Review

SSRIs as Risk Reduction for Cardiovascular Disease in Patients with Schizophrenia

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Abstract: Patients with schizophrenia (SCZ) are at high risk of cardiovascular disease (CVD) due to an inherited predisposition, a sedentary life style and the use of antipsychotic medications. Several approaches have been taken to minimize this risk but results continue to be unsatisfactory. A potential alternative is prescribing Selective Serotonin Reuptake Inhibitors (SSRIs). SSRIs decrease platelet aggregation and reduce the risk of coronary heart disease in patients with depression. We therefore aim to investigate whether there is evidence that supports the use of SSRIs to reduce the risk for CVD in SCZ. A systematic review of the literature revealed five published reports relating to the impact of SSRIs on CV risk in SCZ. Three trials assessed the influence on metabolic parameters of fluvoxamine when combined with clozapine. Two of those studies found improvements with fluvoxamine. Of the other two reports, one indicates SSRIs as a group caused minimal but statistically significant increments in total cholesterol, LDL and triglyceride. The second report suggests that when SSRIs are combined with antipsychotics, the metabolic impact depends on the antipsychotic prescribed. While there are promising results, further studies are needed to establish the impact of SSRIs on CV risk in SCZ.

Keywords: cholesterol; BMI; blood sugar; psychosis; LDL; HDL; antidepressants; antipsychotics; metabolism; metabolic abnormalities, platelet aggregation.

1. Introduction

Life expectancy of patients with schizophrenia (SCZ) is significantly lower than for the rest of the population [1]. While multiple factors are at play, a common culprit is cardiovascular disease [2,3,4,5]. The risk for cardiovascular illness is compounded by several characteristics surrounding SCZ, such as an inherited predisposition to develop metabolic abnormalities [6] and the fact that patients often experience apathy and anhedonia, symptoms that lead to a sedentary lifestyle. In addition, high rates of smoking and diets rich in calories and fat are also common among patients with SCZ [7]. But perhaps even more significant is the impact of antipsychotics, particularly second generation antipsychotics. These medications induce weight gain, hyperlipidemia and diabetes [8] all risk factors for cardiovascular disease.
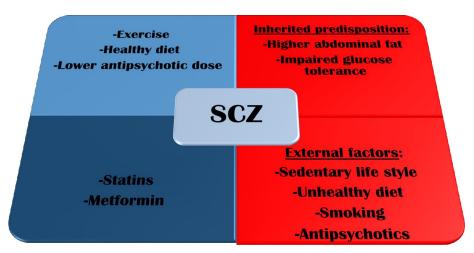
Mitigation of cardiovascular risk in patients with schizophrenia already includes a polydimensional approach (Figure 1) that considers promoting changes in life style such as increased exercise and improved diet, switching or reducing the dose of antipsychotic medications [8], as well as the potential use of statins [9] and metformin [10]. But according to a recent meta-analysis, all these efforts continue to fall short of a desirable outcome [1]. In the general population, patients at risk for cardiovascular disease are often placed on aspirin or an anticoagulant like clopidogrel, but these medications are associated with increased risk of bleeding [11] and thus guidelines for their use are becoming more restrictive [11]. A potential alternative is the use of

Selective Serotonin Reuptake Inhibitors (SSRIs). SSRIs decrease platelet aggregation and appear to have a lower risk of bleeding than other anticoagulants [12,13]. Moreover, there is evidence indicating that SSRIs can reduce the risk of coronary disease [14] and lower the severity of ischemic strokes [15]. Therefore, our hypothesis is that SSRIs could be a safe alternative to reduce the risk of cardiovascular disease in patients with schizophrenia taking antipsychotics.

In order to challenge our hypothesis, we first present evidence indicating patients with SCZ are at an increased risk of cardiovascular disease. Second, we review emerging data on the impact of SSRIs for cardiovascular risk and third, we describe and discuss currently available published literature on the role SSRIs have on cardiovascular disease in patients with SCZ.

2. Materials and Methods

A systematic review of the literature was conducted via MEDLINE and Google Scholar using search terms such as schizophrenia, SSRIs, cardiovascular risk, metabolic abnormalities, metabolic syndrome and morbidity. The search was limited to studies published in English. For each of the scientific manuscripts identified relating to the impact of SSRIs on metabolic or cardiovascular risk in patients with SCZ, its references were thoroughly inspected for secondary publications.

Figure 1. Cardiovascular risk factors and treatment alternatives for patients with schizophrenia (SCZ). The two blocks on the left represent potential approaches to treat and prevent cardiovascular disease in patients with SCZ. Blocks on the right represent factors that increase the risk for cardiovascular disease in patients with SCZ.

3. Results

3.1. Schizophrenia and cardiovascular risk

Patients with SCZ appear to have an inherited predisposition to develop risk factors for cardiovascular disease. For instance, drug-naïve patients have greater than three times as much intra-abdominal fat as age- and BMI- matched individuals [16]. They also have impaired fasting glucose tolerance and are more insulin resistant than healthy subjects [6]. In addition, apathy and anhedonia are symptoms commonly experienced by patients with SCZ. These symptoms lead to limited physical activity which in combination with high intake of fat and sugar often seen in SCZ, ultimately result in the development of metabolic syndrome [7]. Metabolic syndrome understood as dyslipidemias, insulin resistance and elevated blood glucose, frequently results in Diabetes Mellitus Type 2 and cardiovascular disease [17]. Not surprisingly, the prevalence of both diabetes and obesity

is two to four times higher in patients with SCZ than in the general population [18]. Another contributing factor for the high prevalence of diabetes and the increased risk for cardiovascular disease is antipsychotic intake (Figure 1).

All antipsychotics, including older typical neuroleptics, can elicit metabolic abnormalities [19,8]. The rate at which these side effects occur however, differs among medications. In the typical antipsychotic class, lower potency antipsychotics such as chlorpromazine and thioridazine induce greater weight gain compared to higher potency antipsychotics such as fluphenazine and haloperidol [20]. Likewise, chlorpromazine and thioridazine are more strongly associated with diabetes compared to other typical antipsychotics [21]. But comparisons between typical versus atypical antipsychotics, also known as second generation antipsychotics (SGA), have clearly shown that SGA are more commonly associated with metabolic side effects [22]. Among SGA, clozapine and olanzapine appear to have the strongest association with weight gain and diabetes [23,24]. Quetiapine is not far behind in its ability to elicit metabolic dysregulations. According to the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, olanzapine and quetiapine are associated with increases in total cholesterol and triglyceride levels [25]. When ranked for its potential to cause weight gain and other metabolic abnormalities, clozapine and olanzapine are at the top of the list followed by quetiapine and risperidone, while aripiprazole and ziprasidone are found at the bottom of the ranking [23,26,27]. For those medications with higher risk, data indicates there is a dose-dependent relationship between dose and metabolic complications [28]. For aripiprazole and ziprasidone no such relationship has been found [28]. Newer antipsychotics such as lurasidone, cariprazine and paliperidone are poorly studied to date.

3.2. Selective Serotonin Reuptake Inhibitors and cardiovascular disease

Serotonin is needed for platelets to elicit platelet aggregation and vasoconstriction [29]. Platelets rely on reuptake of serotonin as they lack the capacity to synthetize this amine [29]. By inhibiting serotonin reuptake in platelets, SSRIs alter hemostasis [12,13] and therefore, are associated with increased risk for bleeding [30]. This potentially serious side effect however, is most commonly observed in individuals with medical conditions that already carry an increased risk of bleeding [13] or those taking other anticoagulant medications [30]. Overall, SSRIs are safe medications that rarely cause any serious side effects [31].

In the context of cardiovascular disease, disrupting platelet aggregation could become an advantage. Not surprisingly, several studies have tried to establish whether SSRIs can minimize the risk of cardiovascular events. The majority of these publications indicate that SSRIs are cardioprotective in patients with depression (For a review refer to [9] and a recent meta-analysis by [32]) but inconsistencies remain [9,33]. Variations in the cardioprotective effects of SSRIs could be related to differences in its mechanism of action. While all SSRIs diminish vasoconstriction and platelet aggregation by lowering serotonin release in platelets, other signaling cascades are also at play. For instance, sertraline impairs platelet aggregation by inhibiting CD9, GPIb, GPIIb/IIIa surface receptors while its inactive metabolite, N-desmethylsertraline (NDMS), targets P-selectin and PECAM-1 [12]. Sertraline also diminishes E-selectin and β-thromboglobulin (βTG) concentrations [34]. In contrast, citalopram, fluvoxamine and fluoxetine inhibit TNF-α-induced expression of vascular cell adhesion molecule (VCAM-1) and intracellular adhesion molecule (ICAM-1) in human aorta endothelial cells and TNF-α-stimulated adhesiveness to monocytes, resulting in less inflammation and more cardioprotective effects in patients with heart disease [35].

Recent clinical data also indicates there are differences in the potential cardiovascular benefits offered by SSRIs. Escitalopram appears to be the most advantageous for cardiovascular safety in older individuals at risk of coronary heart disease, whereas fluoxetine provided little benefit if at all [32]. In this same study, sertraline, citalopram and paroxetine delivered better caridoprotection than fluoxetine but less than escitalopram [32].

In addition to its effects on platelet aggregation and vasoconstriction, SSRIs could also impact metabolic markers. Diagnosis appears to be an important factor determining the role of SSRIs on metabolic markers. For instance, several studies have shown that SSRIs increase cholesterol levels in patients with panic disorder [36,37,38] with paroxetine being the main offender [37,38]. For women with generalized anxiety disorder (GAD) the impact varies according to the SSRI taken. Paroxetine increased body mass index (BMI), waist circumference, fasting glucose, total cholesterol, low-density lipoprotein (LDL), and triglyceride after 16 weeks, while citalopram and escitalopram only resulted in higher triglyceride levels [39]. This study involving women with GAD also found that sertraline elevated total cholesterol, in contrast, fluoxetine lowered total cholesterol, weight and triglyceride [39]. Similarly, adding fluoxetine to olanzapine for patients with bipolar depression did not affect cholesterol levels or body weight when compared to treatment with olanzapine alone [40].

3.3. SSRIs and cardiovascular risk in patients with schizophrenia

The first study to assess the metabolic impact of SSRIs in SCZ is a randomized, prospective trail published in the year 2000 [41] (Table 1). The authors tested whether clozapine alone or in combination with fluvoxamine differentially impacted body weight, BMI or leptin levels among other parameters during a 6-week follow-up period. They found no changes in weight or BMI between groups. Leptin levels however, were higher in patients receiving the combined therapy. Levels of clozapine, norclozapine or the ratio norclozapine-clozapine were similar between cohorts. Eleven patients received the dual therapy while 12 patients were prescribed only the antipsychotic. Fluvoxamine was prescribed at either 50 or 75mg/day while clozapine was given at doses of 100 to 150mg/day in the combined group and around 300mg/day for patients receiving clozapine alone.

The second study on SSRIs, cardiovascular risk and SCZ is a prospective, randomized, open-label study that also compared clozapine monotherapy versus clozapine with fluvoxamine [42] (Table 1). The medications were prescribed at slightly different doses than on the previous trail. The monotherapy group received up to 600mg/day of clozapine, whereas the combined group could only take up to 250mg/day together with fluvoxamine 50mg/day. The rationale was that fluvoxamine increases the serum clozapine level 2.3 times [43]. Sixty-eight patients were recruited, thirty-four for each group. The authors assessed body weight weekly during the 12-week follow-up period. Fasting glucose, cholesterol and triglycerides were measured at baseline and then at the end of the study. Their results showed that clozapine significantly increased weight, BMI, blood sugar and triglycerides when baseline numbers were compared to values obtained after 12 weeks. Comparisons between groups, revealed that individuals receiving clozapine alone had higher levels of blood sugar and triglycerides by the end of the follow-up period. The authors also found that levels of norclozapine correlated with elevated blood sugar and triglycerides while levels of clozapine did not. It is important to note that this study was conducted entirely with inpatients and therefore, their food intake was restricted to a hospital diet.

Lu and colleagues followed their open-label study on the metabolic effects of fluvoxamine in patients taking clozapine with a double-blind, randomized, clinically controlled trial [44] (Table 1). Eighty-five patients were recruited and followed for 12 weeks, with 43 receiving clozapine monotherapy at a target dose of 300mg/day and 42 given fluvoxamine at 50mg/day and clozapine at 100mg/day. The authors found that the clozapine-fluvoxamine combination limited increments in body weight and waist circumference and reduced levels of insulin resistance, blood glucose, cholesterol and triglyceride when compared with clozapine monotherapy. The Positive and Negative Symptoms Scores (PANSS) also improved on the dual therapy cohort. Liquid chromatography revealed no differences in blood levels of clozapine but, levels of norclozapine and clozapine N-oxide were higher on the monotherapy group. The norclozapine-clozapine ratio was higher in the combination group.

Through a naturalistic, cross-sectional study, Fjukstad and colleagues aimed to determine the effects of SSRIs on total cholesterol, LDL, high-density lipoprotein (HDL), triglyceride, glucose, BMI, waist circumference and blood pressure [45]. Their database included 868 patients with SCZ of whom 169 were taking SSRIs and 433 individuals with bipolar disorder of whom 111 were taking SSRIs (Table 1). Linear regression analyses, indicated that SSRIs caused minimal but statistically significant increments in total cholesterol, LDL and triglyceride. The authors also found that patients taking SSRIs had a slightly higher risk for developing metabolic syndrome. Blood glucose, BMI, waist circumference and blood pressure were not affected by the use of SSRIs. Unfortunately, the authors did not parcel patients by diagnosis. Potential differences among the different SSRIs included in the analysis namely, escitalopram, citalopram, sertraline, fluoxetine and paroxetine were not investigated.

This research group published a second study mining the same cohort of patients (Table 1). Their new objective was to determine whether adding SSRIs to antipsychotic medications would increase metabolic risk factors [46]. Three antipsychotics were included in their analysis, olanzapine, quetiapine and risperidone. SSRIs added to olanzapine or quetiapine led to small but statistically significant elevations in total cholesterol and LDL. Blood glucose increased when olanzapine was given together with SSRIs, in contrast, combining risperidone with SSRIs led to lower blood glucose. The authors reported that none of the other parameters studied were affected by coadministration of risperidone and SSRIs. Dual therapy with SSRIs and either olanzapine or quetiapine also did not alter HDL, triglycerides, BMI or blood pressure. What the authors did not mention but appears to be evident from their figures, is that risperidone alone led to statistically higher levels of LDL but when prescribed in conjunction with SSRIs, LDL did not increase. Likewise, quetiapine monotherapy caused a modest but statistically significant elevation in triglycerides while in combination with SSRIs triglycerides did not change. Quetiapine without SSRIs significantly increased BMI but with these antidepressants, BMI was unaffected. The authors emphasized that their results have to be pondered with caution as their methodology did not allow excluding the potential impact of diet and even more importantly, they did not have access to non-psychotropic medications being taken by their patients such as statins or insulin.

Table 1. SSRIs and cardiovascular risk in patients with schizophrenia

Reference	SSRI Studied	Number of Patients	Sex	Average Age	Duration	Metabolic Parameters
Hinze-Selch et al, 2000	Fluvoxamine*	23	M: 11 F: 12	32±15*	6 weeks	BW, BMI, Leptin
Lu et al, 2004	Fluvoxamine*	68	M: 20 F: 48	32.9±8.5*	12 weeks	BW, BMI, Glucose, Total Cholesterol, TG
Fjukstad et al,	Escitalopram, citalopram,	868**	M: 697	31.7±10.6	Cross sectional	Total Cholesterol, LDL-C, HDL-C, TG, WC, SBP, DBP,

2016	sertraline, fluoxetine and paroxetine		F: 604		study	BMI, Glucose
Lu et al, 2018	Fluvoxamine*	85	M: 61 F: 24	43.6±8.1	12 weeks	SBP, DBP, BW, WC, Insulin, FPG, Uric Acid, Total Cholesterol, TG, HDL-C, LDL-C, HOMA-IR
Fjukstad et al, 2018***	Escitalopram, citalopram, sertraline, fluoxetine and paroxetine	868**	M: 697 F: 604	31.7±10.6	Cross sectional study	Total Cholesterol, LDL-C, HDL-C, TG, WC, SBP, DBP, BMI, Glucose

*In combination with clozapine.

**the authors also included 433 individuals with bipolar disorder.

***The authors studied SSRIs combined with olanzapine, quetiapine and risperidone.

Abbreviations: SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, BW = Body Weight, WC = Waist Circumference, FPG = Fasting Plasma Glucose, TG = Triglycerides, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, WBC = White Blood Cells, HOMA-IR = Homeostasis Model Assessment-Insulin Resistance, BMI = Body Mass Index

4. Discussion

Several factors place individuals with SCZ at risk of CVD including an inherited predisposition to metabolic anomalies [6,16] a sedentary life style prompted at least in part by core symptoms of this psychotic disorder and the use of antipsychotic medications which elicit metabolic syndrome [8]. So far, attempts to reduce all these risk factors have rendered unsatisfactory results [1]. Therefore, the search for new approaches continues.

Because of their capacity to decrease platelet aggregation and vasoconstriction [12,13], SSRIs have been investigated as a potential alternative. Specially, considering that SSRIs have delivered promising cardioprotective results when prescribed for other mental illnesses such as major depressive disorder [14,9]. In addition to its effects on hemostasis, SSRIs can also influence CV risk by altering metabolic markers such as total cholesterol, LDL, BMI, blood glucose and others. But in contrast with its effects on platelet aggregation and vasoconstriction which are directly linked to SSRIs ability to block serotonin [12,13], how these medications elicit changes in metabolic parameters is yet undetermined. What the evidence currently indicates is that SSRIs impact on CV risks varies according to diagnosis and the specific SSRI prescribed. For instance, the risk for CVD is likely to increase if patients with panic disorder take paroxetine [36,37,38]. Gender also has to be considered. If women with GAD receive paroxetine, their likelihood of developing CVD also augments [39]. Conversely, fluoxetine has a cardioprotective effect on women with GAD [39]. Age also appears to be a factor. Older individuals at risk of coronary heart disease obtain no benefit from receiving fluoxetine, whereas, escitalopram can be advantageous [32].

Not surprisingly, how SSRIs affect CV risk in patients with SCZ also depends on which specific one is being prescribed. Two trials developed by the same research team have shown that fluvoxamine diminishes at least some of the metabolic side effects elicited by clozapine [42,44]. These two studies took important steps to limit potential confounding factors such as excluding individuals taking medications known to affect metabolic parameters and at least one of those trails controlled their cohort's food intake. There is also one publication that encountered different results. An independent team that also assessed the effects of fluvoxamine coadministered with clozapine did not find any metabolic benefits [41]. It is possible that the short duration of this study of only 6 weeks could have prevented the authors form finding any significant differences. The two studies that found fluvoxamine to be effective, lasted for 12 weeks. All three studies measured blood levels of clozapine and its metabolites and two of them found norclozapine levels to be associated with metabolic abnormalities. The three trials recruited a relatively small number of patients (Table 1).

The first cross-sectional study that Fjukstad and colleagues published found that SSRIs increased total cholesterol, LDL and triglyceride in patients with SCZ and bipolar disorder [45]. Nonetheless, there are several confounding factors that have to be pondered when assessing these results. Their study design did not allow discrimination of metabolic parameters were different between patients with SCZ and bipolar disorder as they were considered a single cohort. Likewise, escitalopram, citalopram, sertraline, fluoxetine and paroxetine were all clustered together in the analysis and consequently its potential individual impact could not be determined. Diet was not controlled for either this or their second study discussed below. Also applicable for both studies is that the authors did not have access to other medications their patients may have been taken such as statins or insulin which could ultimately impact their results.

Fjukstad and colleagues second cross-sectional study presents intriguing results consistent with previous publications suggesting that SSRIs influence the metabolic impact of antipsychotics in patients with SCZ [46]. The authors found that when olanzapine is combined with an SSRI, several metabolic parameters worsened. Similarly, the combination of quetiapine and SSRIs leads to

increases in total cholesterol and LDL. But this dual therapy prevents increments in triglyceride and BMI caused by quetiapine alone. SSRIs appear to be beneficial when taken with risperidone. This combination lowers blood glucose and prevents rises in LDL elicited by risperidone monotherapy. Unfortunately, whether each of the SSRIs studied differently affects metabolic markers, was not determined as all SSRIs included in the analysis were clustered as one group (Table 1).

The information currently available does not allow us to draw any firm conclusions. However, it suggests that for patients with SCZ, adding fluvoxamine to clozapine brings metabolic benefits [42,44], though clinicians have to be cautious with this combination as fluvoxamine can drastically increase clozapine levels [43]. Similarly, dual therapy with risperidone and SSRIs also appears to improve some metabolic parameters [46] but whether a specific SSRI is more advantageous than others is yet to be established. What appears to be clear is that SSRIs impact CV risk by affecting metabolic markers and that each SSRI has its own unique metabolic advantages and disadvantages depending on gender, age, diagnosis and the presence or absence of antipsychotics. Therefore, when metabolic parameters are being studied, SSRIs should be considered a confounder. Also evident is that further studies are needed to firmly establish the impact of SSRIs on CV risk for patients with SCZ.

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