercise greater caution regarding the metabolic side effects of antidepressants and warn the patients beforehand regarding these side effects. Careful consideration of the clinicians can be shown through proactively discussing the potential for weight gain with patients, especially for those medications that are known to carry higher risks. Carefully determining the patients that are at metabolic risk, such as those with preexisting obesity or family history of diabetes, and informing them with such information could also be crucial. Finally, prescribers should emphasize that in certain circumstances, side effects such as weight gain may be a minor consideration compared to the primary goal of treating the condition. Ultimately, improved care comes down to ensuring that patients are well-informed about their treatment options and feel comfortable with the course of therapy.

Acknowledgements

I would like to thank my mentor, Matthew Johnson, for his guidance and support throughout the project. I am also grateful to my Polygence writing mentors, Hannah and Jackie, for their valuable feedback. Finally, I acknowledge Polygence for providing the platform that made this project possible, and BioRender, which I used to create figures for the paper.

References

[1] Allison, D. B., Mentore, J. L., Heo, M., Chandler, L. P., Cappelleri, J. C., Infante, M. C., & Weiden, P. J. (1999). Antipsychotic-induced weight gain: A comprehensive research synthesis. *American Journal of Psychiatry, 156*(11), 1686–1696. https://doi.org/10.1176/ajp.156.11.1686

[2] American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

[3] Anxiety and Depression Association of America. (2025, August 21). *Facts & statistics*. https://adaa.org/understanding-anxiety/facts-statistics

[4] Anderson, J. W., Greenway, F. L., Fujioka, K., Gadde, K. M., McKenney, J., & O'Neil, P. M. (2002). Bupropion SR enhances weight loss: A 48-week double-blind, placebo-controlled trial. *Obesity Research, 10*(7), 633–641. https://doi.org/10.1038/oby.2002.86

[5] Baptista, T., ElFakih, Y., Uzcátegui, E., Sandia, I., Talamo, E., & Añez, F. (2002). Pharmacological management of atypical antipsychotic-induced weight gain. *CNS Drugs, 16*(2), 85–95. https://doi.org/10.2165/00023210-200216020-00001

[6] De Hert, M., Detraux, J., van Winkel, R., Yu, W., & Correll, C. U. (2011). Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nature Reviews Endocrinology, 8*, 114–126. https://doi.org/10.1038/nrendo.2011.156

[7] Fava, M. (2000). Weight gain and antidepressants. *The Journal of Clinical Psychiatry, 61*(Suppl 11), 37–41.

[8] Malhi, G. S., & Mann, J. J. (2018). Depression. *The Lancet, 392*(10161), 2299–2312. https://doi.org/10.1016/S0140-6736(18)31948-2

[9] National Institute of Mental Health (NIMH). (2023). Mental illness. https://www.nimh.nih.gov/health/statistics/mental-illness

[10] Serretti, A., & Mandelli, L. (2010). Antidepressants and body weight: A comprehensive review and meta-analysis. *Journal of Clinical Psychiatry, 71*(10), 1259–1272. https://doi.org/10.4088/JCP.09r05346blu

[11] Stahl, S. M. (2021). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (5th ed.). Cambridge University Press.

[12] World Health Organization (WHO). (2022). Mental health. https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response

[13] Zimmermann, U., Kraus, T., Himmerich, H., Schuld, A., & Pollmächer, T. (2003). Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. *Journal of Psychiatric Research, 37*(3), 193–220. https://doi.org/10.1016/S0022-3956(03)00018-9

[14] Delgado, P. L. (2000). Role of norepinephrine in depression. *Journal of Clinical Psychiatry*, *61*(suppl 1), 5–12. https://pubmed.ncbi.nlm.nih.gov/10703757/

[15] Katzman, M. A., Bleau, P., Blier, P., Chokka, P. R., Kjernisted, K., & van Ameringen, M. (2022). A systematic review of serotonin and its role in major depressive disorder. *Neuroscience & Biobehavioral Reviews*, *131*, 252–265. https://doi.org/10.1016/j.neubiorev.2021.10.003

[16] Fava, M. (2020). Weight gain and antidepressants. *Journal of Clinical Psychiatry, 81*(3), 19ac13181. https://doi.org/10.4088/JCP.19ac13181

[17] Hainer, V., Kabrnova, K., Aldhoon, B., Kunesova, M., & Wagenknecht, M. (2006). Serotonin and norepinephrine reuptake inhibition and eating behavior. *Annals of the New York Academy of Sciences, 1083*, 252–269. https://nyaspubs.onlinelibrary.wiley.com/doi/10.1196/annals.1367.017

[18] Moss, L., Laudenslager, M., Steffen, K. J., Sockalingam, S., & Coughlin, J. W. (2025). *Antidepressants and Weight Gain: An Update on the Evidence and Clinical Implications*. Current Obesity Reports, 14(1), Article 2. https://link.springer.com/article/10.1007/s13679-024-00598-5

[20] Commons, K. G. (2019). Delayed antidepressant efficacy and the desensitization hypothesis. *ACS Chemical Neuroscience*, *10*(7), 3048–3052. https://pubs.acs.org/doi/10.1021/acschemneuro.8b00698

[21] Hers. (2022, January 10). *Amitriptyline weight gain: Why it happens and what to do*. https://www.forhers.com/blog/amitriptyline-weight-gain

[22] Grajales, D., Carli, M., & Rojas, G. (2019). Second-generation antipsychotics and dysregulation of glucose homeostasis: The role of muscarinic M3 receptor antagonism. *Cells, 8*(11), 1336. https://doi.org/10.3390/cells8111336

[23] Anderson, J. W., et al. (2002). Bupropion SR enhances weight loss: A 48-week double-blind, placebo-controlled, multicenter trial. Obesity, 10(6), 387–397. https://pubmed.ncbi.nlm.nih.gov/12105285/

[24] Cantú, T. G. (1988). Monoamine oxidase inhibitors and weight gain. *Drug Intelligence & Clinical Pharmacy,22(10), 923–926. https://pubmed.ncbi.nlm.nih.gov/3068037/

[25] Lechner, K., et al. (2023). Weight-gain independent effect of mirtazapine on fasting metabolism and energy substrate partitioning in healthy men. Frontiers in Pharmacology. https://pmc.ncbi.nlm.nih.gov/articles/PMC10409833/

[26] Patel, K., et al. (2016). Bupropion: a systematic review and meta-analysis. Pharmacotherapy, 36(10), 1105–1119. https://pmc.ncbi.nlm.nih.gov/articles/PMC4837968/

[27] U.S. Food and Drug Administration. (2020). REMERON (mirtazapine) label. Section 5.6: Increased Appetite and Weight Gain.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020415s029,%20021208s019lbl.pdf

[28] Wharton, S. (2018). Medications that cause weight gain and alternatives in Canada: A narrative review. Problems in Managing Obesity, 10, 123–130. https://pmc.ncbi.nlm.nih.gov/articles/PMC6109660/

[29] Harvard Health Blog. (2022, July 18). Managing weight gain from psychiatric medications. Harvard Medical School. https://www.health.harvard.edu/blog/managing-weight-gain-from-psychiatric-medications-20220 7182781

[30] Cantú, T. G., & Korek, J. S. (1988). *Monoamine oxidase inhibitors and weight gain*. Drug Intelligence & Clinical Pharmacy, 22(10), 755–759. https://doi.org/10.1177/106002808802201002
International Center for Neuroscience. (2023). *How psychedelic drugs may help with depression*. NIH Research Matters. https://www.nih.gov/news-events/nih-research-matters/how-psychedelic-drugs-may-help-depression

[31] Mayo Clinic. (2024, August 17). *Antidepressants and weight gain: What causes it?* Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/depression/expert-answers/antidepressants-and-weight-gain/faq-20058127

[32] Cameron, L. P., Tombari, R. J., Lu, J., Pell, A. J., Hurley, Z. Q., Ehinger, Y., ... & Olson, D. E. (2021). *Chronic administration of psychedelics reduces weight gain and adiposity in diet-induced obese rats.* Frontiers in Psychiatry. https://www.frontiersin.org/articles/10.3389/fpsyt.2022.891512/full

[33] de la Fuente Revenga, M., Shah, U. H., & Olson, D. E. (2022). *Psilocybin does not alter feeding behavior or body weight in mice.* Neuropsychopharmacology. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372155

[34] Olson, D. E., et al. (2022). *Body mass index does not predict therapeutic response to psilocybin-assisted therapy.*https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9834321

[35] Downey, L. A., et al. (2014). *Neurobehavioral consequences of repeated MDMA in adolescent rats.*https://pubmed.ncbi.nlm.nih.gov/24121061

[36] Mitchell, J. M., et al. (2023). *MDMA-assisted therapy for moderate to severe PTSD: A randomized, double-blind, placebo-controlled Phase 3 study.* Nature Medicine. https://pubmed.ncbi.nlm.nih.gov/38654146

[37] Phelps, J., et al. (2024). *Review of adverse effects in MDMA-assisted therapy trials.* PsyPost.

https://www.psypost.org/mdma-therapy-side-effects-appear-mild-but-there-are-problems-with-the-evidence

[38] University of California, San Francisco. (2022). *Psilocybin rewires the brain for people with depression*. UCSF News. https://www.ucsf.edu/news/2022/04/422606/psilocybin-rewires-brain-people-depression

[39] Stahl, S. M., Pradko, J. F., Haight, B. R., Modell, J. G., Rockett, C. B., & Learned-Coughlin, S. (2004). *A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor*. Primary care companion to the Journal of clinical psychiatry. https://pmc.ncbi.nlm.nih.gov/articles/PMC514842?utm_source=chatgpt.com

[40] Rege, S. (2021, April 7). *Monoamine Oxidase Inhibitors (MAOI) - Mechanism of Action | Psychopharmacology*. Psych Scene Hub. https://psychscenehub.com/psychinsights/maoi-psychopharmacology/