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Review

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Metabolic risk in depression and treatment with selective serotonin reuptake inhibitors: are the metabolic syndrome and an increase in cardiovascular risk unavoidable?

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Abstract

Depression is one of the most common psychiatric disorders, and has become an epidemic in modern medical practice; notorious for frequently co-occurring with multiple comorbidities, especially cardiovascular disease (CVD), type 2 diabetes mellitus (DM2), and its various risk factors comprised in the metabolic syndrome (MS). Selective serotonin reuptake inhibitors (SSRIs) are the most widely used class of psychotropic drugs in this and many other clinical scenarios; yet their impact on cardiometabolic health has not been elucidated. The objective of this review was to summarize current views on the pharmacology of SSRIs and cardiometabolic risk, as well as available epidemiological evidence regarding its clinical significance. SSRIs appear to intervene in cardiometabolic physiology fundamentally by modulating chronic inflammation, a key pathophysiologic phenomenon in MS, DM2 and CVD. However, the dosing necessary to achieve a beneficial impact in this regard, as well as their clinical correlations, remain controversial. Each SSRI displays a particular profile regarding each of the components of the MS: weight gain seems to be the most common effect of SSRIs, more frequent with paroxetine, followed by citalopram and escitalopram. As a drug class, SSRIs also appear to promote hypercholesterolemia rather uniformly, while fluoxetine and citalopram appear to particularly increase triacylglyceride levels. In contrast, fluvoxamine and paroxetine seem to have the greatest impact on dysglycemia. Lastly, most SSRIs appear to be innocuous or even beneficial regarding blood pressure and

high-density lipoprotein cholesterol. Nevertheless, many of these effects may vary significantly upon specific clinical circumstances, especially timing. This topic remains rather unexplored in clinical psychopharmacology, and further, larger-scale epidemiological studies are needed in order to offer improved care in this field.

Keywords: Depression, selective serotonin reuptake inhibitors, metabolic syndrome, cardiovascular risk, cardiovascular disease, type 2 diabetes mellitus, chronic inflammation

INTRODUCTION

Depression has become an emerging epidemic in recent years, with prevalence rates of 10%-15% across the globe[1]. This trend has resulted in ever-increasing financial costs, along with a significant decay in the life quality of patients[2]. A substantial portion of this burden may stem from the multiple medical comorbidities associated with depression, in particular, cardiovascular disease (CVD)[3], with these conditions coexisting in up to 15% of cases[4].

CVD remains the leading cause of morbidity and mortality worldwide[5], significantly driven by a myriad of modifiable risk factors consequent upon a predominantly Westernized lifestyle[6]. The metabolic syndrome (MS), conceptualized as a cluster of cardiovascular risk factors - obesity, hypertension, hyperglycemia and atherogenic dyslipidemia - which in co-occurrence substantially increase the risk of CVD and type 2 diabetes mellitus (DM2), is widely regarded as a useful clinical tool in the prevention of these conditions[7]. These factors also appear to be involved in the pathophysiology of depression, and may account for the higher cardiovascular risk observed in this disorder[8,9].

In this context, the pharmacological management of depression presents a clinical conundrum: depression is accompanied by increased risk of MS - and by extension, CVD and DM2 - yet many antidepressant drugs appear to exacerbate these risks as well[10,11]. However, in contrast with antipsychotic drugs, whose clinical relevance in regards to deleterious cardiometabolic effects has been well-characterized[12,13], the impact of antidepressant drugs in clinical outcomes remains less clear. This is an especially pressing matter in the field of neuropsychopharmacology, as antidepressant drugs, and selective serotonin reuptake inhibitors (SSRIs) in particular, have become one of the most prescribed drug classes in contemporary medical practice[14,15]. This review aims to summarize current views on the pharmacology of SSRIs and cardiometabolic risk, as well as available epidemiological evidence regarding its clinical significance.

SSRI-ASSOCIATED CARDIOMETABOLIC RISK: MOLECULAR PATHWAYS

SSRIs have become very popular in clinical use owing to various beneficial characteristics, including their ease of administration, increased pharmacodynamic specificity, and enhanced tolerability with relatively minor side effects; in contrast to the "dirtier", less specific and tolerable older antidepressant drugs, such as tricyclics and monoamine oxidase inhibitors[16]. Although this distinction is notorious regarding cardiovascular safety, the underlying molecular differences in their pharmacologic profiles remain largely elusive[17].

Chronic systemic inflammation may be an especially important target for SSRIs in this context, given the comprehensive involvement of this phenomenon in the pathophysiology of MS, CVD and DM2[18]. Furthermore, this kind of low-grade inflammation is also present in depression, as patients with disorder tend to show increased levels of proinflammatory biomarkers such as tumor necrosis factor alpha (TNFα), C-reactive protein, interleukin (IL)-6 and IL-1β[19]. This is compounded by the frequent accompaniment of depression with unhealthy dietary habits and physical inactivity, which themselves also promote chronic inflammation[20], and are prominent in the development of depressive symptoms such as loss of energy, sleep disturbances and irritability[21].

Interestingly, the onset of the antidepressant effect of SSRIs has been reported to coincide with a reduction in the circulating levels of proinflammatory biomarkers[22]. A novel hypothesis posits these changes to be due to a T helper (Th1)-like response, triggering inflammatory activity via interferon γ (IFNγ)-related pathways[23]. SSRIs appear to decrease the production of INFγ and stimulate the release of IL-10, by modulating the corresponding mRNA in immune cells[24]. Consistent with this, SSRIs also appear to upregulate the expression of genes involved in apoptotic pathways in T cells[25]. In addition, blockade of serotonin reuptake results in increased circulating serotonin levels, which have been reported to be able to suppress cytokine synthesis by T cells, B cells, natural killer cells and monocytes/macrophages[26-29], resembling what occurs in sepsis after massive platelet degranulation[30].

Macrophages may be particularly relevant regarding the immunomodulatory effects of SSRIs due to their high expression of serotonin receptors[31,32]. By acting as ambient serotonin level sensors, macrophages could modulate genotype expression patterns in macrophages: activation of $5HT_7$ receptors in macrophages has been noted to induce polarization towards the antiinflammatory M2 phenotype[33,34]. Inhibition of TNFα and IL-6 release, as well as promotion of IL-10 synthesis, are prominent among the antiinflammatory features of M2 macrophages[33,35,36].

Nevertheless, these antiinflammatory effects have been speculated to occur only at doses greater than the usual therapeutic range[37], and SSRIs may rather be proinflammatory at lower doses, especially with prolonged use[38]. This is consistent with evidence from Kubera *et al.*[27], who found physiological levels of intracellular serotonin tend to promote TNFα and IL-6 synthesis in macrophages, whereas supraphysiological levels of extracellular serotonin were linked with downregulation of serotonin receptors serotonin receptors and with decreased release of with decreased release of proinflammatory cytokines. Further research is required to elucidate the clinical correlates and significance of this molecular framework for SSRI-mediated immunomodulation.

Chronic inflammation is also closely linked to insulin resistance and obesity, two fundamental elements of the MS. Thus, by intervening through immunomodulation, SSRIs could have a pivotal role in the pathophysiology of this cluster of manifestations[39]. Paroxetine may be a particularly powerful inductor of insulin resistance by interfering with IRS-1 signaling[40]. Indeed, each SSRI seems to exert distinct effects on insulin resistance, body weight composition, and serum lipids, independently of their impact on chronic inflammation. For example, paroxetine has been linked with higher low-density lipoprotein cholesterol (LDL-C) levels, possibly due to increased appetite[41]; whereas fluoxetine, by inhibiting PON1 activity, may favor lower high-density lipoprotein cholesterol (HDL-C) levels[42]. In addition, certain pharmacokinetic interactions, such as that of fluoxetine with statins - including inhibition of CYP3A and modulation of glucuronidation, P-glycoprotein (Pgp) and organic anion transport peptide 1B1 (OATP), may result in potentiated reduction of cholesterol[43]. This complexity warrants further insight and an individual assessment of each specific SSRI in this context. In stark contrast, SSRIs seem to be relatively innocuous regarding blood pressure, unlike other antidepressant drug classes such as serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants[44-46].

Lastly, the prominent role of serotonin in platelet physiology has ignited speculation regarding SSRIs as antiplatelet agents[47,48]. The higher concentrations of circulating serotonin induced by SSRIs could reduce platelet aggregation[49,50] and impair reactivity to vasoconstriction[51]. However, SSRIs do not appear to intervene in the functionality of vitronectin - a fundamental component of glycoprotein IIb/IIIa[48] - or fibrinogen[52]; but are able to regulate the expression of vascular adhesion molecules such as VCAM-1, ICAM-1, P-selectin and E-selectin[53,54]. Nevertheless, the relative relevance of these effects remains unknown in the context of the chronic inflammatory milieu which SSRIs could promote simultaneously, as does the clinical significance of this antiplatelet activity.

Table 1. Comparison of the clinical effects of SSRIs in key metabolic variables

SSRIs	Body weight	Glycemia	Serum Lipids				Blood pressure	References
			TAG	HDL-C	LDL-C	TC		
Paroxetine	Short-term: N Long-term: ↑↑↑	Short-term: ↓ Long-term: ↑↑↑	↑	N	↑	↑	N	[59,67,68,75,80,81,85, 88-90,94,96,99,101-104]
Fluoxetine	Short-term: ↓ Long-term: N	↓	↑↑	N	↑	↑	N	[58,59,64,65,67-70,78,85, 90-92,94,96,99,105-107]
Fluvoxamine	N	↑↑↑	SE	SE	SE	↑	SE	[58,75,84,108-110]
Sertraline	Short-term: ↓ Long-term: N	↓	↑	N	↑	↑	N	[62,63,67,76,85,89,90,93, 94,96,99,111]
Citalopram	Short-term: ↑ Long-term: ↑	N	↑↑	N	↑	↑	N	[58,68,71,79,84,85,90,92, 94,96,99,112]
Escitalopram	Short-term: ↑ Long-term: ↑	↓	↑	↑	↑	↑	N	[66,71,77,85,96,99,113,114]

↑: increase; ↑↑: high increase; ↑↑↑: very high increase; ↓: decrease; N: neutral; SE: scarce evidence; TAG: triacylglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; SSRI: selective serotonin reuptake inhibitor

SSRI-ASSOCIATED CARDIOMETABOLIC RISK: CLINICAL EVIDENCE

Management of metabolic risk is a frequent clinical challenge when prescribing psychiatric medications[55]. However, in contrast to other psychotropic drug classes - which tend to behave more or less uniformly in regards to metabolic risk[56], SSRIs appear to have more heterogeneous patterns[57,58]. The following sections summarize key clinical evidence regarding the impact of SSRIs on each of the components of the MS [Tables 1 and 2].

Obesity

Historically, weight changes have been a hallmark in the side effect profile of most antidepressant classes[59-61]. In the case of SSRIs, the specific agent used and the length of therapy may account for the very variable effects these drugs appear to have on body weight[59]. For example, in two multicenter, double-blind, randomized, placebo-controlled clinical trials assessing sertraline therapy in 376 pediatric patients with major depressive disorder (MDD) over 10 weeks, Wagner *et al.*[62] found a mean weight loss of 0.38 kg in subjects treated with sertraline. Croft *et al.*[63] obtained similar outcomes in an 8-week case-control study, with an average weight loss of 0.79 kg in patients treated with sertraline. Likewise, use of fluoxetine has been linked to short-term weight loss, as reported by de Jonghe *et al.*[64] in a randomized, double-blind 6-week study, where patients treated with fluoxetine showed an average loss of 0.84 kg; as well as by Michelson *et al.*[65] in a prospective, placebo-controlled trial, where subjects on fluoxetine showed an average weight loss of 0.35 kg after 12 weeks. However, escitalopram has been linked with a significant increase in waist circumference in the short term[66].

Nevertheless, the clinical value of these findings may be limited due to the short length of these studies, especially when considering treatment guidelines for MDD suggest use of antidepressants for at least 6 months. Therefore, in recent years, more studies have attempted to evaluate the long-term effect of SSRIs on weight[67-71]. In a similar 32-week study by Fava *et al.*[67] with fluoxetine, sertraline and paroxetine, weight gain was significantly higher with the latter. Mansoor *et al.*[68] found a similar outcome, where citalopram and paroxetine were associated with long-term weight gain, whereas fluoxetine and venlafaxine were not. Fluoxetine in particular is consistently reported not to be linked with any major long-term weight changes[69,70]. In contrast, Calarge *et al.*[71] found citalopram and escitalopram are associated with significant changes in all body composition parameters, including visceral fat mass, after 2 years in treatment for MDD and generalized anxiety disorder.

Notwithstanding this outline, some research has suggested patients with MDD are intrinsically more susceptible to changes in body weight, and these shifts may occur independently of antidepressant use[72]. At any rate, at present, there is sufficient evidence to highlight long-term weight gain as a clinically relevant effect for certain SSRIs, underlining the importance of patient-centric prescribing in psychopharmacology.

Table 2. Summary of key clinical evidence regarding SSRIs and the components of the metabolic syndrome

Authors	SSRIs studied	Methodology	Relevant results
Andersohn *et al*.[75]	Paroxetine, sertraline, fluoxetine, fluvoxamine and citalopram	Case-control study with data from the UK General Practice Research Database, including 165,968 patients with depression who received at least one prescription for antidepressants between January 1990 and June 2005	Fluvoxamine and paroxetine were associated with increased risk of type 2 diabetes mellitus: OR 9.0 (95% CI 1.08-75.58) and OR 1.75 (95% CI 1.13-2.72), respectively
Raeder *et al*.[58]	Paroxetine, sertraline, fluoxetine, fluvoxamine and citalopram	Cross-sectional study with data from the Hordaland Health Study, including 25,315 subjects with ages between 40-49 years and 70-74 years	As a group, SSRIs were significantly associated with type 2 diabetes mellitus, hypercholesterolemia and abdominal obesity. Paroxetine showed the strongest association with general and abdominal obesity. Conversely, citalopram was not linked with any of the aforementioned metabolic variables
Wagner *et al*.[62]	Sertraline	Two multicenter, double-blind, randomized, placebo-controlled clinical trials which assessed the safety and efficacy of sertraline during 10 weeks in 376 pediatric patients diagnosed with MDD	Use of sertraline was associated with a mean weight loss of 0.38 kg at 10 weeks
Fava *et al*.[67]	Fluoxetine, sertraline and paroxetine	Double-blind, randomized trial which assessed body weight changes during treatment with SSRIs over 26-32 weeks	Patients treated with paroxetine had significant weight gain, while those treated with sertraline and fluoxetine had non-significant weight gain and loss, respectively
Olguner Eker *et al*.[66]	Sertraline, escitalopram and fluoxetine	Case-control study on 40 patients and 32 control aged 29-49 years with symptoms of depression and anxiety, treated with SSRIs during 8 weeks, assessing metabolic variables	As a group, SSRI use was related to higher body weight, waist circumference and HDL-C, and lower insulin and HOMA index levels. Escitalopram was also associated with lower fasting glucose. Anthropometric changes were seen after treatment only in patients with depression and not anxiety. No anthropometric or biochemical changes were found in subjects on sertraline, fluoxetine or venlafaxine
Pigott *et al*.[114]	Escitalopram	Double-blind, randomized, placebo-controlled trial during 8 months, which aimed to compare the safety and efficacy of duloxetine and escitalopram in patients with MDD	Escitalopram was associated with increased systolic blood pressure and body weight in comparison to duloxetine. No significant changes were observed regarding diastolic blood pressure
Beyazyüz *et al*.[90]	Paroxetine, fluoxetine, citalopram and escitalopram	Prospective cohort study including 97 female patients with Generalized Anxiety Disorder treated with SSRIs during 16 weeks, evaluating various metabolic variables	After 16 weeks, subjects on paroxetine had significantly higher LDL-C, TC and TAG, while those on citalopram or escitalopram only had higher TAG. In contrast, subjects on fluoxetine showed lower TC and TAG
Serodio *et al*.[85]	All SSRIs	Cross-sectional study on 219 participants from the National Health and Nutrition Examination Survey treated with SSRIs, with the objective of evaluating their influence on obesity and cardiovascular risk	Independently of body mass index, subjects on SSRIs showed lower systolic blood pressure and higher HDL-C in comparison with subjects not on this medication
Wei *et al*.[89]	Paroxetine and setraline	Observational cohort study on 2682 adults who received paroxetine or sertraline for at least 60 continuous days and had LDL-C measured twice, on and off the medication	Mixed regression model analyses adjusting for age, gender, comorbidities and hypolipemic medication, longer periods of time on paroxetine or sertraline were associated with increased LDL-C. Conversely, longer periods of time since suspending paroxetine and sertraline were related to lo lower LDL-C
Fjukstad *et al*.[99]	Paroxetine, fluoxetine, sertraline, escitalopram and citalopram	Cross-sectional study on 280 patients with schizophrenia or bipolar disorder treated with SSRIs, evaluating their effect on metabolic variables and prevalence of the metabolic syndrome	After adjusting for confounders, SSRI use was associated with increased TC, LDL-C and TAG, and increased incidence of metabolic syndrome. There were significant correlations between SSRI doses and TC and LDL-C levels
Yosmaoğlu *et al*.[83]	Sertraline and citalopram	Experimental trial on 14 male subjects treated with SSRI at least 3 months. Resting metabolic rates, anthropometric measures and serum lipids were assessed	Resting metabolic rates decreased with increasing doses of SSRIs, yet no relation was found between this variable and body weight. Resting metabolic rates remained unchanged with constant doses of SSRIs. Body weight was reduced between the first and third weeks of treatment, but changes were non-significant by the third month. TC levels were significantly higher after 3 months of therapy

TAG: triacylglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; SSRI: selective serotonin reuptake inhibitor; MDD: major depressive disorder; OR: odds ratio

Dysglycemia

Although research on the effect of SSRIs on dysglycemia has been notoriously hindered by ample heterogeneity of study methodology, current evidence suggests each SSRI behaves distinctly regarding different outcome variables[73,74]. In particular, fluvoxamine has shown the strongest association with the development of DM2, obtaining an odds ratio of 9.05 (95% CI 1.08-75.58) in a recent large case-control study by Andersohn *et al*.[75]. On the other hand, sertraline has been reported to be associated with significant reductions in glycated

hemoglobin levels in patients with DM2 and MDD at 10 weeks of treatment[76], and escitalopram has been linked with significant reductions in fasting glucose levels[77]. Fluoxetine has been related to improved insulin sensitivity in patients with DM2, independently of weight loss[78]; while citalopram does not appear to impact measures of insulin sensitivity[79] or be associated with DM2[58].

Evidence regarding paroxetine on this aspect is more controversial. Although this SSRI tends to be associated with increased risk of DM2 and obesity[75], in short-term uses, it has proved to be innocuous, or even beneficial regarding glucose homeostasis: in a 5-week double-blind, randomized study by Weber-Hamann *et al.*[80] on non-diabetic patients with MDD, paroxetine was associated with improved insulin sensitivity. Paile-Hyvärinen *et al.*[81] echoed these findings in a 10-week, single-blind study on 15 patients with MDD. The time-dependent effects of paroxetine on glucose metabolism highlight the importance of long-term prospective clinical studies in the characterization of the effects of SSRIs in cardiometabolic risk.

In summary, although SSRIs as a drug class are typically believed to increase the risk of DM2[82], current clinical evidence supports this notion predominantly for fluvoxamine and paroxetine[75]. This underlines the importance of pondering the metabolic profiles for each individual SSRI, especially in subjects with risk factors for DM2 or CVD.

Dyslipidemia

Similar to dysglycemia, SSRIs have been frequently linked to dyslipidemia. In the large Hordaland Health Study, subjects who used SSRIs were more prone to presenting components of the MS in comparison to subjects who did not use any psychotropic drugs, especially high triacylglycerides (TAG), high LDL-C, and low HDL-C[58]. Yosmaoğlu *et al.*[83] obtained similar results in an Anatolian sample after 3 months of SSRI use, although comparable changes have been ascertained as early as after 5 weeks of treatment[84]. Nevertheless, some findings also suggest SSRIs to have no impact on or be beneficial for lipid profiles[85-87].

These discrepancies may reflect the distinct characteristics of each specific SSRI. For example, in an 8-week case-control study on patients with symptoms of depression and anxiety, use of escitalopram was linked with a significant increase in HDL-C[66]. In contrast, in a 20-week follow-up study, both paroxetine and sertraline were related to higher total cholesterol and LDL-C[88,89]. Similarly, after a 16-week follow-up, Beyazyuz *et al.*[90] found paroxetine to increase total cholesterol and TAG levels, while fluoxetine lowered both parameters. Lastly, most SSRIs - including fluoxetine, paroxetine, sertraline, and citalopram, as well as venlafaxine - have been associated with high TAG after 8-12 weeks of therapy[91-93].

Thus, in general, SSRI use tends to be associated with high TAG in the earlier weeks, and then with hypercholesterolemia in the later months; while the effect on HDL-C appears not to be significant. This outlines SSRIs as important promoters of atherogenic dyslipidemia, and may worsen cardiometabolic risk in conjunction with other factors.

Hypertension

In contrast to the previously discussed risk factors, the impact of SSRIs on the development of hypertension may be more negligible[94-100]. Hypertension is notoriously not among the most frequent cardiovascular side effects of SSRIs, which include cardiac dysrhythmias, orthostatic hypotension, bradycardia, first-degree atrioventricular block, and syncope[94-96]. Among these, dysrhythmias are the most common (4%), whether as a consequence of overdose or chronic use; in the case of the latter, the dysrhythmias tend to be well-tolerated[97]. This profile renders SSRIs relatively safe regarding atherothrombotic risk[98].

Various large-scale clinical epidemiological studies have reported that, as a drug class, SSRIs seem to be unrelated to significant increases in systolic or diastolic blood pressure, in patients with depression, anxiety

disorders, bipolar disorder and schizophrenia[58,90,93,99]. At most, specific SSRIs such as sertraline and paroxetine may be linked to hypertension in < 1% of cases, while fluoxetine and citalopram appear to be innocuous in this regard[94].

On the contrary, SSRIs may have a beneficial effect on blood pressure, especially by diminishing mean or systolic blood pressure, presumably via an inhibitory effect on the autonomic nervous system[100]. Notably, a report by Serodio *et al*.[85] found that, at any body mass index, systolic blood pressure was significantly lower in subjects treated with SSRIs than in those without antidepressant treatment, although this corresponded to a small 4 mmHg difference. In summary, although scarce, currently available evidence suggests no relationship between SSRIs and hypertension, and this might not be one of the principal contributions of these drugs in the development of MS.

CONCLUSIONS

At present, enough evidence is available to affirm SSRIs intervene in the pathogenesis of certain components of MS. However, this impact is not equal for all SSRIs; rather, each drug in this groups has shown a particular cardiometabolic profile, differentially affecting body weight and composition, serum lipids, glycemia, blood pressure, and other parameters. These findings highlight the importance of holistic, patient-centered prescribing as a fundamental principle in clinical psychopharmacology. Further research is required to determine optimal approaches for the management of the metabolic effects of SSRIs. Future developments in psychopharmacology should consider the metabolic safety of novel drugs, in view of the burden CVD implies for public health, and the close association between mental and cardiometabolic disorders.

DECLARATIONS

Authors' contributions

Manuscript writing and editing, workgroup supervision, academic and methodological advisory: Chávez-Castillo M, Velasco M, Bermúdez V, Rojas-Quintero J
Data gathering and manuscript writing: Ortega Á, Nava M, Fuenmayor J, Lameda V

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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