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Metabolic changes associated with antidepressants: Understanding the risks to achieve more than a pyrrhic victory

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Summary

Major depressive disorder is a leading cause of mortality and morbidity and is associated with an increased cardiometabolic risk on its own. On the other hand, antidepressants are being prescribed to more patients every day and these medications carry some important nuances in terms of side effects regarding their effects on metabolic profile. In this narrative review, we provide a drug class oriented overview to antidepressants, including their proven effects on various metabolic parameters such as lipid markers, blood glucose, waist circumference, body mass index and body weight. It is of utmost importance to choose the metabolically correct antidepressant for each patient, taking their metabolic risk profile into account, in order not be deceived by the pyrrhic victory presenting itself as mere psychiatric symptom control.

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INTRODUCTION

Major depressive disorder (MDD) is a major public health issue associated with an increased cardiovascular disease risk and associated mortality. In adults living with depression, other "traditional" atherosclerotic cardiovascular disease (ASCVD) risk factors are already more prevalent, when compared with controls (Al-Khatib et al., 2022). This might be contributing to excess mortality associated with this condition (Al-Khatib et al., 2022). On the other hand, the mainstay mainstay options for the treatment of depression include antidepressants and psychotherapy.

The most commonly prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs), which exert their effects specifically on a single neurotransmitter, namely serotonine.

This mechanism of action makes them the first option to treat many psychiatric disorders for a great number of practitioners, as it is also associated with a more favorable side-effect profile.

The other antidepressants can be classified roughly as the following: serotonin noradrenaline reuptake inhibitors (SNRI), monoamine oxidase inhibitors (MAOI), cyclic antidepressants including tricyclic (TCA) and tetracyclic (TeCA) antidepressants, and all others.

Although almost all of these antidepressants are associated with various types of adverse effects in terms of cardiovascular health (Morriss et al., 2021), their effects on cardiometabolic variables, still require further investigation. Adiditonally, a study involving 14,875 participants showed significant associations with metabolic syndrome in individuals with depressive symptoms or individuals being treated with antidepressants (Meshkat et al., 2025). Metabolic syndrome prevalence is also known to be high but is also known to show great variations among the studies (Kozumplik & Uzun, 2011).

Furthermore, the current data focuses on specific medications despite the great diversity of antidepressants. Emphasizing the choice of appropriate drug, based on established cardiometabolic risk profile, is of utmost importance, as antidepressant medications are very commonly prescribed. This review aims, therefore, to provide an overview to the cardiometabolic profile of the most commonly prescribed antidepressants.

AN OVERVIEW OF ANTIDEPRESSANT CLASSES

Selective serotonin reuptake inhibitors

SSRIs are the most commonly prescribed antidepressants worldwide (Wozniak et al. 2011), with escitalopram being the most selective of them for serotonin receptors (5-HTR), SSRIs are, in general, however known to modulate various receptors alongside (Rami et al., 2018). SSRIs mainly prevent depletion of serotonin (5-HT) in the synaptic cleft, leading to greater amounts of serotonin available (Rami et al. 2018). As a result, this leads to amelioration of symptoms in many psychiatric disorders, where the lack of 5-HT plays a significant role (Rami et al., 2018). On the other hand, it is widely appreciated that the effects of SSRIs are not only limited to serotonin in the central nervous system (Rami et al., 2018). In the meantime, peripheral serotonin also plays important roles, not only in the regulation of vascular tone and permeability but also in the platelet degranulation and aggregation (Rami et al., 2018).

Furthermore, 5-HT is known to inhibit the production of tumor 1 necrosis factor alpha (TNF-α), a cytokine associated with endothelial damage, which is known to be increased along with other proinflammatory cytokines such as interleukin (IL) 1ß, IL-6 and interferon (IFN) γ, in cases of psychosocial stress, including depression (Annam et al., 2023). Thus, leading to the diminution of the overall vascular inflammation in the affected individual (Narita et al., 2006). Consequently, patients with remitted depression, under maintenance therapy with SSRIs, have lower levels of TNF-α, which suggest that SSRIs may have a protective role against atherosclerosis (Narita et al., 2006). Additionally, adiponectin, an adipokine which is known to be protective against atherosclerosis, is detected to be increased in this same patient group, when compared to the controls, which might further contribute to the positive effects of SSRIs in atherosclerosis (Wozniak et al., 2011).

On the contrary, an vitro study conducted using cardiac organoids showed that fluxoetine, paroxetine and sertraline interefered with cardiac development and altered the sarcomere structure in the developing cardiomyocytes (Shen et al., 2025).

Some authors propose a classification of SSRIs in two groups regarding their affinity for 5-HT2 and H1 receptors, as all SSRIs have similar affinities for the serotonin transporter (SERT) (Cao et al., 2022). These two groups comprise strong-affinity SSRIs, including citalopram, escitalopram and fluoxetine, which show greater affinity for 5-HT2c and H1c receptors, relative to SERT (Cao et al., 2022). On the other hand, the weak-affinity group includes paroxetine, sertraline and fluvoxamine (Cao et al., 2022).

It's widely known that SSRIs carry a risk for type 2 diabetes (T2DM) in youth, especially in those who have normal or low weight and were previously treated with antipsychotics (Cao et al., 2022). Nevertheless, there is no significant advantage of one SSRI over another when it comes to the risk of developing T2DM (Cao et al., 2022).

Atherosclerosis Risk in Communities (ARIC) study showed that participants treated with SSRIs have a higher risk for ASCVD (HR: 1.10) and stroke (HR: 1.07) when compared to others treated with non-SSRI antidepressants, after a median follow up of 13.5 years (Richards-Belle et al. 2023). Additionally, SSRI use might be associated with various metabolic risk factors such as abdominal obesity (OR = 1.40, 95% CI = 1.08 to 1.81) and hypercholesterolemia (OR = 1.36, 95% CI = 1.07 to 1.73) (Richards-Belle et al. 2023). Citalopram might be the exception in the group; however, the data is controversial about its metabolic effects. Some authors suggest that it's associated with hypercholesterolemia, though less than other SSRIs (Richards-Belle et al. 2023), others suggesting no association with hypercholesterolemia or abdominal obesity (Raeder et al., 2006). Moreover, some authors suggest that metabolic alterations such as weight gain and waist circumference change occur only in patients treated for depression, with no change being observed in patients treated for anxiety disorders (Olguner Eker et al., 2017).

The first drug of the class, fluoxetine, has been associated with carotid atherosclerotic lesion formation and progression even in the 2nd week of treatment, in apolipoprotein E-deficient mice fed with high-fat diet (Rami et al., 2018). Surprisingly, this effect is not mediated by its effect on serotonergic receptors (Rami et al., 2018). In situations where C-C domain chemokine ligand 5 (CCL5/RANTES) is present, fluoxetine promotes the activation of β1 and β2 integrins, leading to increased binding of circulating leukocytes, in addition to resulting in an increased vascular permeability (Rami et al., 2018). Fluoxetine might additionally cause transient weight loss in the first weeks of treatment, which might, in longer term, contribute to the further treatment of overweight patients (Scheen 2023, Drieling et al., 2007).

Paroxetine, a highly selective SSRI, is known to cause the greatest weight gain in patients, along with other non-SSRI antidepressants such as mirtazapine and amitriptyline (Scheen, 2023). Also, concomitant treatment with antidepressants might result in less-than-expected weight loss in patients treated with glucagon-like-peptide 1 receptor agonists (Scheen, 2023).

Overall, in youth with anxiety and depression, along with paroxetine, citalopram can also cause significant weight gain, with the smallest risk of weight change appearing to be in sertraline (Strawn et al., 2023).

In a rat model of high fat induced atherosclerosis, escitalopram, is associated with significantly decreased levels of low-density lipoproteins (LDLs), very low-density lipoproteins (VLDLs) and triglycerides (TGs), and an increase in HDLs compared to atorvastatin, after 6 weeks of treatment (Unis et al. 2014). In these rats, aortic tissue examination revealed the regression of atherosclerosis and decreased expressions of vascular cell adhesion molecule-1 (VCAM-1) in both groups (Unis et al., 2014). Hence, escitalopram might be of use especially in elderly individuals with known atherosclerotic burden (Unis et al. 2014). It's important to note and not to confuse that, citalopram, an enantiomer of escitalopram, might promote leukocyte binding to endothelium, therefore carries the potential risk of accelerating atherosclerosis (Ungyari et al., 2019). A study suggested that citalopram can cause more significant weight gain in CYP2C19 poor/intermediate metabolizers at 6 months of treatment, whereas such an association could not be established with other SSRIs (Ricardo-Silgado et al., 2022).

The most significant negative effects on total cholesterol (TC) and LDL-C are reported to be observed in paroxetine and sertraline, whereas citalopram having no significant effect on these two parameters, however resulting in slightly elevation of HDL-C levels (Colotto et al., 2012). Paroxetine, when used for a longer duration and in higher doses, can cause greater increases in LDL-C beyond 100mg/dL, especially in individuals with established cardiovascular disease, who usually require a more aggressive lipid lowering therapy (Le Melledo et al., 2009). However, sertraline, fluoxetine and paroxetine can cause similar increases in TC and LDL-C, and similar decreases in HDL-C (Richards-Belle et al., 2023). Sertraline is found to be associated with a higher TC: HDL ratio, when compared with fluoxetine, paroxetine and citalopram/escitalopram (Richards-Belle et al., 2023). The most remarkable increase in TG levels is observed in paroxetine, followed by sertraline and fluoxetine, escitalopram/citalopram, respectively (Richards-Belle et al., 2023). Fluoxetine is observed to decrease apolipoprotein (Apo)-B/Apo-A1 ratio, an important predictor of CVD, in overweight patients (Hu et al., 2021).

Paradoxically, despite the metabolic disadvantages of sertraline, the SADHART-CHF study examining the effect of sertraline for 12 weeks on individuals with congestive heart failure (CHF) showed that sertraline is widely safe in this group, although not leading to better outcomes in terms of depression and cardiovascular health (O'Connor et al., 2010). The reason for the proposed safety of sertraline might be the short duration of follow-up, not allowing the metabolic deterioration associated with sertraline reflect its effect on cardiovascular outcomes (O'Connor et al., 2010).

Fluvoxamine, a less-studied low-affinity SSRI, can help lower TC levels in overweight females trying to lose weight, more effectively provided that the initial TC levels are high (≥ 200 mg/dL) (de Zwaan et al., 1996). Adjunctive use of fluvoxamine may help alleviate clozapine-associated weight gain and metabolic derangement, in terms of serum glucose and TG levels, when compared with the clozapine monotherapy (Lu et al., 2004).

In summary, SSRI use alone (HR: 1.32; 1.14–1.53) or in combination with other antidepressants, such as TCAs (HR: 1.86; 1.23–2.82), is associated with the development of CVD, sertraline and citalopram carry the highest risks (Morriss et al., 2021). In addition, SSRIs are also associated with the development of diabetes, a metabolic risk factor for CVD, alone (HR: 1.28; 1.10–1.49) or in combination (HR: 1.76; 1.12–2.76), while citalopram and fluoxetine being the most commonly implicated agents among SSRIs (Morriss et al., 2021).

Escitalopram might prove itself especially useful in patients with existing metabolic burden due to its positive impact on blood lipids. Caution might be taken when prescribing paroxetine in individuals with a high risk for ASCVD, as it is associated with weight gain, which might negatively affect the metabolic profile. On the other hand, fluoxetine might lead to the false impression that it is associated with weight loss, however, it shouldn't hinder the prescriber from controlling metabolic parameters as this effect is mostly transitionary. Additionally, fluoxetine and citalopram might deteriorate existing atherosclerotic vascular disease, due to their proinflammatory effects on the atherosclerotic vascular niche.

Overall, SSRIs are, in general, safer in patients with established CVD, when compared with other antidepressants, despite their association with metabolic derangements. The reasons include but not limited to their inhibition on platelet aggregation and their positive effects on inflammatory mediators, resulting in an overall improved endothelial function (Andrade et al. 2013). Another reason is that they tend to less interact with medications used in patients with metabolic and cardiovascular diseases (Andrade et al., 2013).

Serotonin noradrenaline reuptake inhibitors

Unlike antidepressants effective on only a single type of neurotransmitter such as SSRIs, serotonin noradrenaline reuptake inhibitors function mainly by blocking the reuptake of these two neurotransmitters from the synaptic cleft, leading to the inhibition of their transporter proteins on the presynaptic neuronal membrane (Cashman et al., 2009). In addition to their use in a great variety of psychiatric disorders, they, especially duloxetine, have proven themselves useful in the treatment of chronic and neuropathic pain (Wright et al., 2017).

Venlafaxine, although being considered as an SNRI, has lower affinities to both 5-HT and noradrenaline (NA) receptors, despite its potent inhibitory effect on the reuptake of both neurotransmitters (Béïque et al., 1998). The data on the effect of venlafaxine on weight is controversial (Drieling et al., 2007). However, venlafaxine can result in higher increases in TC, LDL-C, TC: HDL-C ratio and TG, compared to many SSRIs such as fluoxetine, paroxetine, sertraline and citalopram/escitalopram (Richards-Belle et al., 2023). Its HDL-C lowering effect is, as a result, similar to sertraline and paroxetine (Richards-Belle et al., 2023). In addition, in toxic doses, venlafaxine might induce severe hypoglycemia (Bekka et al., 2022) and, in predisposed individuals with multiple comorbidities, remarkable hypertriglyceridemia (Lin et al., 2017).

Another SNRI, duloxetine, which has a stronger affinity for 5-HT and NA receptors than venlafaxine (Béïque et al., 1998), is associated with increases in plasma glucose, glycosylated hemoglobin (HbA1c) and TC levels (Yasuda et al., 2016; Oakes et al., 2013). Duloxetine, on the other hand, can lead to weight gain in elderly individuals with diabetic neuropathic pain or depression, however statistically irrelevant, therefore leading to no safety concerns (Yasuda et al., 2016, Oakes et al., 2013).

Milnacipran has shown to effect metabolic parameters positively in depressed patients with comorbid diabetes, leading to a decrease in the rate of patients with HbA1c > 8% (>63.9 mmol/mol) from 31.9% to 11.9% during the treatment for 6 months (Abrahamian et al., 2012). TC and TG levels have shown, in the meantime, modest decreases (Abrahamian et al., 2012). Milnacipran additionally reduces body weight significantly (Abrahamian et al., 2012).

Cyclic antidepressants

Similar to SNRIs, cyclic antidepressants inhibit SERT along with NA transporters (NET), and they are still used in inpatient setting in complicated cases, resistant to first-line treatments such as SSRIs. Nevertheless, they have been replaced by SSRIs and SNRIs to a larger extent in outpatient settings (Trindade et al., 1998; Tatsumi et al., 1997).

Trimipramine, a TCA, can lead to increases in weight (3.3%) 1 and appetite, it may additionally lead to an increased preference for carbohydrates in diet (Harris et al., 1987). It also interferes with the glucose and lipid metabolism in adipose tissues, resulting in increased release of free fatty acids and glycerol, as a result, increasing their circulating plasma levels (Flechtner-Mors et al., 2008).

Doxepin, in low-doses, can lead to statistically significant increases in TG, TC, LDL-C and fasting blood glucose values (Zhang et al., 2022). It also causes non-significant increases in BMI and body weight, however, no significant changes in HDL-C levels when compared with pretreatment values (Zhang et al., 2022). In a review of studies on doxepin, it is found to be associated with a weight gain of 27% of the initial body weight, within 4 to 13 weeks (Drieling et al., 2007).

Another TCA, nortriptyline can induce significant weight gain (more than 17% of initial body weight), in 5-7 months (Drieling et al., 2007). Nortriptyline may also increase VLDLs and TGs significantly, however having neutral effect on TC or LDL-C (Pollock et al., 1994).

Amitriptyline, which leads to an increase in weight ranging from 1.7 to 7.3 kgs in 6 months, is the most common cause of weight gain among TCAs (Drieling et al., 2007). The weight gain can be observed in 20-72% of patients treated, according to different studies (Drieling et al., 2007). Amitriptyline caused also drop-out in 10% of all the patients in one study, due to weight gain (Drieling et al., 2007). However, when compared with SSRIs such as fluoxetine, paroxetine, sertraline and SNRIs such as venlafaxine, amitriptyline is associated with a more modest increase in TC (Richards-Belle et al., 2023). It is also safer in terms of LDL-C than many SSRIs except citalopram/escitalopram (Richards-Belle et al., 2023). Amitriptyline can cause an increase in both TG and TC: HDL-C ratio, similar to many SSRIs except citalopram/escitalopram, which shows less increases in both parameters (Richards-Belle et al., 2023). Eventually, its effect on lowering the HDL-C is more prominent than many SSRIs (Richards-Belle et al., 2023).

Clomipramine, another TCA, is considered especially useful in the treatment of obsessive compulsive disorder, which is furthermore known to have a slightly decreasing effect on TC and LDL-C, while increasing HDL-C to a smaller extent, however decreasing TC: HDL-C ratio significantly. It can increase the level of HDL2-C but not affecting HDL3-C levels. Additionally, it increases apolipoprotein A-I levels minimally, all of which having an alleviating effect on the overall coronary risk (Skinner

et al., 1989). A 34.8% of all obsessive-compulsive disorder patients treated with clomipramine gained ≥ 7% in weight when compared with many SSRIs, in a study with a follow-up duration of 2.5 years (Maina et al., 2004) Long-term therapy was associated with food craving and increased body weight in an animal model treated with clomipramine, however clomipramine doesn't lead to a change in the preference of one type of diet (fat-rich or protein rich) over another (Calegari et al., 2007).

Desipramine, a different TCA, can lead to minimal weight gain in short duration (4-5 weeks) treatments, however usually considered neutral in terms of body weight (Drieling et al., 2007). Weight gain is only observed in those who responded to the treatment with desipramine (Drieling et al., 2007). Additionally, as an inhibitor of acid sphingomyelinase, a potent promoter of atherosclerosis and cardiovascular events, desipramine can attenuate oxidized-LDL-induced apoptosis of the macrophages, leading eventually to smaller plaque size and higher smooth muscle content of the plaque and reduced matrix metalloproteinase activity, contributing to a more stable atherosclerotic plaque in animal model, an effect similar to those of atorvastatin (Zhao et al., 2023).

Imipramine leads to a weight gain of 5%, when compared with baseline, in the first 8 weeks of treatment, reaching up to 25% after 16-46 weeks (Drieling et al., 2007). In an open-label clinical trial comparing fluoxetine and imipramine, imipramine was associated with significant increasesin TC and TG, most pronounced in the 8th week of the treatment (Ananloo et al., 2013).

Although the data on tianeptine is limited, a single study showed that tianeptine causes a continuous weight loss when administered for 12 months (Svacina, 2005).

Maprotiline, a TeCA, is associated with a significant increase in BMI, ghrelin and insulin levels, along with Homeostasis Model Assessment (HOMA) indexes, accompanied by a decrease in adiponectin concentration after 30 days of treatment in lean patients with depression (Pinar et al., 2008). Another study showed that maprotiline can cause 22% weight gain after a treatment period of only 40 weeks (Drieling et al., 2007). Maprotiline decreases the phosphorylation of sterol regulatory element-binding protein 2 (SREBP2), which activates the expression of HMG-CoA reductase, HMG-CoA synthase and mevalonate kinase, all of which are responsible for cholesterol synthesis, which in turn results in diminished cholesterol synthesis (Madison, 2016). Additionally, SREBP2 leads to increased expression of LDL receptors (Madison, 2016), increasing its uptake from the circulation (Zheng et al., 2021), however due to the availability of limited data, the effects of maprotiline on cholesterol metabolism require further investigation.

Mirtazapine, a TeCA, along with other weight gain promoting antidepressants such as TCA, can negatively impact lipid parameters compared to weight-neutral antidepressantssuch as bupropion, venlafaxine and duloxetine (McIntyre et al., 2006). Mirtazapine is also one of the most notorious antidepressants when it comes to weight gain, leading to a mean weight increase of 3 kgs even after 6 weeks of treatment (McIntyre et al., 2006), allowing psychiatrists to exploit it in depressed patients with concomitant appetite and eating problems. Mirtazapine leads to a weight gain in 10-30% of the patients, reaching 2,9 kgs in 24 weeks, with the maximum weight gain being observed after 12 weeks (Drieling et al., 2007). It can, additionally, negatively affect TC (+7.6 mg/dl), TG and LDL-C levels (Richards-Belle et al., 2023), even though some studies suggest that no changes in lipid parameters (TC, HDL-C, LDL-C and TG) or fasting glucose and insulin levels occur (McIntyre et al., 2006).

Monoamine oxidase inhibitors

Monoamine oxidases (MAO) are responsible for the metabolism of various neurotransmitters, especially MAO-A being responsible for the catabolism serotonin, melatonin, norepinephrine and epinephrine (Yeung et al., 2019). MAOI are indicated in the treatment of various psychiatric and neurological problems, however they are associated with significant drug and food interactions, which might lead to severe side effects (Fiedorowicz & Swartz, 2004).

As a first generation MAOI, isocarboxazid is a nonselective inhibitor of MAO-A and MAO-B, it is associated with weight gain (2.8%) and an increased preference for carbohydrates (Hyman Rapaport, 2007). On the other hand, some authors suggest that it can lead to weight loss (Gadde et al., 2006).

Different studies suggested that, phenelzine, a nonselective MAOI, was associated with weight gain in 8-36% of patients (Drieling et al., 2007). In a murine model, phenelzine-treated animals had lower body fat and reduced lipid accumulation in skeletal muscles compared to controls, however did not show change in weight or food consumption behavior. Phenelzine reduced non-fasting blood sugar levels in these animals. The consecutive in-vivo treatment of mouse adipocytes with high-doses of phenelzine caused both lipolytic and lipogenic responses. As a result, phenelzine is suggested to reduce body fat without interfering with cardiovascular function in this model (Carpéné et al., 2018). Another similar study also proved that phenelzine can not only reduce total body fat but also proinflammatory markers and insulin resistance

associated with it, in mice treated with a high fat diet (Mercader et al., 2019). On the other hand, phenelzine is shown to inhibit insulin-dependent glucose uptake function of the adipocytes, however did not interfere with glucose transport but lead to decreased intracellular triacylglycerol accumulation (Carpéné et al., 2018). First generation MAOIs such as phenelzine and isocarboxazid are nonselective inhibitors of both subtypes of MAO, therefore, they require strict dietary modifications due to drug interactions and significant weight gain (Hyman Rapaport, 2007).

Tranylcypromine is known to be associated with a weight gain of no more than 6.8 kgs in treated individuals, as suggested by a retrospective study conducted by Rabkin et al, 1985 (Drieling et al., 2007).

Selegiline**,** a selective MAO-B inhibitor, can reduce adiposity and adipose inflammation in animal models of high fat diet, with no effects on weight gain or no impairment of glucose homeostasis (Nagy et al., 2018). Selegiline can also ameliorate hepatic steatosis and dyslipidemia in mice treated with a high-fat diet, by reducing the hepatic inflammation associated proinflammatory cytokines IL-6, TNF-α, IL-1β, and IL-1α (Tian et al., 2023).

Other antidepressants

Vortioxetine is a serotonin modulator and stimulator (SMS), therefore belonging to a novel class of antidepressants, which is usually not associated with side effects of other antidepressants (Tovilla-Zárate et al., 2019). In a study comparing vortioxetine and sertraline in patients with depression and concomitant T2DM, vortioxetine is detected to be associated with decreased body weight, weight circumference and HbA1c, although body weight increased in those treated with sertraline, with waist circumference and HbA1c remaining unchanged (Tovilla-Zárate et al., 2019). Therefore, vortioxetine may promote glycemic control in this patient group (Tovilla-Zárate et al., 2019). Vortioxetine can reduce total cholesterol and triacylglycerols in patients with T2DM and depression, unlike sertraline which is known to increase serum triacylglycerol levels (Tovilla-Zárate et al., 2019). Some authors suggest that it can even decrease HbA1c levels (De Diego-Adeliño et al., 2022).

Reboxetine, a norepinephrine reuptake inhibitor approved only in Europe but not in the United States, a 4-week-long treatment of patients with unipolar depression led to statistically significant decrease in TC, LDL-C and BMI (Paslakis et al., 2011). BMI reduction under reboxetine therapy can also be observed in adolescent population (Bozkurt & Şahin, 2016). Reboxetine may also attenuate weight gain associated with second generation antipsychotics such as olanzapine, when prescribed concomitantly (Poyurovsky et al., 2007).

As a norepinephrine-dopamine reuptake inhibitor and a nicotinic receptor antagonist, bupropion differs from the other antidepressants, as it is not associated with side effects associated with other medications, including weight gain (Patel et al., 2016). Bupropion can be used as an effective bariatric treatment in adults with BMI 30-44 kg/m^2 with depressive symptoms, even without fulfilling the criteria for a major depression. It results in a weight loss of 4.4 kgs versus 1.7 kgs when compared with placebo (McIntyre et al., 2006). Considered as a "weight-neutral" antidepressant, bupropion is less likely to interfere with lipid parameters (McIntyre et al., 2006) and might result in significantly reduced levels of TC and LDL-C. Patients treated with sustained-release bupropion can even have an increase in HDL-C and TG levels after a 24-week long of treatment (McIntyre et al., 2006). As an add-on medication to the commonly prescribed antipsychotic olanzapine, bupropion might alleviate olanzapine-associated weight gain (Gadde et al., 2006).

Atomoxetine is originally a stimulant, is indicated in the treatment of patients with attention deficit hyperactivity disorder, however it can be used off-label in some patients with depression and eating disorders (Dadashova & Silverstone, 2012). One the most common side effects of atomoxetine include weight loss, requiring regular body weight controls during the treatment (Dean, 2012)**.** Its effects on lipid profile and other metabolic parameters require still further investigation.

An NMDA receptor antagonist, ketamine and its enantiomers esketamine and arketamine drew attention as they have proven themselves as promising agents with their fast-acting antidepressant effects even in treatment-resistant patients (Hashimoto, 2019). The data on their long-term metabolic safety in psychiatric population is however scarce, with only one case report showing that after three months of treatment with esketamine, no weight changes were observed in depressed patients, refractory to other treatment modalities (Stultz et al., 2020).

CONCLUSION

Following the development of novel therapeutic agents, partly due to the side effects associated with the previous modalities and partly due to the necessity of new treatment modalities for the resistant cases, the number of antidepressants in circulation has grown significantly. Table 1. provides an overview of all the above-mentioned side effects.

Table 1. Summary of metabolic effects associated with various antidepressants

Antidepressants		Summary of metabolic effects
SSRI	Fluoxetine	↑ carotid plaque progression, transient initial weight loss, increased vascular inflammation
	Paroxetine	↑ LDL-C, ↑ TC, ↓ HDL-C, greatest ↑ BW effect among SSRI,
	Escitalopram	↑ LDL-C, ↑ VLDL-C, ↑ TG, ↓ plaque burden
	Citalopram	↑ BW, ∅ TC, ∅ LDL-C, proinflammatory effects on atherosclerotic niche
	Fluvoxamine	↓ TC (when overweight and TC>200 mg/dl), alleviates clozapine-associated metabolic risk
	Sertraline	↑ LDL-C, ↑ TC, ↓ HDL-C, ↑ TC:HDL ratio, smallest risk of weight gain among SSRI
SNRI	Venlafaxine	↑ TC, LDL-C, ↑ TC:HDL ratio, ↑ TG, ↓ HDL-C, controversial data on BW
	Duloxetine	↑ Glucose, ↑ HbA1c, ↑ TC
Cyclics	Milnacipran	↓ HbA1c (when >8%), ↓ TC, ↓ TG, ↓ BW
	Trimipramine	↑ BW, ↑ FFA, ↑ glycerol
	Doxepin	↑ TG, ↑ TC, ↑ LDL-C, ↑ glucose, ↑ BW, ∅ HDL-C
	Nortriptyline	↑ VLDL-C, ↑ TG, ↑ BW, ↓ TC, ↓ LDL-C
	Amitriptyline	↑ BW, ↑ TC, ↑ TG, ↑ TC:HDL-C ratio, ↓ HDL-C (more prominent than SSRI)
	Clomipramine	↓ TC, ↓ LDL-C, ↓ TC: HDL-C ratio, ↑ HDL-C (slightly), ↑ Apo-AI, ↑ BW, ↑ food craving
	Desipramine	↓ BW (in 4-5 weeks of treatment), ↓plaque size, ↑ plaque stability
	Imipramine	↑ BW, ↑ TC, ↑ TG
MAOI	Tianeptine	↓ BW, (when used >12 months)
	Maprotiline	↑ BMI, ↑ ghrelin, ↑ insuline, ↑ HOMA-IR, ↓ adiponectin, ↑ BW, ↓ cholesterol synthesis
	Mirtazapine	↑ BW, ↑ TC, ↑ LDL-C, ↑ TG
	Isocarboxazid	↑ BW, ↑ appetite for carbohydrates
	Phenelzine	↓ Body fat, ↓ glucose, ↓ insulin resistance, ∅ BW
	Tranylcypromine	↑ BW
	Selegiline	∅ BW, ↓ hepatosteatosis, ↓ dyslipidemia
Others	Vortioxetine	↓ BW, ↓ WC, ↓ HbA1c, ↓ TC and ↓ TAG (in T2DM and MDD)
	Reboxetine	↓ TC, ↓ LDL-C, ↓ BMI, alleviation of weight gain due to 2nd generation antipsychotics
	Bupropion	↓ BW (especially in severe obesity), ↓ TC, ↓ LDL-C; ↑ HDL-C, ↑ TG (after 24 months of treatment), alleviation of olanzapine associated weight gain
	Atomoxetine	↓ BW
	Ketamine derivatives	∅ BW in esketamine (after 3 months of treatment)

BW: body weight, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides, Apo-AI: apolipoprotein AI, HOMA-IR: Homeostasis Model Assessment Index, FFA: free fatty acid, TAG: triacylglycerols, HbA1c: glycosylated hemoglobin, WC: waist circumference, T2DM: type 2 diabetes mellitus, MDD: major depressive disorder, BMI: body mass index, MAOI: monoamine oxidase inhibitor, SNRI: serotonin norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor, ↓: increase, ↑ decrease, ∅ no change

Although, widely considered safe and therefore prescribed very commonly, it is important not to forget that even the SSRIs are associated with metabolic risk factors, which differ significantly depending on the medication. Additionally, they are especially of use in patients requiring polypharmacy, as they tend to less interact with other medications prescribed to ASCVD patients (Morriss et al., 2021, Andrade et al., 2013). SNRIs, on the other hand, are safe options in overweighted patients and may have favorable contribution to lipid profile. Nevertheless, they might cause significant changes in blood pressure and should be prescribed carefully in patients with established ASCVD (Oakes et al., 2013). TCA and TeCA show different metabolic profiles, with a majority of them having unfavorable effects on either weight or lipid profile, not rarely on both. Some medications in this group, especially mirtazapine even in short-term and clomipramine in long-term, can increase appetite, requiring caution in patients with increased metabolic risk (McIntyre et al., 2006; Richards-Belle et al., 2023). MAOI, although being rarely prescribed in patients with depression, are notorious, as they tend to interact with many other drugs and foods, requiring the patient to take strict dietary measures. The data on their effects on lipid profile or body weight composition differ significantly within the group, leading to the necessity of special attention for choosing the right drug for the right patient (Hyman Rapaport, 2007; Drieling et al., 2007; Nagy et al., 2018; Tian et al., 2023). Vortioxetine shows a positive metabolic risk profile, however the data on metabolic effects of other SMSs is limited, especially for vilazodone (Tovilla-Zárate et al., 2019). Reboxetine also has positive effects on lipid profile and body weight, however due to its limited allowance in some markets and the small number of studies on its metabolic effects, the data is still limited (Paslakis et al., 2011; Bozkurt & Şahin, 2016; Poyurovsky et al., 2007). Bupropion, is widely recognized as a bariatric agent, leads to weight loss, especially in longer treatment durations, and can be considered safe for patients with increased metabolic risk (Patel et al., 2016; McIntyre et al., 2006; Gadde et al., 2006). Originally a stimulant, atomoxetine can cause weight loss and its effects on blood lipid profile is a mystery, and it is an off-label option for depression and eating disorders (Dadashova & Silverstone, 2012; Dean, 2012). Finally, ketamine and its derivatives, as novel promising agents especially in patients with multiple drug resistant depression and acute suicidality (Hashimoto, 2019), require more attention in terms of their metabolic profile, even though the data on their effects on symptoms are abundant (Stultz et al., 2020).

To summarize, in order not to be deceived by a pyrrhic victory in form of successful psychiatric symptom management, by overseeing the needs of the cardiometabolic field, it is important to understand the metabolic side effects of the commonly prescribed or emerging antidepressants, which may, as a result, improve mortality and morbidity significantly in long-term.

Ethical Considerations: Does this study include human subjects? NO

Conflict of interest: All authors declare that there is no conflict of interest regarding this work.

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