Review

MAY SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) PROVIDE SOME BENEFIT FOR THE TREATMENT OF SCHIZOPHRENIA?

Massimiliano Buoli, MD*; Marta Serati, MD; Valentina Ciappolino, MD; A. Carlo Altamura, MD

Department of Psychiatry, University of Milan, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122, Milan, Italy

*Please direct all correspondence to:

Massimiliano Buoli, MD, Department of Psychiatry, University of Milan, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122, Milan, Italy

Tel.: +39-02-55035983; Fax: +39-02-55033190

(email: massimiliano.buoli@hotmail.it)

DECLARATION OF INTEREST

AC Altamura has served as a consultant or on Advisory Boards for Roche, Merck, Astra Zeneca, Bristol-Myers Squibb, Janssen/Cilag and Lundbeck. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

ABSTRACT

Introduction: The treatment of some psychopathological dimensions of schizophrenia (e.g. negative and depressive symptoms) is still challenging for the modest efficacy of atypical antipsychotics. Among pharmacological alternatives, augmentative Selective Serotonin Reuptake Inhibitors (SSRIs) to antipsychotics are frequently prescribed in clinical practice to improve negative/depressive symptoms of schizophrenia patients, however the data about the efficacy of these molecules on negative, depressive and obsessive-compulsive symptoms of schizophrenia are contrasting.

Areas Covered: Research using the main database sources has been conducted to obtain an overview of the use and efficacy of SSRIs in schizophrenia.

Expert Opinion: Data are too scanty to draw definitive recommendations. In a preliminary way, it can be said that available data do not show effectiveness of SSRIs on depressive symptoms of schizophrenia. Regarding negative symptoms, studies are contrasting, but paroxetine appears to be the most effective compound among SSRIs. Despite limited data, SSRIs appear to be useful for the treatment of obsessive-compulsive symptoms of schizophrenia, particularly fluvoxamine. Close clinical and pharmacological monitoring is needed in case of concomitant administration of antipsychotics and antidepressants for potential serious side effects and influence on plasma drug dosages

Keywords: Selective Serotonin Reuptake Inhibitors (SSRIs), schizophrenia, negative symptoms, depression, obsessive-compulsive symptoms

Article highlights

- Atypical antipsychotics have a modest effect on negative and depressive symptoms of schizophrenia
- Antidepressants, including SSRIs, are prescribed for the treatment of negative, depressive, obsessive-compulsive symptoms of schizophrenia, despite the current contrasting data about their efficacy
- Studies with small samples and the potential dangerous sides effects of antipsychotic/SSRI combination prevent from recommending the use of SSRIs for schizophrenia treatment
- Available data indicate that SSRIs have no effect on depressive symptoms of schizophrenia, but most studies are underpowered
- SSRIs have a doubtful effect on negative symptoms of schizophrenia: paroxetine might be more effective than other compounds, but currently head-to-head double-blind trials are lacking
- Fluvoxamine might be useful for the treatment of obsessive-compulsive symptoms, but data with other SSRIs are scanty and the positive data have to be replicated by further double-blind controlled studies and meta-analytical approaches

1. INTRODUCTION

Schizophrenia is a highly disabling disorder with a heterogeneous clinical presentation [1]. Different factors have been associated with poor outcome including predominant negative and cognitive symptoms [2]. All antipsychotics have showed efficacy in improving positive symptoms (delusions and hallucinations of schizophrenia patients) and atypicals were seen as promising molecules for all different symptoms of schizophrenia patients [3]. Unfortunately, atypical antipsychotics resulted to have only a modest effect on negative symptoms of schizophrenia patients (d=0.58), as also confirmed by a recent meta-analysis [4]. In addition, atypical antipsychotics have not a clear evidence of efficacy in controlling obsessive-compulsive [5, 6] and depressive symptoms of schizophrenia [7]. Depressive symptoms impact negatively on quality of life, social functioning, overall psychopathology and the severity of comorbid medical conditions [8]. In the light of the mentioned unmet needs, several authors assessed the effectiveness of alternative compounds (including Selective Serotonin Reuptake Inhibitors-SSRIs) for negative, obsessive-compulsive and depressive symptoms of schizophrenia patients [9]. Of note, antidepressants, including SSRIs, are frequently prescribed both in hospitalized and outpatient schizophrenics [10, 11]. As previous reviews/meta-analyses about the use of SSRIs in schizophrenia focussed only on specific symptoms of this disorder (e.g. depressive ones) or on specific molecules (e.g. fluvoxamine) [12], purpose of the present review is to ascertain the real utility and effectiveness of these antidepressants for the different psychopathological dimensions of schizophrenia. In addition, data reported by previous meta-analyses are discordant: a first paper concluded that there is no global support for an improvement in negative symptoms with SSRIs augmentation therapy in schizophrenia [13], while a subsequent meta-analysis stated the efficacy of antidepressants and in particular fluoxetine in improving negative symptoms of schizophrenia patients [14].

2. METHODS

A careful search of articles on MEDLINE, PsycINFO, Isi Web of Knowledge, Medscape was performed in order to obtain a comprehensive review about the use of SSRIs in schizophrenia. Only SSRIs were taken into account, being the most prescribed antidepressants [15] and to avoid dissipating information. In addition, the focus on SSRIs has the advantage to give indirect information about the role of serotonin on psychopathology of schizophrenia. The words "SSRI", "fluoxetine", "sertraline", "citalopram", "escitalopram", "fluvoxamine", "paroxetine" have been associated with "schizophrenia". A manual selection of papers was then performed in order to consider only those concerning with the topic of the present article. No restriction criteria were established for study design. Exclusion criteria included: 1) animal studies, 2) studies with mixed samples (e.g. schizophrenia and schizoaffective patients), 3) studies with pooled analyses 4) studies assessing the efficacy of SSRIs in ameliorating medical conditions in comorbidity with schizophrenia (e.g. weight gain). With regard to the second exclusion criterion, studies with $\leq$ 10% of schizoaffective patients were included, while, with regard to the third criterion, the results of single studies of pooled analyses were taken into consideration. Only papers in English were included. Two reviewers searched independently eligible articles for inclusion.

Table 1 summarizes the results of the included studies and their effect sizes. In the table the studies in which it was impossible to calculate the effect sizes were not included, but they have been described in the results. Table 2 reports evaluation of quality of studies according to sample size, use of a double-blinded design and administration of at least one specific rating scale to assess schizophrenia symptoms in relation to primary study outcomes (e.g. The Calgary Depression Scale for Schizophrenia-CDSS with respect to The Montgomery-Asberg Depression Rating Scale-MADRS)

3. RESULTS

Six hundred seventy five papers were initially identified, 513 dealt with the topic of the review and 69 satisfied the inclusion criteria (Figure 1). Antidepressant treatment was combined with antipsychotics in all the selected studies. In the following paragraphs, data about the efficacy of each SSRI on different symptoms of schizophrenia will be described and discussed.

4. Fluoxetine

A first paper reported a decrease of violent incidents and an increase in socialization after introduction of adjunctive fluoxetine (20 mg/day) in eight chronic schizophrenia patients [16]. Another open-label trial found the effectiveness of fluoxetine (20 mg/day) in improving negative and depressive symptoms of 14 antipsychotic-resistant schizophrenia patients [17]. In two schizophrenia patients, adjunctive treatment with fluoxetine produced a limited effect on compulsive behaviour and a worsening of psychotic symptoms [18], while in other two cases fluoxetine resulted to be effective in improving obsessive-compulsive symptoms [19, 20]. In a first 12-week double-blind study with 34 chronic schizophrenia patients, fluoxetine (20 mg/day) treatment was associated with greater improvement on Scale for the Assessment of Negative Symptoms (SANS) and Hamilton Depression Rating Scale (HAM-D) scores than placebo without a worsening of psychotic symptoms [21]. An open-label study reported the non-effectiveness of fluoxetine in improving clinical symptoms of 13 male chronic schizophrenia patients [22]. A subsequent 6-week double-blind study failed to demonstrate a greater efficacy of fluoxetine 20 mg/day than placebo in ameliorating symptoms of 41 schizophrenia patients with the exception of negative ones [23]. Another double-blind placebo-controlled study found that, after 8 weeks, there were not significant differences in positive, negative, depressive or obsessive-compulsive symptoms between patients given adjunctive fluoxetine or placebo [24]. These results were confirmed by a subsequent double-blind study [25]. In contrast, two open-

label trials reported the effectiveness of fluoxetine in improving respectively obsessive-compulsive symptoms [26] and general psychopathology of schizophrenia patients [27]

5. Sertraline

In two schizophrenia patients, sertraline was found to have a beneficial effect in improving clozapine-induced obsessive-compulsive symptoms [28, 29]. A 12-week open-label trial reported improvement of positive and negative symptoms in 20 chronic schizophrenia patients [30]. In contrast, two schizophrenia patients presented no improvement in obsessive compulsive symptoms and exacerbation of psychotic symptoms after treatment with sertraline (50 mg/day) [31]. Similarly, in another schizophrenia subject, sertraline showed no benefit on depressive and cognitive symptoms [32]. An imipramine-controlled study found that sertraline (50 mg/day) was faster than the active comparator in improving post-psychotic depressive symptoms of schizophrenia patients [33]. In contrast, a double-blind placebo-controlled study failed to demonstrate that the addition of sertraline 50 mg/day to antipsychotics had a beneficial effect on positive and negative symptoms of chronic schizophrenia inpatients [34]. In addition, in a further double-blind placebo-controlled study, treatment with sertraline (50 mg/day) did not ameliorate depressive symptoms of 48 remitted schizophrenia patients [35]. Another double-blind study reported a slight effect of sertraline (100 mg/day) on anxiety/depressive symptoms of schizophrenia patients without a significant effect on negative ones [36]. Augmentative sertraline (150 mg/day) to olanzapine improved obsessive-compulsive symptoms of two schizophrenia patients [37], while augmentative sertraline (50 mg/day) to perphenazine and lithium resulted to improve post-psychotic depression of another schizophrenia patient, but with a worsening of extrapyramidal side effects (EPS) [38]. Finally, somatic complaints were reported to be improved by augmentative sertraline (till 100 mg/day) in a simple schizophrenia adolescent [39].

6. Citalopram

A first double-blind cross-over study demonstrated the efficacy of citalopram (20-60 mg/day) over placebo in reducing the number of daily aggressive incidents of 15 violent schizophrenia patients [40]; however no greater improvement of scores on rating scales -including the Staff Observation Rating Scale (SOAS)- was observed for treatment with citalopram than placebo. A following double-blind placebo-controlled 12-week study with 90 chronic schizophrenia patients failed to find a superiority of citalopram till 40 mg/day than placebo in improving psychopathological symptoms (Positive and Negative Syndrome Scale-PANSS scores), while citalopram might increase subjective well-being of these patients (statistically significant improvement of Visual Analogue Scale (VAS) scores in citalopram group than placebo)[41]. In another study citalopram appeared to alleviate depressive and anxious symptoms of schizophrenia patients without improvement of other psychopathological dimensions [42]. Similar results were found by a subsequent 10-week single-blind trial, reporting a greater improvement on HAM-D/Clinical Global Impression (CGI) scores for citalopram than placebo and no statistically significant difference on PANSS scores [43]. A cross-over double-blind study failed to find statistically significant differences between citalopram 40 mg/day and placebo on any clinical or cognitive measure of 19 schizophrenia patients [44]. A nationwide cohort study reported that the current use of citalopram is associated with decreased all-cause and suicide mortality in suicidal patients with schizophrenia [45]. Finally two double-blind placebo-controlled studies did not find a beneficial effect of citalopram (mean dose 30 mg/day) with respect to placebo on negative symptoms of schizophrenia [46, 47].

7. Escitalopram

A first double-blind trial reported no advantage for escitalopram (20 mg/day) than placebo for global, negative and depressive symptoms of schizophrenia patients [48]. In contrast, a subsequent open-label study found that adjunctive treatment with escitalopram (20 mg/day) ameliorated obsessive-compulsive symptoms of schizophrenia patients [49]. Finally, escitalopram was reported to be effective in treating antiandrogen-related mood disorder of a patient with chronic schizophrenia [50] and in improving negative symptoms of a patient with simple schizophrenia [51].

8. Fluvoxamine

A preliminary 5-week double-blind placebo-controlled study found fluvoxamine (50-100 mg/day) to be beneficial in improving negative symptoms of 30 chronic schizophrenia inpatients [52]. In the same year, a case of fluvoxamine-induced acute exacerbation was reported in a residual schizophrenia patient [53]. In addition, co-administration of fluvoxamine with haloperidol was found to worsen cognitive performances of 4 chronic schizophrenia patients [54]. In contrast, low-dose (25-50 mg/day) augmentative fluvoxamine to clozapine was associated with improvement of negative symptoms in a paranoid schizophrenia patient and in an undifferentiated one [55, 56]. In two schizophrenia patients, add-on fluvoxamine (150-200 mg/day) to antipsychotics caused an improvement of negative symptoms, but a worsening of cognitive abilities and exacerbation of psychotic symptoms [57]: these observations were confirmed by two subsequent case reports [31]. Clozapine-induced obsessive-compulsive symptoms ameliorated in two schizophrenia patients after the introduction of treatment with fluvoxamine [58]. In an open-label study, eight schizophrenia patients benefited from adjunctive fluvoxamine (25-100 mg/day) to clozapine (improvement of negative and global symptoms without psychotic exacerbation) [59]: these results were confirmed by a subsequent open trial with 16 schizophrenia patients [60]. A 6-week double-blind study found fluvoxamine

(100 mg/day) to be more efficacious than maprotiline in improving negative symptoms of 25 schizophrenia patients [61]. In addition, fluvoxamine up to 150 mg/day resulted to be effective in improving obsessions and negative symptoms of ten neuroleptic-stabilized chronic schizophrenia patients [62]. A subsequent 8-week double-blind trial confirmed the efficacy of add-on fluvoxamine (100-200 mg/day) to neuroleptics for obsessive symptoms of schizophrenia patients, but not for negative ones [63]. An open-label study by the same authors further remarked the effectiveness of fluvoxamine (100-200 mg/day) augmentation to neuroleptics in reducing obsessive-compulsive symptoms of 16 schizophrenia patients [64]. Negative symptoms were improved by fluvoxamine (50-100 mg/day) in a randomized double-blind placebo controlled study with 52 chronic schizophrenia patients [65]. In addition, fluvoxamine 100 mg/day improved obsessive thoughts of a 13-year-old schizophrenia girl [66]. In contrast, no changes in depressive symptoms of 8 schizophrenia patients resulted by augmentative treatment to olanzapine with fluvoxamine (100 mg/day) [67]. Similar results were found with regard to negative symptoms and general psychopathology by a 12-week open-label study in which 30 risperidone-resistant schizophrenia patients received add-on fluvoxamine (100 mg/day) [68]. On the other hand, augmentative fluvoxamine (50-100 mg/day) to clozapine ameliorated global functioning of 12 schizophrenia patients [69]. Fluvoxamine (till 150 mg/day) was also reported to improve negative symptoms of 12 haloperidol-treated schizophrenia inpatients [70]. Furthermore, obsessive-compulsive symptoms were ameliorated by adjunctive treatment with fluvoxamine 200 mg/day) to clozapine in a young schizophrenia boy [71]. A single-blind prospective study found that olanzapine plus fluvoxamine (50 mg/day) combined treatment improved general psychopathology, but not specifically negative symptoms of 20 schizophrenia patients [72]. Adjunctive fluvoxamine (50 mg/day) to risperidone (4 mg/day) improved cognitive impairment of a young female schizophrenia patient [73], differently from other two schizophrenia cases in whom fluvoxamine resulted to be ineffective in ameliorating

obsessive-compulsive symptoms (250 mg/day) [74,75]. Finally, a double-blind study failed to find a superiority of fluvoxamine (150 mg/day) over placebo in improving global, negative, cognitive and depressive symptoms of 48 chronic schizophrenia patients [76].

9. Paroxetine

Adjunctive paroxetine (50 mg/day) resulted to improve obsessive-compulsive symptoms of a chronic schizophrenia woman in treatment with a combination of clozapine (275 mg/day) and risperidone (6 mg/day) [77]. Similarly, depressive symptoms of a schizophrenia patient improved after adjunctive treatment with paroxetine (20 mg/day) to clozapine [78]. A further schizophrenia patient showed a significant improvement in both psychotic and obsessive compulsive symptoms by combination of clozapine (200 mg/day) and paroxetine (30 mg/day) [79]. A similar improvement on obsessive-compulsive symptoms was observed in another schizophrenia case [71]. Eight chronic schizophrenia patients improved negative symptoms after a 12-week treatment with paroxetine (30 mg/day) as an add-on therapy to antipsychotics [80]. These results were confirmed by a further open-label trial with 12 schizophrenia patients treated with a combination of risperidone and paroxetine (10-40 mg/day) [81] and by a double-blind placebo-controlled study [82]. However, both these studies did not find a significant effect of paroxetine on depressive symptoms of schizophrenia patients [82]. In an open-label prospective study, the combination of olanzapine plus paroxetine resulted to be less effective than the combination of olanzapine plus fluvoxamine in improving negative symptoms of 50 schizophrenia patients [83]. Finally, Paroxetine (10-20 mg/day) added to aripiprazole did not produce significant clinical improvement in 14 schizophrenia patients [84].

10. CONCLUSION

Studies about the use of SSRIs in schizophrenia have focused mainly on negative symptoms and depression and to a lesser extent on the general psychopathology and obsessive-compulsive symptoms. In contrast, few data were published about the impact of SSRIs on cognitive impairment of schizophrenia patients [85, 86]. In addition, with a few exceptions [45], small sample sizes of the studies prevent from drawing precise considerations about the effectiveness of SSRIs across the different psychopathological dimension of schizophrenia. Finally, the studies use different scales for the assessment of the heterogeneous symptoms of schizophrenia (e.g. Brief Psychiatric Rating Scale –BPRS- and SANS for negative symptoms) and this makes the overall interpretation of the results even more difficult.

Going into details, with regard to fluoxetine, exactly half of the double-blind studies [21,23] have found some utility in the prescription of this compound for negative symptoms of schizophrenia, while the other half (which are also the most recent studies) [24, 25] did not show the usefulness of this drug in the management of the disorder. Regarding sertraline, the results of studies agree in the non-effectiveness of the compound on negative symptoms of schizophrenia, with results rather contradictory concerning depressive symptoms. Similar considerations may be done for citalopram which, however, might have some utility for prevention of suicide in schizophrenia patients [45], although long-term prospective studies have to confirm preliminary evidence. Few studies investigated escitalopram for the treatment of schizophrenia: no evidence of efficacy resulted for negative and depressive symptoms, but the compound might be useful in case of obsessive-compulsive symptoms, although, again, double-blind studies have to replicate the results of a small sample size open-label study [49]. Most studies indicate that fluvoxamine may improve negative symptoms of schizophrenia, but the most recent study with the largest sample of schizophrenia patients disconfirms the first positive results [76]. Furthermore, one of the double-blind studies reported a very slight advantage of fluvoxamine over placebo on negative symptoms of schizophrenia [65]. With the

exclusion of two case reports [74, 75], available preliminary data agree in showing the effectiveness of augmentative fluvoxamine (100-200 mg/day) to antipsychotics for obsessive-compulsive symptoms of schizophrenia patients. Finally, fluvoxamine has currently no evidence of efficacy for depressive symptoms in schizophrenia. Three open-label studies [80, 81,83] and one double-blind trial [82] for a total of 95 patients with schizophrenia show the effectiveness of paroxetine on negative symptoms of schizophrenia, but more evidence is needed to define the usefulness of this molecule in the treatment of these patients. On the other hand, current data do not support the use of this compound for ameliorating depressive symptoms of schizophrenia subjects.

Taken as a whole, current evidence prevents from recommending the use of SSRIs for the treatment of schizophrenia patients, since even the few favourable results (e.g. fluvoxamine for obsessive symptoms) come from studies with a limited number of patients.

11. EXPERT OPINION

Only preliminary considerations can be made about the effectiveness of SSRIs on different psychopathological dimensions of schizophrenia

Regarding the negative symptoms, no evidence of efficacy is currently available for sertraline, citalopram and escitalopram. With regard to fluoxetine and fluvoxamine results are mixed, while the paroxetine may actually have some efficacy on negative symptoms of schizophrenia. The data on the use of paroxetine on negative symptoms of schizophrenia are predominantly from open-label studies with limited samples, but the effect sizes are higher than those associated with atypical antipsychotics (d=0.97-1.56 versus 0.58). These positive results of paroxetine on negative symptoms of schizophrenia may be due to its specific pharmacodynamic properties: its action as a noradrenaline reuptake inhibitor at medium to high doses (those used in most studies) [87] and its anticholinergic effects, which could improve

parkinsonism and negative symptoms associated with the use of first-generation antipsychotics [88]. With very few exceptions [23, 43], there is no evidence of the effectiveness of SSRIs on depressive symptoms of schizophrenia: this observation may reflect different biological mechanisms underlying major depression compared with depressive symptoms in schizophrenia [89]. Depressive symptoms affect about 20% of schizophrenia patients [90] and a similar percentage of patients take antidepressant medications [91]; furthermore a quite recent systematic review about instruments to measure depressive symptoms in schizophrenia patients concluded that the CDSS was the most appropriate tool to rate depression in schizophrenia [92]. In addition, the CDSS is even more specific to detect depressive symptoms during acute exacerbations of schizophrenia [93]. Despite the appropriateness of the CDSS, most studies about depression and schizophrenia use other rating scales (e.g. MADRS), including those about the effectiveness of SSRIs in acute schizophrenia symptoms. In this way the results about the effects of SSRIs on depressive symptoms of schizophrenia must be interpreted in the light of the use of tools not always adequate for the measurement of depression in schizophrenia (table 3). SSRIs may have some utility on obsessive symptoms of schizophrenia, but studies are few and they have so limited samples that it is not possible to draw any reliable conclusion. The effect of SSRIs on other aspects of schizophrenia such as impulsivity, suicidal ideation, cognition and global functioning was studied sporadically so that it is impossible to give even a preliminary opinion about these topics (table 4).

We must keep in mind that in all studies SSRIs are combined with antipsychotics and this may result in variations of drug plasma concentrations. This has two key clinical implications: first, there may be an increase of side effects (e.g. QT interval prolongation) [94] and, second, a decrease of antidepressant effectiveness. Fatal clozapine overdose has been reported in one patient treated with a combination of the antipsychotic and fluoxetine [95]. In addition, sudden cardiac death resulted by the combination of clozapine (200 mg/day), risperidone (6 mg/day)

and sertraline (200 mg/day) in a young paranoid schizophrenia patient [96]. Exacerbation of idiopathic priapism may be the effect of risperidone-sertraline [97] or risperidone-citalopram [98] combinations. Paroxetine may impair the elimination of risperidone by inhibition of cytochrome CYP2D6 with the possibility to develop parkinsonism [99]. An incipient neuroleptic malignant syndrome was observed in a young paranoid schizophrenia patient with quetiapine/paroxetine combination treatment [100]. Co-administration of fluvoxamine increases plasma concentrations of clozapine [101] with the likely increase of agranulocytosis, seizures, extrapyramidal symptoms [102] and clozapine-associated obsessive-compulsive symptoms [75]. Combination of fluvoxamine with olanzapine has been reported to be associated with increased tremor and rigidity [103]. From a pharmacokinetic point of view, citalopram and escitalopram are hypothetically the most suitable SSRIs to combine with antipsychotics for their poor interaction with cytochromes [104], however a case of urinary obstruction has been reported as a consequence of the combination of aripiprazole and citalopram [105].

Future studies should take into account the following observations to get a more precise evaluation of the use of SSRIs in schizophrenia:

1) it is not always precisely defined in the studies if certain symptoms are part of schizophrenia or are the result of comorbid psychiatric conditions such as obsessive-compulsive disorder [106-108];

2) trials should use appropriate rating scales for the evaluation of the different clinical dimensions of schizophrenia in order to allow pooled analyses and meta-analytical approaches of large samples of patients;

3) most of available studies are underpowered: researches with large samples are required to obtain more reliable data;

4) clinical aspects need to be monitored for an extended period of time to verify if the efficacy of SSRIs in schizophrenia is sustained in the long-term and to ascertain possible iatrogenic causes of psychotic symptoms;

5) combined treatments might be associated with potential dangerous side effects and future studies should quantify the risk/benefit ratio of antipsychotic/antidepressant concomitant administration in schizophrenia patients;

6) pharmacokinetic interactions should be monitored in the long-term, measuring drug plasma levels regularly

REFERENCES

1. Buoli M, Caldiroli A, Panza G, Altamura AC. Prominent clinical dimension, duration of illness and treatment response in schizophrenia: a naturalistic study. Psychiatry Investig 2012;9: 354-60.

2. Silver H. Selective serotonin re-uptake inhibitor augmentation in the treatment of negative symptoms of schizophrenia. Expert Opin Pharmacother 2004;5: 2053-2058.

3. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373:31-41

4. Fusar-Poli P, Papanastasiou E, Stahl D, et al. Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials. Schizophr Bull 2015;41:892-9.

•• Meta-analysis of pharmacological treatments for negative symptoms in schizophrenia

5. Schirmbeck F, Esslinger C, Rausch F, Englisch S, Meyer-Lindenberg A, Zink M. Antiserotonergic antipsychotics are associated with obsessive-compulsive symptoms in schizophrenia. Psychol Med 2011;41:2361-73.

• Worsening of obsessive-compulsive symptoms in schizophrenia patients by clozapine and olanzapine

6. Schirmbeck F, Rausch F, Englisch S, et al. Differential effects of antipsychotic agents on obsessive-compulsive symptoms in schizophrenia: a longitudinal study. J Psychopharmacol 2013; 27: 349-357.

7. Bosanac P, Castle DJ. Schizophrenia and depression. Med J Aust 2013;199: S36-9.

8. Kasckow JW, Zisook S. Co-occurring depressive symptoms in the older patient with schizophrenia. Drugs Aging 2008;25: 631-47.

9. Silver H. Selective serotonin reuptake inhibitor augmentation in the treatment of negative symptoms of schizophrenia. Int Clin Psychopharmacol 2003;18: 305-313.

• Efficacy of SSRIs in improving negative symptoms of schizophrenia

10. Micallef J, Fakra E, Blin O. [Use of antidepressant drugs in schizophrenic patients with depression]. Encephale 2006;32: 263-9

11. Xiang YT, Ungvari GS, Wang CY, et al. Adjunctive antidepressant prescriptions for hospitalized patients with schizophrenia in Asia (2001-2009). Asia Pac Psychiatry 2013;5: 81-7.

12. Kishi T, Hirota T, Iwata N. Add-on fluvoxamine treatment for schizophrenia: an updated meta-analysis of randomized controlled trials. Eur Arch Psychiatry Clin Neurosci 2013;263:633-41.

• Efficacy of add-on fluvoxamine in schizophrenia patients

13. Sepehry AA, Potvin S, Elie R, Stip E. Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative symptoms of schizophrenia: a meta-analysis. J Clin Psychiatry 2007; 68: 604-10.

• Efficacy of add-on SSRIs in improving negative symptoms of schizophrenia

14. Singh SP, Singh V, Kar N, Chan K. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. Br J Psychiatry. 2010;197: 174-9.

•• Meta-analysis about the efficacy of antidepressants in improving negative symptoms of chronic schizophrenia patients.

15. Abbing-Karahagopian V, Huerta C, Souverein PC, et al. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. Eur J Clin Pharmacol 2014;70: 849-57.

16. Goldman MB, Janecek HM. Adjunctive fluoxetine improbe global function in chronic schizophrenia. J Neuropsychiatry Clin Neurosci 1990;2: 429-431.

17. Goff DC, Brotman AW, Waites M, McCormick S. Trial of fluoxetine added to neuroleptics for treatment-resistant schizophrenic patients. Am J Psychiatry 1990;147: 492-494.

18. Lindenmayer JP, Vakharia M, Kanofsky D. Fluoxetine in chronic schizophrenia. J Clin Psychopharmacol 1990;10: 76.

19. Cassady SL, Thaker GK. Addition of fluoxetine to clozapine. Am J Psychaitry, 1992; 149: 1274.

20. Tejera CA, Mayerhoff DJ, Safferman AZ, Ramos-Lorenzi JR. Fluoxetine for obsessional symptoms in schizophrenia. Am J Psychiatry 1994; 151: 149-150.

21. Spina E, De Domenico P, Ruello C, et al. Adjunctive fluoxetine in the treatment of negative symptoms in chronic schizophrenic patients. Int Clin Psychopharmacol 1994;9: 281-5.

22. Bacher NM, Sanzone MM, Kaup B. Cyproheptadine in treatment-resistant chronic schizophrenics with prior negative response to fluoxetine. J Clin Psychopharmacol 1994;14: 424-5.

23. Goff DC, Midha KK, Sarid-Segal O, Hubbard JW, Amico E. A placebo-controlled trial of fluoxetine added to neuroleptic in patients with schizophrenia. Psychopharmacology (Berl) 1995;117: 417-23.

24. Buchanan RW, Kirkpatrick B, Bryant N, Ball P, Breier A. Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. Am J Psychiatry. 1996;153: 1625-7.

25. Arango C, Kirkpatrick B, Buchanan RW. Fluoxetine as an adjunct to conventional antipsychotic treatment of schizophrenia patients with residual symptoms. J Nerv Ment Dis 2000;188: 50-3.

26. Agarwal V, Agarwal KM. Treatment of obsessive compulsive symptoms in schizophrenia with fluoxetine. Indian J Psychiatry 2000; 42: 291-4.

27. Shrim JC, Kelly DL, Kim YH, et al. Fluoxetine augmentation of haloperidol in chronic schizophrenia. J Clin Psychopharmacol 2003;23: 520-2.

28. Allen L, Tejera C. Treatment of clozapine-induced obsessive-compulsive symptoms with sertraline. Am J Psychiatry 1994;151: 1096-10

29. Rahman MS, Grace JJ, Pato MT, Priest B. Sertraline in the treatment of clozapine-induced obsessive-compulsive behavior. Am J Psychiatry 1998;155: 1629-30.

30. Thakore JH, Berti C, Dinan TG. An open trial of adjunctive sertraline in the treatment of chronic schizophrenia. Acta Psychiatr Scand 1996; 94:194-7.

31. Chong SA, Tan CH, Lee HS. Worsening of psychosis with clozapine and selective serotonin reuptake inhibitor combination: two case reports. J Clin Psychopharmacol 1997; 17:68-9

32. Purdon SE, Snaterse M. Selective serotonin reuptake inhibitor modulation of clozapine effects on cognition in schizophrenia. Can J Psychiatry 1998;43: 84-5.

33. Kirli S, Caliskan M. A comparative study of sertraline versus imipramine in postpsychotic depressive disorder of schizophrenia. Schizophr Res 1998;33: 103-11.

34. Lee MS, Kim YK, Lee SK, Suh KY. A double-blind study of adjunctive sertraline in haloperidol-stabilized patients with chronic schizophrenia. J Clin Psychopharmacol 1998;18: 399-403.

35. Addington D, Addington J, Patten S, et al. Double-blind, placebo-controlled comparison of the efficacy of sertraline as treatment for a major depressive episode in patients with remitted schizophrenia. J Clin Psychopharmacol 2002;22: 20-5.

36. Mulholland C, Lynch G, King DJ, Cooper SJ. A double-blind, placebo-controlled trial of sertraline for depressive symptoms in patients with stable, chronic schizophrenia. J Psychopharmacol 2003;17: 107-12.

37. Poyurovsky M, Kurs R, Weizman A. Olanzapine-sertraline combination in schizophrenia with obsessive-compulsive disorder. J Clin Psychiatry 2003;64: 611.

38. Ros LT. Treatment of postpsychotic depression with sertraline in patients with schizophrenia--own experience. Neuropsychopharmacol Hung 2006;8: 155-6.

39. Valentí M, Castro-Fornieles J, Lázaro ML, Sugrañes G, Baeza I. Simple schizophrenia in an adolescent. J Child Adolesc Psychopharmacol 2009;19: 589-90.

40. Vartiainen H, Tiihonen J, Putkonen A, et al. Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. Acta Psychiatr Scand 1995; 91: 348-51.

41. Salokangas RK, Saarijärvi S, Taiminen T, et al. Citalopram as an adjuvant in chronic schizophrenia: a double-blind placebo-controlled study. Acta Psychiatr Scand 1996; 94: 175-80.

42. Taiminen TJ, Syvälahti E, Saarijärvi S, et al. Citalopram as an adjuvant in schizophrenia: further evidence for a serotonergic dimension in schizophrenia. Int Clin Psychopharmacol 1997; 12: 31-5.

43. Kasckow JW, Mohamed S, Thallasinos A, Carroll B, Zisook S, Jeste DV. Citalopram augmentation of antipsychotic treatment in older schizophrenia patients. Int J Geriatr Psychiatry 2001;16: 1163-7.

44. Friedman JI, Ocampo R, Elbaz Z, et al. The effect of citalopram adjunctive treatment added to atypical antipsychotic medications for cognitive performance in patients with schizophrenia. J Clin Psychopharmacol 2005;25: 237-42.

45. Haukka J, Tiihonen J, Härkänen T, Lönnqvist J. Association between medication and risk of suicide, attempted suicide and death in nationwide cohort of suicidal patients with schizophrenia. Pharmacoepidemiol Drug Saf 2008;17: 686-96.

46. Hinkelmann K, Yassouridis A, Kellner M, Jahn H, Wiedemann K, Raedler TJ. No effects of antidepressants on negative symptoms in schizophrenia. J Clin Psychopharmacol 2013;3: 686-90.

47. Usall J, López-Carrilero R, Iniesta R, et al.; Abordaje Síntomas Negativos Esquizofrenia Group. Double-blind, placebo-controlled study of the efficacy of reboxetine and citalopram as

adjuncts to atypical antipsychotics for negative symptoms of schizophrenia. J Clin Psychiatry 2014;75: 608-15.

48. Iancu I, Tschernihovsky E, Bodner E, Piconne AS, Lowengrub K. Escitalopram in the treatment of negative symptoms in patients with chronic schizophrenia: a randomized double-blind placebo-controlled trial. Psychiatry Res 2010;179: 19-23.

49. Stryjer R, Dambinsky Y, Timinsky I, et al. Escitalopram in the treatment of patients with schizophrenia and obsessive-compulsive disorder: an open-label, prospective study. Int Clin Psychopharmacol 2013;28: 96-8.

50. Kao LC, Chen LF, Hsu YC, et al. Escitalopram in treatment of antiandrogen-related mood disturbance in a patient with chronic schizophrenia and adenocarcinoma of the prostate. Gen Hosp Psychiatry 2015;37: e11-2

51. Tsai CH, Chen TT, Huang WL. Combination of escitalopram and aripiprazole causes significant improvement of negative symptoms of simple schizophrenia. Psychiatry Clin Neurosci 2014;68: 582-3.

52. Silver H, Nassar A. Fluvoxamine improves negative symptoms in treated chronic schizophrenia: an add-on double-blind, placebo-controlled study. Biol Psychiatry 1992;31: 698-704.

53. Rocco PL, De Leo D. Fluvoxamine-induced acute exacerbation in residual schizophrenia. Pharmacopsychiatry 1992;25: 245.

54. Daniel DG, Randolph C, Jaskiw G, et al. Coadministration of fluvoxamine increases serum concentrations of haloperidol. J Clin Psychopharmacol 1994;14: 340-3.

55. Silver H, Kaplan A, Jahjah N. Fluvoxamine augmentation for clozapine-resistant schizophrenia. Am J Psychiatry 1995;152: 1098

56. Szegedi A, Wiesner J, Hiemke C. Improved efficacy and fewer side effects under clozapine treatment after addition of fluvoxamine. J Clin Psychopharmacol 1995;15: 141-3.

57. Silver H, Jahjah N, Kushnir M. Psychotic symptoms in schizophrenics during chronic fluvoxamine treatment. A report of two cases. Schizophr Res 1995;16: 77-79.

58. Poyurovsky M, Hermesh H, Weizman A. Fluvoxamine treatment in clozapine-induced obsessive-compulsive symptoms in schizophrenic patients. Clin Neuropharmacol 1996;19: 305-13.

59. Silver H, Kushnir M, Kaplan A. Fluvoxamine augmentation in clozapine-resistant schizophrenia: an open pilot study. Biol Psychiatry 1996;40: 671-4.

60. Szegedi A, Anghelescu I, Wiesner J, et al. Addition of low-dose fluvoxamine to low-dose clozapine monotherapy in schizophrenia: drug monitoring and tolerability data from a prospective clinical trial. Pharmacopsychiatry 1999;32: 148-53.

61. Silver H, Shmugliakov N. Augmentation with fluvoxamine but not maprotiline improves negative symptoms in treated schizophrenia: evidence for a specific serotonergic effect from a double-blind study. J Clin Psychopharmacol 1998;18: 208-11.

62. Poyurovsky M, Isakov V, Hromnikov S, et al. Fluvoxamine treatment of obsessive-compulsive symptoms in schizophrenic patients: an add-on open study. Int Clin Psychopharmacol 1999;14: 95-100.

63. Reznik I, Sirota P. Obsessive and compulsive symptoms in schizophrenia: a randomized controlled trial with fluvoxamine and neuroleptics. J Clin Psychopharmacol 2000;20: 410-6.

64. Reznik I, Sirota P. An open study of fluvoxamine augmentation of neuroleptics in schizophrenia with obsessive and compulsive symptoms. Clin Neuropharmacol 2000;23: 157-60.

65. Silver H, Barash I, Aharon N, Kaplan A, Poyurovsky M. Fluvoxamine augmentation of antipsychotics improves negative symptoms in psychotic chronic schizophrenic patients: a placebo-controlled study. Int Clin Psychopharmacol 2000;15: 257-61.

66. Dwivedi S, Pavuluri M, Heidenreich J, Wright T. Response to fluvoxamine augmentation for obsessive and compulsive symptoms in schizophrenia. J Child Adolesc Psychopharmacol 2002;12: 69-70.

67. Hiemke C, Peled A, Jabarin M, et al. Fluvoxamine augmentation of olanzapine in chronic schizophrenia: pharmacokinetic interactions and clinical effects. J Clin Psychopharmacol 2002;22(5):502-6.

68. Takahashi H, Sugita T, Higuchi H, Shimizu T. Fluvoxamine augmentation in risperidone-resistant schizophrenia: an open trial. Hum Psychopharmacol. 2002;17(2):95-8

69. Lu ML, Lane HY, Jann MW, Chang WH. Dosing strategies of clozapine-fluvoxamine cotreatment. J Clin Psychopharmacol 2002;22: 626-8.

70. Yasui-Furukori N, Kondo T, Mihara K, Inoue Y, Kaneko S. Fluvoxamine dose-dependent interaction with haloperidol and the effects on negative symptoms in schizophrenia. Psychopharmacology 2004;171: 223-227.

71. Ke CL, Yen CF, Chen CC, Yang SJ, Chung W, Yang MJ. Obsessive-compulsive symptoms associated with clozapine and risperidone treatment: three case reports and review of the literature. Kaohsiung J Med Sci 2004;20: 295-301.

72. Chaichan W. Olanzapine plus fluvoxamine and olanzapine alone for the treatment of an acute exacerbation of schizophrenia. Psychiatry Clin Neurosci 2004;58: 364-8.

73. Iyo M, Shirayama Y, Watanabe H, et al. Fluvoxamine as a sigma-1 receptor agonist improved cognitive impairments in a patient with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2008;32: 1072-3.

74. Rodriguez CI, Corcoran C, Simpson HB. Diagnosis and treatment of a patient with both psychotic and obsessive-compulsive symptoms. Am J Psychiatry 2010;167: 754-61.

75. Gahr M, Rehbaum K, Connemann BJ. Clozapine-associated development of second-onset obsessive compulsive symptoms in schizophrenia: impact of clozapine serum levels and fluvoxamine add-on. Pharmacopsychiatry 2014;47: 118-20.

76. Niitsu T, Fujisaki M, Shiina A, et al. A randomized, double-blind, placebo-controlled trial of fluvoxamine in patients with schizophrenia: a preliminary study. J Clin Psychopharmacol 2012;32: 593-601.

77. Patel JK, Salzman C, Green AI, Tsuang MT. Chronic schizophrenia: response to clozapine, risperidone, and paroxetine. Am J Psychiatry 1997;154: 543-6.

78. Altamura AC, Bignotti S, Tura G, Curreli R, Pioli R. Depressive symptomatology during clozapine treatment: two case reports. Eur Neuropsychopharmacol 1998;8: 239-40.

79. Strous RD, Patel JK, Zimmet S, Green AI. Clozapine and paroxetine in the treatment of schizophrenia with obsessive-compulsive features. Am J Psychiatry 1999;156: 973-4.

80. Jockers-Scherübl M, Godemann F, Pietzcker A. Negative symptoms of schizophrenia are improved by paroxetine added to neuroleptics: a pilot study. J Clin Psychiatry 2001;62: 573.

81. Saito M, Yasui-Furukori N, Nakagami T, Furukori H, Kaneko S. Dose-dependent interaction of paroxetine with risperidone in schizophrenic patients. J Clin Psychopharmacol. 2005;25: 527-32.

82. Jockers-Scherübl MC, Bauer A, Godemann F, Reischies FM, Selig F, Schlattmann P. Negative symptoms of schizophrenia are improved by the addition of paroxetine to neuroleptics: a double-blind placebo-controlled study. Int Clin Psychopharmacol 2005; 20: 27-31.

83. Rusconi AC, Carlone C, Muscillo M, et al.SSRI antidepressants and negative schizophrenic symptoms: differences between paroxetine and fluvoxamine in patients treated with olanzapine. Riv Psichiatr 2009;44: 313-9.

84. Nemoto K, Mihara K, Nakamura A, et al. Effects of paroxetine on plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. Ther Drug Monit 2012;34: 188-92.

85. Vernon JA, Grudnikoff E, Seidman AJ, et al. Antidepressants for cognitive impairment in schizophrenia--a systematic review and meta-analysis. Schizophr Res 2014;159: 385-94.

86. Buoli M, Altamura AC. May non-antipsychotic drugs improve cognition of schizophrenia patients? Pharmacopsychiatry 2015;48: 41-50.

87. Nemeroff CB, Owens MJ. Neuropharmacology of paroxetine. Psychopharmacol Bull 2003; 37: 8-18.

88. Bermanzohn PC, Siris SG. Akinesia: a syndrome common to parkinsonism, retarded depression, and negative symptoms of schizophrenia. Compr Psychiatry 1992;33: 221-32.

89. Holcomb HH, Rowland LM. How schizophrenia and depression disrupt reward circuitry. Curr Treat Options Neurol 2007;9: 357-62.

90. Zisook S, McAdams LA, Kuck J, et al. Depressive symptoms in schizophrenia. Am J Psychiatry 1999;156:1736-43.

91. Nykänen S, Puska V, Tolonen JP, et al. Use of psychiatric medications in schizophrenia and other psychoses in a general population sample. Psychiatry Res 2016 30;235:160-8

92. Lako IM, Bruggeman R, Knegtering H,et al. A systematic review of instruments to measure depressive symptoms in patients with schizophrenia. J Affect Disord.2012;140:38-47.

93. Schennach R, Obermeier M, Seemüller F, et al. Evaluating depressive symptoms in schizophrenia: a psychometric comparison of the Calgary Depression Scale for Schizophrenia and the Hamilton Depression Rating Scale. Psychopathology 2012;45:276-85..

94. Sala M, Vicentini A, Brambilla P, et al. QT interval prolongation related to psychoactive drug treatment: a comparison of monotherapy versus polytherapy. Ann Gen Psychiatry 2005;4:1.

95. Ferslew KE, Hagardorn AN, Harlan GC, McCormick WF. A fatal drug interaction between clozapine and fluoxetine. J Forensic Sci 1998;43: 1082-5.

96. Hoehns JD, Fouts MM, Kelly MW, Tu KB. Sudden cardiac death with clozapine and sertraline combination. Ann Pharmacother 2001;35: 862-866.

97. Haberfellner EM. Priapism with sertraline-risperidone combination. Pharmacopsychiatry 2007;40: 44-45.

98. Freudenreich O. Exacerbation of idiopathic priapism with risperidone-citalopram combination. J Clin Psychiatry 2002;63: 249-250.

99. Spina E, Avenoso A, Facciolà G, Scordo MG, Ancione M, Madia A. Plasma concentrations of risperidone and 9-hydroxyrisperidone during combined treatment with paroxetine. Ther Drug Monit 2001;23: 223-7.

100. Grignon S, Ianic Brethes J, Chamberland M, Guimaraes DB. Incipient neuroleptic malignant syndrome with quetiapine/paroxetine combination treatment: atypical presentation and early, successful rechallenge with olanzapine. Int J Psychiatry Clin Pract 2005;9: 296-8.

101. Altamura AC, Caldiroli A, Buoli M. Pharmacokinetic evaluation of fluvoxamine for the treatment of anxiety disorders. Expert Opin Drug Metab Toxicol 2015;11: 649-60.

102. Kuo FJ, Lane HY, Chang WH. Extrapyrmaidal symptoms after addition of fluvoxamine to clozapine. J Clin Psychopharmacol 1998;18: 483-484.

103. De Jong J, Hoogenboom B, van Troostwijk LD, de Haan L. Interaction of olanzapine with fluvoxamine. Psychopharmacology 2001;155: 219-220

104. Syvälahti EK, Taiminen T, Saarijärvi S, et al. Citalopram causes no significant alterations in plasma neuroleptic levels in schizophrenic patients. J Int Med Res 1997;25: 24-32.

105. Padala PR, Sadiq HJ, Padala KP. Urinary obstruction with citalopram and aripiprazole combination in an elderly patient. J Clin Psychopharmacol 2006;26: 667-8.

106. Devulapalli K, Nasrallah HA. Schizophrenia and obsessive-compulsive disorder. Am J Psychiatry 2010;167: 1407-8.

107. De Haan L, Schirmbeck F, Zink M. Obsessive-compulsive symptoms in schizophrenia. Springer, 2015

108. Poyurovsky M. Schizo-Obsessive Disorder. Cambridge University Press, 2013.

Table 1. Selective Serotonin Reuptake Inhibitors (SSRIs) and Schizophrenia: Summary of Studies

Paper	Molecule	Double-Blind	Sample	Primary Outcomes	Effect sizes (r/d)
Goff et al., 1990 [17]	Fluoxetine (20 mg/day)	No	N=14 (1 SKA)	BPRS score reduction (compared to baseline)	0.65/1.7
				NSS score reduction (compared to baseline)	0.41/0.9
				HAM-D score reduction (compared to baseline)	0.29/0.6
				GAS score improvement (compared to baseline)	0.41/0.91
Spina et al., 1994 [21]	Fluoxetine (20 mg/day)	Yes	N=30	SANS score reduction (compared to placebo)	0.54/1.28
Goff et al., 1995 [23]	Fluoxetine (20 mg/day)	Yes	N=41 (3 SKA)	BPRS score reduction (compared to placebo)	**N.S.** 0.17/0.34
				BPRS negative score reduction (compared to placebo)	0.34/0.73
				HAM-D score reduction (compared to placebo)	**N.S.** 0.16/0.32
				GAS score improvement (compared to placebo)	**N.S.** 0.06/0.12
Buchanan et al., 1996 [24]	Fluoxetine (20-80 mg/day)	Yes	N=33	BPRS positive score reduction (compared to placebo)	**N.S.** 0.16/0.33
				SANS score reduction (compared to placebo)	**N.S.** 0.23/0.47
				HAM-D score reduction (compared to placebo)	**N.S.** 0.10/0.21
				HAM-D obsession item score reduction (compared to placebo)	**N.S.** 0.24/0.49
Arango et al., 2000 [25]	Fluoxetine (36.2 mg/day)	Yes	N=27	BPRS positive score reduction (compared to placebo)	**N.S.** 0.19/0.38
				BPRS negative score reduction (compared to placebo)	**N.S.** 0.03/0.06
				SANS score reduction (compared to placebo)	**N.S.** 0.19/0.38
				HAM-D score reduction (compared to placebo)	**N.S.** 0.19/0.38
Agarwal and Agarwal, 2000 [26]	Fluoxetine (80 mg/day)	No	N=7	YBOCS score reduction (compared to baseline)	0.69/1.92
Shim et al., 2003 [27]	Fluoxetine (20-60 mg/day)	No	N=15	PANSS score reduction (compared to baseline)	0.53/1.24
Kirli and Caliskan, 1998 [33]	Sertraline (50 mg/day)	Yes	N=40	"Good" or "Very Good" efficacy (compared to imipramine 150 mg/day)	0.22/0.45
Lee et al., 1998 [34]	Sertraline (50 mg/day)	Yes	N=36	PANSS positive score reduction (compared to placebo)	**N.S.** 0.12/0.25

				PANSS negative score reduction (compared to placebo)	**N.S.** <0.01/0.01
				PANSS general score reduction (compared to placebo)	**N.S.** 0.03/0.05
				CGI-S score reduction (compared to placebo)	**N.S.** 0.06/0.13
Addington et al., 2002 [35]	Sertraline (50-100 mg/day)	Yes	N=48 (4 SKA)	CDSS score at endpoint (compared to placebo)	**N.S.** 0.015 /0.03
				HAM-D score at endpoint (compared to placebo)	**N.S.** 0.03/0.06
Mulholland et al., 2003 [36]	Sertraline (till 100 mg/day)	Yes	N=26	BDI score reduction (compared to placebo)	**N.S**. 0.1/0.2
				HAM-D score reduction (compared to placebo)	**N.S.** 0.24/0.5
				BPRS score reduction (compared to placebo)	**N.S**. 0.37/0.8
				BPRS Depression Item score reduction (compared to placebo)	**N.S.** 0.37/0.79
				BPRS Anxiety Depression Factor score reduction (compared to placebo)	0.55/1.3
				SANS score reduction (compared to placebo)	**N.S.** 0.12/0.25
Vartiainen et al., 1995 [40]	Citalopram (20-60 mg/day)	Yes	N=15	SOAS scores at endpoint (compared to placebo)	**N.S.** 0.10/0.21
				BPRS scores at endpoint (compared to placebo)	**N.S.** 0.23/0.47
				SDAS scores at endpoint (compared to placebo)	**N.S.** 0.3/0.63
				GAS scores at endpoint (compared to placebo)	**N.S.** 0.25/0.51
				CGI-S scores at endpoint (compared to placebo)	**N.S.** 0.1/0.2
Salokangas et al., 1996 [41]	Citalopram (till 40 mg/day)	Yes	N=90	PANSS score reduction (compared to placebo)	**N.S.** 0.1/0.2
Kasckow et al., 2001 [43]	Citalopram (20-40 mg/day)	No	N=19	HAM-D score reduction (compared to placebo)	0.76/2.33
				CGI-S score reduction (compared to placebo)	0.6/1.51
				PANSS score reduction (compared to placebo)	**N.S.** 0.48/1.1
Friedman et al., 2005 [44]	Citalopram (40 mg/day)	Yes	N=19	PANSS positive score reduction (compared to placebo)	**N.S.** 0.18/0.36

				PANSS negative score reduction (compared to placebo)	**N.S.** 0.11/0.23
				PANSS general score reduction (compared to placebo)	**N.S.** 0.21/0.43
Haukka et al., 2008 [45]	Citalopram	No	N=1611	Rate of suicides in citalopram users (compared to non-antidepressant users)	0.20/0.42
Hinkelmann et al., 2013 [46]	Citalopram (30 mg/day)	Yes	N=51	PANSS negative score reduction (compared to placebo)	**N.S.** 0.1/0.21
				HAM-D score reduction (compared to placebo)	**N.S.** 0.14/0.28
Usall et al., 2014 [47]	Citalopram (30 mg/day)	Yes	N=90	PANSS negative score reduction (compared to placebo)	**N.S.** 0.09/0.19
				SANS score reduction (compared to placebo)	**N.S.** 0.06/0.13
Iancu et al., 2010 [48]	Escitalopram (20 mg/day)	Yes	N=40	PANSS score reduction (compared to placebo)	**N.S.** 0.19 /0.39
				PANSS negative score reduction (compared to placebo)	**N.S.** 0.18/0.36
				SANS score reduction (compared to placebo)	**N.S.** 0.19 /0.39
				SFS score change (compared to placebo)	**N.S.** 0.14/0.29
				HAM-D score reduction (compared to placebo)	**N.S.** 0.09 /0.18
Stryjer et al., 2013 [49]	Escitalopram (20 mg/day)	No	N=15	YBOCS score reduction (compared to baseline)	0.33/0.7
Silver et al., 1992 [52]	Fluvoxamine (50-100 mg/day)	Yes	N=30	SANS score reduction (compared to placebo)	0.40/0.86
Silver et al., 1996 [59]	Fluvoxamine (25-100 mg/day)	No	N=8	BPRS scores at endpoint (compared to baseline)	0.36/0.78
				BPRS positive scores at endpoint (compared to baseline)	**N.S.** 0.02 /0.04
				BPRS negative scores at endpoint (compared to baseline)	0.39/0.85
				SANS scores at endpoint (compared to baseline)	**N.S.** 0.23 /0.47
Silver and Shmugliakov, 1998 [61]	Fluvoxamine (100 mg/day)	Yes	N=25	SANS score reduction (compared to maprotiline)	0.21/0.42
				BPRS negative score reduction (compared to maprotiline)	0.25/0.51
				MADRS	**N.S.** 0.21/0.42

Reznik and Sirota, 2000 [63]	Fluvoxamine (100-200 mg/day)	Yes	N=30	YBOCS score reduction (compared to placebo)	0.39/0.85
				PANSS negative score reduction (compared to placebo)	**N.S.** 0.18/0.36
				CGI-I change (compared to placebo)	**N.S.** 0.18/0.36
Reznik and Sirota, 2000 [64]	Fluvoxamine (100-200 mg/day)	No	N=16	YBOCS score reduction (compared to baseline)	0.59/1.45
				BPRS negative score reduction (compared to baseline)	0.64/1.67
Silver et al., 2000 [65]	Fluvoxamine (50-100 mg/day)	Yes	N=52	SANS score reduction (compared to placebo)	0.14/0.28
Hiemke et al., 2002 [67]	Fluvoxamine (100 mg/day)	No	N=8	CDSS score reduction (compared to baseline)	**N.S.** 0.44/0.98
Lu et al., 2002 [69]	Fluvoxamine (50-100 mg/day)	No	N=12	CGI-S score reduction (compared to baseline)	0.65/1.71
				GAF change (compared to baseline)	0.71/2.01
Takahashi et al., 2002 [68]	Fluvoxamine (100 mg/day)	No	N=30	PANSS positive score reduction (compared to baseline)	**N.S.** 0.12/0.24
				PANSS negative score reduction (compared to baseline)	**N.S.** 0.14/0.29
				PANSS general score reduction (compared to baseline)	**N.S.** 0.13/0.26
Yasui-Furukori et al., 2004 [70]	Fluvoxamine (till 150 mg/day)	No	N=12	BPRS positive score reduction (compared to baseline)	**N.S.** <0.01/0.01
				BPRS negative score reduction (compared to baseline)	0.5/1.16
Chaichan, 2004 [72]	Fluvoxamine 50 mg/day	No	N=20	BPRS total score reduction (compared to placebo)	0.37/0.79
				BPRS positive score reduction (compared to placebo)	0.26/0.54
				BPRS negative score reduction (compared to placebo)	**N.S.** 0.045/0.09
Niitsu et al., 2012 [76]	Fluvoxamine (150 mg/day)	Yes	N=48	PANSS score reduction (compared to placebo)	**N.S.** 0.27/0.55
				SANS score reduction (compared to placebo)	**N.S.** 0.07/0.15
				MADRS score reduction (compared to placebo)	**N.S.** 0.15/0.31
Jockers-Scherübl et al., 2005 [82]	Paroxetine (30 mg/day)	Yes	N=25	PANSS negative score reduction (compared to placebo)	0.44/0.97
				HAM-D score reduction (compared to placebo)	**N.S.** 0.035/0.07

Saito et al., 2005 [81]	Paroxetine (till 40 mg/day)	No	N=12	PANSS negative score reduction (compared to baseline)	0.62/1.56
				PANSS depression score reduction (compared to baseline)	**N.S.** 0.15/0.3
				CDSS score reduction (compared to baseline)	**N.S.** 0.33/0.7
Nemoto et al., 2012 [84]	Paroxetine (20 mg/day)	No	N=14	CGI-S score reduction (compared to baseline)	**N.S.** 0.17/0.35

Legend

BDI: The Beck Depression Inventory

BPRS: Brief Psychiatric Rating Scale

CDSS: Calgary Depression Scale for Schizophrenia

CGI-I: Clinical Global Impression (improvement)

CGI-S: Clinical Global Impression (severity of illness)

GAF: Global Assessment of Functioning

GAS: Global Assessment Scale

HAM-D: Hamilton Depression Rating Scale

MADRS: Montgomery-Asberg Depression Rating Scale

NSS: Negative Symptom Scale

PANSS: Positive and Negative Syndrome Scale

SANS: Scale for the Assessment of Negative Symptoms

SDAS: The Social Dysfunction and Aggression Scale

SFS: Social Functioning Scale

SKA: Schizoaffective

SOAS: The Staff Observation Aggression Scale

YBOCS: Yale Brown Obsessive Compulsive Scale

N.S.: not significant

Note: Case reports or studies for which it was impossible to calculate the effect sizes were not included

Table 2. Evaluation of quality of included studies

Studies	Molecule	Quality
Goldman and Janecek, 1990 [16]	Fluoxetine	0
Goff et al., 1990 [17]	Fluoxetine	0
Spina et al., 1994 [21]	Fluoxetine	++
Bacher et al., 1994 [22]	Fluoxetine	0
Goff et al., 1995 [23]	Fluoxetine	+
Buchanan et al., 1996 [24]	Fluoxetine	++
Arango et al., 2000 [25]	Fluoxetine	++
Agarwal and Agarwal, 2000 [26]	Fluoxetine	0
Shim et al., 2003 [27]	Fluoxetine	+
Thakore et al., 1996 [30]	Sertraline	0
Kirli and Caliskan, 1998 [33]	Sertraline	+
Lee et al., 1998 [34]	Sertraline	++
Addington et al., 2002 [35]	Sertraline	++
Mulholland et al., 2003 [36]	Sertraline	++
Vartiainen et al., 1995 [40]	Citalopram	+
Salokangas et al., 1996 [41]	Citalopram	++
Taiminen et al., 1997 [42]	Citalopram	+
Kasckow et al., 2001 [43]	Citalopram	+
Friedman et al., 2005 [44]	Citalopram	+
Haukka et al., 2008 [45]	Citalopram	+
Hinkelmann et al., 2013 [46]	Citalopram	+
Usall et al., 2014 [47]	Citalopram	++
Iancu et al., 2010 [48]	Escitalopram	++
Stryjer et al., 2013 [49]	Escitalopram	0
Silver et al., 1992 [52]	Fluvoxamine	++
Silver et al., 1996 [59]	Fluvoxamine	+
Szegedi et al., 1999 [60]	Fluvoxamine	+
Silver and Shmugliakov, 1998 [61]	Fluvoxamine	++
Poyurovsky et al., 1999 [62]	Fluvoxamine	+
Reznik and Sirota, 2000 [63]	Fluvoxamine	++

Reznik and Sirota, 2000 [64]	Fluvoxamine	+
Silver et al., 2000 [65]	Fluvoxamine	++
Hiemke et al., 2002 [67]	Fluvoxamine	+
Lu et al., 2002 [69]	Fluvoxamine	0
Takahashi et al., 2002 [68]	Fluvoxamine	+
Yasui-Furukori et al., 2004 [70]	Fluvoxamine	0
Chaichan, 2004 [72]	Fluvoxamine	0
Niitsu et al., 2012 [76]	Fluvoxamine	++
Jockers-Scherübl et al., 2001 [80]	Paroxetine	+
Jockers-Scherübl et al., 2005 [82]	Paroxetine	++
Saito et al., 2005 [81]	Paroxetine	+
Rusconi et al., 2009 [83]	Paroxetine	+
Nemoto et al., 2012 [84]	Paroxetine	0

Legend for quality of studies

Each + corresponds with one of these criteria:

1) Sample size > 100

2) Double-blinded design

3) Administration of specific rating scales to assess schizophrenia symptoms in relation to primary study outcomes (The Calgary Depression Scale for Schizophrenia, The Positive and Negative Syndrome Scale, The Scale for the Assessment of Negative Symptoms)

0: none of the above criteria

Note:

Case reports have not been reported in the present table

Table 3. Summary of results and appropriateness of assessment about the use of SSRIs for depressive symptoms in schizophrenia

Studies	Molecule	CDSS use	Improvement of depressive symptoms
Goff et al., 1990 [17]	Fluoxetine	No	Yes
Spina et al., 1994 [21]	Fluoxetine	No	Yes
Bacher et al., 1994 [22]	Fluoxetine	No	No
Goff et al., 1995 [23]	Fluoxetine	No	No
Buchanan et al., 1996 [24]	Fluoxetine	No	No
Arango et al., 2000 [25]	Fluoxetine	No	No
Kirli and Caliskan, 1998 [33]	Sertraline	No	Yes
Addington et al., 2002 [35]	Sertraline	Yes	No
Mulholland et al., 2003 [36]	Sertraline	No	No
Taiminen et al., 1997 [42]	Citalopram	No	Yes (depression/anxiety dimension of PANSS), No (HAM-D scores)
Kasckow et al., 2001 [43]	Citalopram	No	Yes
Hinkelmann et al., 2013 [46]	Citalopram	No	No
Iancu et al., 2010 [48]	Escitalopram	No	No
Silver and Shmugliakov, 1998 [61]	Fluvoxamine	No	No
Hiemke et al., 2002 [67]	Fluvoxamine	Yes	No
Niitsu et al., 2012 [76]	Fluvoxamine	No	No
Jockers-Scherübl et al., 2001 [80]	Paroxetine	No	Yes
Jockers-Scherübl et al., 2005 [82]	Paroxetine	No	No
Saito et al., 2005 [81]	Paroxetine	Yes	No

Legend

CDSS: The Calgary Depression Scale for Schizophrenia

PANSS: The Positive and negative Syndrome Scale

HAM-D: Hamilton Depression Rating Scale

Note: Case reports have not been reported

Table 4. Summary of the effects of SSRIs in schizophrenia according to psychopathological dimensions

Psychopathological dimension	Compound	Positive Results	Negative Results
Negative	Fluoxetine	1 open-label study (N=14) and 2 double-blind studies (N=71)	2 double-blind studies (N=60)
	Sertraline	1 open-label study (N=20)	2 double-blind studies (N=62)
	Citalopram	No studies	3 double-blind studies (N=160)
	Escitalopram	No studies	1 double blind study (N=40)
	Fluvoxamine	5 open-label studies (N=62) and 3 double-blind studies (N=107)	3 open-label studies (N=58) and 2 double-blind studies (N=78)
	Paroxetine	2 open-label studies (N=20) and 1 double-blind study (N=25)	Fluvoxamine > Paroxetine in 1 open-label study (N=50)
Cognitive	Fluoxetine	No studies	No studies
	Sertraline	No studies	No studies
	Citalopram	No studies	1 double-blind study (N=19)
	Escitalopram	No studies	No studies
	Fluvoxamine	No studies	1 double-blind study (N=48)
	Paroxetine	No studies	No studies
Depressive	Fluoxetine	2 open-label studies (N=44)	1 open label study (N=13) and 3 double-blind studies (N=101)
	Sertraline	1 double-blind study (N=40)	2 double-blind studies (N=74)
	Citalopram	1 single-blind study (N=19)	1 open-label study (N=51)
	Escitalopram	No studies	1 double-blind study (N=40)
	Fluvoxamine	No studies	1 open-label study (N=8) and 2 double-blind studies (N=73)
	Paroxetine	1 open-label study (N=8)	1 open-label study (N=12) and 1 double-blind study (N=25)
Impulsive-Aggressive	Fluoxetine	1 open-label (N=8)	No studies
	Sertraline	No studies	No studies
	Citalopram	1 cohort study (N=1611)	1 double-blind study (N=15)
	Escitalopram	No studies	No studies
	Fluvoxamine	No studies	No studies
	Paroxetine	No studies	No studies
Obsessive-Compulsive	Fluoxetine	1 open-label study (N=7)	1 double-blind study (N=33)
	Sertraline	No studies	No studies
	Citalopram	No studies	No studies

	Escitalopram	1 open-label study	No studies
	Fluvoxamine	2 open-label studies (N=26) and 1 double-blind study (n=30)	No studies
	Paroxetine	No studies	No studies

Note: The sum of sample sizes of studies are reported into brackets. Case reports have not been reported

Figure 1. Prisma Diagram for systematic reviews