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Fluvoxamine as an Adjunctive Agent in Schizophrenia

Henry Silver[1]

Sha'ar Menashe Mental Health Center,
Rappaport Faculty of Medicine, Technion, Haifa, Israel

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ABSTRACT

Schizophrenia is a common mental disorder that has an early onset and rates high as a cause of medical disability. Antipsychotic agents are the mainstay of treatment but response is often inadequate. Negative symptoms (disturbances in volition, social interaction and affective functions) are particularly difficult to treat and form a major obstacle to rehabilitation. A promising approach to improve response of negative symptoms has been to add a selective serotonin reuptake inhibitor (SSRI) antidepressant to antipsychotic treatment. This review examines evidence pertaining to the efficacy, tolerability, and safety of the SSRI fluvoxamine, combined with antipsychotic agents, in the treatment of negative symptoms in schizophrenia. Important methodological issues, such as differentiating primary and secondary negative symptoms, are discussed. The balance of available evidence indicates that fluvoxamine can improve primary negative symptoms in chronic schizophrenia patients treated with typical antipsychotics and suggests that it may also do so in some patients treated with clozapine. This combination is generally safe and well tolerated although, as antipsychotic drug concentrations may be elevated, attention to dose and drug monitoring should be considered appropriately. Combination with clozapine may require particular caution because of potential toxicity if serum clozapine levels rise steeply. The fluvoxamine doses effective in augmentation are lower than those usually used to treat depression. Evidence regarding the use of fluvoxamine augmentation to treat phenomena, such as obsessions and aggression, which may be associated with schizo-

Address correspondence and reprint requests to: Dr. Henry Silver, Deputy Director, Sha'ar Menashe MHC, Mobile Post Hefer 38814, Israel.
Tel: +972 (4) 627-8160. Fax: +972 (4) 627-8004. E-mail: mdsilver@tx.technion.ac.il.

[1] Dr. Silver is Deputy Director of the Shaar Menashe Mental Health Center and Senior Lecturer in the Faculty of Medicine, Technion, Haifa and has no ties with either manufacturer or distributor of fluvoxamine. One of the studies reviewed (ref. 155) was supported in part by an investigator-initiated grant from Solvay Pharmaceuticals, The Netherlands.

phrenia, is also examined. An important goal of future studies will be to define which patient groups can benefit from combined treatment.

INTRODUCTION

Schizophrenia is a complex disorder with an incidence of 1%. It has an early onset and ranks fifth as a cause of medical disability in developed countries. Antipsychotic agents are the mainstay of treatment but response is inadequate in some 20 to 30% of patients. Negative symptoms (disturbances in volition, social interaction, and affective functions) are particularly difficult to treat and form a major obstacle to rehabilitation. One approach to improve response of negative symptoms has been to add adjuvant medication to antipsychotic treatment [reviewed by Evins and Goff (61) and Siris (169)]; some of the SSRI antidepressants have shown promising results.

This review will critically examine evidence pertaining to the efficacy and safety of fluvoxamine combined with antipsychotic agents in the treatment of negative symptoms in schizophrenia. In addition, potential uses of fluvoxamine in some other syndromes that can be associated with the schizophrenic process will also be touched upon.

BASIC PHARMACOLOGY

The pharmacologic properties of fluvoxamine have been previously reviewed (22,85,136). Fluvoxamine is a potent and selective inhibitor of serotonin reuptake *in vitro.* The selectivity of fluvoxamine for blocking the uptake of serotonin is markedly higher than that of norepinephrine or dopamine (22,97,150). It has low affinity for serotonergic, noradrenergic, dopaminergic, and most other neurotransmitter receptors *in vitro* (22) with the exception of s1 receptors (129), the clinical significance of which is unclear (113).

Fluvoxamine is almost completely (>90%) absorbed from the gastrointestinal tract after oral dose (52,187). Maximum plasma concentrations are reached within 2 to 8 h of ingestion and are not affected by concomitant intake of food (136) or route of administration (189). The drug is extensively and rapidly metabolized in the liver; its bioavailability after first pass is reduced to 53% (189). It is excreted in the urine almost completely in the changed form (48). The drug is widely distributed throughout the body (V_d = 25 L/kg) (189). It accumulates in the brain more than fluoxetine and takes three times longer to reach steady state there than in plasma (182). Plasma protein binding is low (77%) and below that of fluoxetine (94%), paroxetine (95%), and sertraline (98%) (42,96). Fluvoxamine displays nonlinear pharmacokinetics, which becomes most prominent at doses in excess of 50 mg/day (54,80,87,177). This may result in steady state not being reached before 10 days of treatment with fluvoxamine (87). This is likely to be due to multiple parallel metabolic pathways (87).

The pharmacokinetics of fluvoxamine does not depend on age (54), although its clearance may be decreased in the elderly (29) suggesting that slow titration may be indicated in this group. The pharmacokinetics of fluvoxamine are not affected by renal

function but they are affected by liver impairment with an increase of 50% in AUC and $t_{1/2}$ in patients with cirrhosis (188). Women may develop higher blood levels than men at oral doses less than 200 mg, perhaps because of a saturable enzyme that is more active in males (87).

The main route of elimination is by hepatic metabolism including oxidative desmethylation and oxidative deamination (135). Eleven metabolites have been detected; all are pharmacologically inactive (41). Studies in healthy volunteers attempting to identify the CYP enzymes involved in the hepatic metabolism of fluvoxamine have identified significant effects of CYP2D6 and CYP1A2 (32,176), although due to methodological limitations this may not reflect the clinical situation (87).

There is no evidence of a relationship between blood concentration and clinical response and no therapeutic window has been demonstrated (104,194). There is no evidence that high doses have clinical benefits (55), and in a fixed-dose study of depressed patients treated with 100 mg/day of fluvoxamine, Hartter et al. (81) found all responders had serum levels below 85 ng/mL. Side effects may correlate more directly with serum concentrations (104). Unlike fluoxetine and paroxetine, fluvoxamine is a weak inhibitor of CYP2D6, and no dosage adjustment is necessary when combined with substrates of this isoenzyme (52). However, it interacts potently with the CYP1A2 isoenzyme.

CYP1A2 is important for bioactivation of procarcinogens, such as heterocyclic arylamine food mutagens (71), raising the possibility that fluvoxamine has a protective function (154).

It is also involved in metabolism of many drugs including caffeine (101,146,175) clozapine (13,51,56,83,88,107,119,132,198), propranolol (22), tacrine (21,22), tertiary amine tricyclic antidepressants (TCAs) (44,153,180,191,199), theophylline (53,147,186), and warfarin (85). Since it also inhibits CYP2C19 (100,102) and moderately inhibits CYP3A4 (69,193), it may impair metabolism of alprazolam(69), diazepam (139), and methadone (5,25). No significant interaction has been found with lithium (123), digoxin (131), or alcohol (188).

FLUVOXAMINE AND SCHIZOPHRENIA

General Introduction

The effect of fluvoxamine in schizophrenia has been studied in patients with chronic illness. Typically, treatment with fluvoxamine was initiated after antipsychotic treatment alone failed to produce sufficient improvement. The studies were usually short-term, ranging over weeks.

Negative Symptoms

The negative syndrome of schizophrenia

The earliest descriptions of schizophrenia noted that many patients suffered from social withdrawal, emotional blunting, and disturbances in initiative and volition. These phenomena were considered by Kraepelin and Bleuler to be fundamental to the illness. More

recently, this group of clinical phenomena, now termed negative symptoms, has been the subject of intensive research (10,45). Factor analytic studies have consistently shown that three dimensions best describe schizophrenic symptoms: a negative factor (including anhedonia, avolition, affective blunting, and alogia), a disorganization factor (including thought disorder), and a distortion factor (including delusions and hallucinations). Negative symptoms are a core feature of the illness and tend to remain stable over time in patients with established illness (14). They are often already present at the onset of illness and have been found to persist despite treatment (59,137).

Measuring negative symptoms

Study of negative symptoms is complicated by a lack of agreement as to which symptoms should be included in the negative syndrome and by difficulties in measuring absence rather than presence of phenomena (174). Scales commonly used to rate negative symptoms include the Scale for the Assessment of Negative Symptoms (SANS) (9), Positive and Negative Syndrome Scale (PANSS) (105), the withdrawal scale derived from the Brief Psychiatric Rating Scale (BPRS) (134), and the Scale for Deficit Syndrome (106). Less commonly used are the Negative Symptom Rating Scale (98) and the Negative Symptom Assessment (6). They generally have good inter-rater reliability (6,7,11,105, 106) and identify similar patients as having negative and deficit syndromes (46,185). Despite differences in the number and nature of individual items, correlation between total scores of the different scales is high (63). Yet the scale used can significantly influence the identification of a "case" of negative syndrome (59) and may show different sensitivity to change (163).

Primary vs. Secondary Symptoms

A particular problem in studying negative symptoms is the difficulty in distinguishing between those that are primary to the illness and those secondary to other causes. Major sources of confusion are depressive symptoms, extrapyramidal side effects (EPS) of medication, social withdrawal due to positive symptoms, demoralization due to chronic illness, and understimulation due to poor environmental influences (33). Studies of negative symptoms must take steps to exclude such confounding factors and incorporate appropriate measures for their control (125,126,170). Such measures include selecting the study population for presence of negative symptoms, excluding subjects with prominent positive or depressive symptoms, and reducing EPS by reducing antipsychotic dose, using antiparkinsonian drugs to minimize EPS (128), and perhaps using an anticholinergic challenge to test for EPS (61). Comprehensive and reliable scales should be included to assess the impact of confounding variables and used in final analysis of data. The most important element is the correct methodological design as even sophisticated statistical methodology, such as path analysis, may be insufficient to differentiate between response of primary and secondary negative symptoms (148).

Studies of Add-On Fluvoxamine for Treatment of Negative Symptoms

Controlled studies

Three double-blind, randomized, controlled studies totaling 108 patients have examined the effect of adding fluvoxamine to typical antipsychotics on negative symptoms.

The subjects studied were chronically ill, hospitalized patients suffering from chronic schizophrenia with prominent negative symptoms despite extensive antipsychotic treatment. These and other studies are reviewed and summarized in Table 1.

In the first study, Silver and Nassar (164) examined 30 chronic schizophrenic (DSM-III) inpatients selected for the presence of negative symptoms (SANS global item score ≥3) and few positive symptoms. Patients were on stable doses of typical antipsychotics (mean dose = 474 mg/day chlorpromazine equivalents) for at least 4 weeks prior to the study. Patients with prominent depressive or positive symptoms were excluded. Extrapyramidal symptoms were minimized by adjustment of anticholinergic medication 2 weeks previously and then given in a stable dose. Baseline depressive symptoms [Hamilton Depressive Rating Scale (HAM–D) (77), mean score = 7.7], positive symptoms [the Scale for the Assessment of Positive Symptoms (SAPS) (8), mean score = 1.7], and EPS [Rating Scale for Extrapyramidal Side Effects (SA) (168) mean score = 3.6] were low. Fluvoxamine, (50 mg/day in the first week and 100 mg/day in the second and subsequent weeks) or placebo were added to the treatment in a randomized double-blind manner. The dose was continued for 4 weeks, reduced to 50 mg/day for 1 week and then ceased. Weekly assessments were done using SANS, SAPS, HAM-D, and SA scales. Significant improvement in total SANS scores was noted in the fluvoxamine group compared with placebo after 5 weeks and was maintained at 7 weeks. Among the negative symptoms, alogia first showed significant improvement after 3 weeks of treatment, affective blunting after 5 weeks and anhedonia after 7 weeks. Depressive and extrapyramidal and positive symptoms were low and did not change in either group.

A second randomized, double-blind study (166) compared fluvoxamine with maprotiline, an antidepressant that inhibits norepinephrine uptake but has little action on the serotonergic system. The subjects were 25 inpatients suffering from chronic schizophrenia (DSM-III-R) with prominent negative symptoms (SANS global score of at least moderate). The patients had been ill for long periods (mean = 13 years; 53 months of current hospitalization) and were receiving typical antipsychotics (mean dose = 502 mg/day chlorpromazine equivalents), the dose having been unchanged for at least 4 weeks prior to the study. Fluvoxamine or maprotiline (50 mg/day in the first week and 100 mg/day in the second and subsequent weeks) was added to the regular (typical) antipsychotic treatment for 6 weeks. Patients were assessed using the BPRS, SANS, SAPS, the Montgomery–Asberg Depression Rating Scale (MADRS) (127), and SA scales. Baseline depressive symptom (MADRS mean score = 9.6), positive symptom (SAPS mean score = 5.1), and EPS (SA mean score = 1.0) levels were low. Negative symptoms, as measured by SANS total score and BPRS negative factor, improved significantly in the fluvoxamine but not the maprotiline group. Improvement was noted in affective blunting, alogia, avolition, and anhedonia. Using ≥20% improvement as criterion, responder rates in the fluvoxamine group were 46.2% on the affective blunting factor of the SANS and 38.5% in the SANS total score compared with none in the maprotiline group. No change was found in MADRS scores, positive symptoms, or EPS in either treatment group.

The third study (155) examined the efficacy and safety of adding fluvoxamine to antipsychotic treatment in schizophrenia patients with mixed positive and negative symptoms. Subjects were inpatients suffering from chronic schizophrenia (DSM-III-R). Inclusion criteria included a history of at least 2 years of illness, a current hospitalization of at least 2 months and at least moderate scores (≥3) on the global items on both the SANS and the

TABLE 1. Studies of add-on fluvoxamine in patients with chronic schizophrenia

Authors	Study type	Number of patients	Clinical features	Fluvoxamine compared to:	Antipsychotic agent	Results	Reference No.
Silver et al., 2000	Controlled, double-blind	53	NS and PS	Placebo	typical	NS improved, not other symptoms, no exacerbation of PS	155
Silver and Nassar, 1992	Controlled, double-blind	30	NS, low PS	Placebo	typical	NS improved, not others	164
Silver and Shmugliakov, 1998	Controlled, double-blind	25	NS, low PS	Maprotiline	typical	NS improved with fluvoxamine not with maprotiline	166
Silver et al., 1995b	Open, naturalistic	19	Mixed symptoms	NA	typical	NS improved and other symptoms improved	160
Silver et al., 1995a	Case report	2	NS	NA	typical	NS improved	158
Lammers et al., 1999	Open	18	Mixed symptoms	NA	clozapine	Improvement in cognitive speed and BPRS scores	110
Szegedi et al., 1999	Open	16	Mixed symptoms	NA	clozapine	Improvement in psychopathology	183
Silver et al., 1996	Open	11	NS	NA	clozapine	NS improved	162
Silver et al., 1995c	Case report	1	NS	NA	clozapine	NS improved	159
Szegedi et al., 1995	Case report	1	Mixed symptoms	NA	clozapine	NS improved	184
Reznik and Sirota, 2000	Controlled, open	30	OC symptoms	Antipsychotic alone	typical and atypical	Improvement in both groups, greater improvement in OC symptoms in fluvoxamine group	149
Poyurovsky et al., 1999	Open	10	OC symptoms	NA	typical and atypical	Improvement in OC, PS, NS	145
Poyurovsky et al., 1996	Case report	4	OC symptoms	NA	typical	Improvement in OC and other symptoms	144
Silver and Kushnir, 1998	Case report	1	aggression	NA	typical	Improvement in aggression and clinical state	161

NS, Negative symptoms; PS, positive symptoms; NA, not applicable; OC, obsessive-compulsive.

SAPS scales after not less than 2 months of continuous treatment with typical antipsychotics. Patients meeting DSM-III-R criteria for depression or those with a history of organic brain damage or alcohol or drug abuse were excluded from the study. Subjects were randomly allocated to add-on fluvoxamine (50–100 mg/day) or placebo in a double-blind manner. The duration of the study was 6 weeks. Assessment included SANS, SAPS, BPRS, and SA scales. Depressive symptoms were assessed with depressive measures derived from BPRS (BPRS-DEP consisting of the mean of three items: depressed mood, guilt and anxiety). Baseline levels of depressive symptoms (BPRS-EP mean score = 1.0) and EPS (SA mean score = 5.6) were low. Baseline SANS (mean = 72) and SAPS (mean = 45) scores were high. Fifty-three patients started and 46 patients completed 6 weeks of treatment. Fluvoxamine treatment was associated with significant improvement in negative symptoms (SANS total) compared with placebo. Positive, depressive, and extrapyramidal symptoms did not change significantly during treatment.

Case Reports and Open Studies

In addition to a case description (158), Silver et al. (160) reported an open naturalistic study of 19 severely disabled treatment resistant inpatients. The subjects suffered from chronic schizophrenia (DSM-III-R), were severely or extremely severely ill (score ≥6 on the Clinical Global Impression [CGI] of Severity scale) and had very low levels of function (Global Assessment of Function [GAF] < 30). They were treated with various typical antipsychotics and the dose was constant for at least 4 weeks prior to the study. Fluvoxamine was added to the ongoing treatment and the dose was adjusted on clinical grounds. Maximum doses ranged from 25 to 200 mg/day. Assessment included BPRS, SANS, and CGI scales, and the follow-up period ranged from 1.8 to 7.5 months. In 6 patients the degree of clinical disturbance was such that only CGI assessments could be reliably determined. Fourteen patients (74%) showed improvement using a criterion of ≥15% change in SANS score or CGI improvement of one or more points.

Atypical Antipsychotics

To date no controlled studies have examined the effect of add-on fluvoxamine in patients treated with atypical antipsychotics. Available evidence relies on case reports and open studies. These typically studied small numbers of subjects and were not designed specifically to study negative symptoms. Silver et al. (159) and Szegedi et al. (184) published case reports presenting favorable results of adding fluvoxamine. Silver et al. (162) studied 11 inpatients suffering from chronic schizophrenia (DSM-III-R). Patients were chosen if they had persistent negative symptoms (SANS global item score of ≥3) after at least 4 months of continuous clozapine treatment (clozapine dose range = 300 to 750 mg; mean treatment period = 1.4 years). Fluvoxamine (dose range = 25 to100 mg/day, mean dose = 50 mg/day) was added to clozapine treatment. Assessments included CGI, BPRS, and SANS scales. Eight patients completed the 6-week study period; 3 patients dropped out after the third week of treatment. Comparison of pre- and post-treatment values in the 8 completers showed significant improvement in affective blunting and avolition factors of the SANS, BPRS negative factor and BPRS total scores. Analysis of variance (ANOVA) in all 11 patients using the last observation carried forward (LOCF) approach

showed significant improvement in affective blunting and anhedonia factors of the SANS. Depressive symptoms (depressive item of the BPRS) did not change with treatment.

Lammers et al. (110) studied 18 psychotic patients in an open protocol. Fluvoxamine 50 mg/day was given throughout the study period, while the clozapine dosage was increased individually reaching a mean of 96.9 ± 37.2 mg in the fifth week. Significant improvement was found in cognitive speed and BPRS scores. Five patients were considered treatment responders (BPRS reduction > 50%). Ten patients continued combination treatment after the study period and 9 of these patients were in clinical remission when discharged.

Szegedi et al. (183) added fluvoxamine 50 mg/day to clozapine in 16 schizophrenic patients and found improvement in psychopathology. In all patients, the serum concentrations of clozapine and metabolites were markedly increased (average: 2- to 3-fold, up to 5-fold for clozapine) after addition of fluvoxamine. Side effects remained almost unchanged in frequency and severity, despite pharmacokinetic interactions, and electrocardiogram (ECG) or laboratory parameters and orthostatic tests were unchanged.

In summary, the current evidence indicates that fluvoxamine produces amelioration in negative symptoms in chronic patients treated with typical antipsychotics and suggests that it may also be of benefit in patients on atypical drugs, although to date only combination with clozapine has been studied.

The doses of fluvoxamine found effective in controlled studies ranged from 50 to 100 mg/day and improvement with doses as low as 25 mg/day was reported in some patients (160). Response to fluvoxamine 50 mg/day did not differ from that to 100 mg/day (155). However, these doses were not directly compared but administered at different phases of the study. Definitive studies to determine the minimum effective dose of fluvoxamine for the treatment of negative symptoms remain to be done.

Is the Effect of Fluvoxamine on Primary Negative Symptoms?

As mentioned, a critical question is whether the fluvoxamine-related improvement involves primary features of the illness or secondary negative symptoms. Since depressive symptoms respond better than negative symptoms to antidepressants (171), distinguishing between them is especially important when antidepressants are tested for putative anti-negative symptom activity. Phenomenologically, depressive symptoms, such as reduced expression of emotions and responsiveness to emotional stimuli, psychomotor retardation, lack of initiative, and social withdrawal are similar to negative symptoms. Depressive symptoms are not uncommon in schizophrenic patients including those without a diagnosis of depressive disorder (202), and may be difficult to distinguish from primary negative symptoms (109). However, the distinction can usually be made (108,109,141,171) and may be less problematic in chronic than in acute patients (17,19,90). In acute illness, depressive symptoms are more common (3) yet even in patients with a first psychotic episode negative symptoms are mainly primary in character (137).

The scales used to assess depression in schizophrenia (e.g., HAM-D and MADRS) were developed for affective illness or are extracted from measures of schizophrenic pathology (e.g., depressive factor of the BPRS or PANSS) and may overlap with positive and negative symptoms. The Calgary Depression Rating Scale (CDRS) (4) was developed to measure depressive symptoms in schizophrenia and may be less limited in this regard (1,43). Assessing how well a study succeeded in differentiating between depressive and

negative symptoms is made more complicated by use of different depressive scales. However, comparisons in schizophrenia patients have shown high correlation between depressive scales, including BPRS-derived depression factor and HAM-D (130), CDRS and HAM-D (2), and the depression subscale of the PANSS (PANSS-D) (43), as well as the CDRS and HAM-D and Beck depressive inventory (1). Consequently, low scores on a depressive scales can be taken to indicate low levels of depressive symptoms, but high scores may indicate contamination between negative and depressive symptoms.

In the controlled studies reviewed here (155,164,166), depressive scale scores were low at the onset (HAM-D average score = 7.7 (166); MADRS score = 12.1 and 7.2 in the fluvoxamine and placebo groups, respectively (164); BPRS-derived depression factor score = 1 (155)) and did not change with treatment, indicating that depressive symptoms were not significant confounding factors. Furthermore, since maprotiline, an equally effective antidepressant, did not improve negative symptoms (166), the action of fluvoxamine on negative symptoms appears distinct from "nonspecific" antidepressant action and related to its serotonergic mechanism. A second potential source of confusion is differentiating negative symptoms from EPS, which can be associated with reduced emotional expressiveness, initiative, spontaneity, motivation, and movements. Akinesia induced by antipsychotic treatment can improve with antiparkinsonian treatment or with reduction of the antipsychotic dose (82,103,118,190). In the studies described here, measures of EPS were low and did not change during treatment, indicating that these too were not significant confounds.

Patients with positive symptoms, such as paranoid or persecutory delusions, can become socially withdrawn and isolated (33), and improvement in these positive symptoms can result in better social functioning and mimic improvement in negative symptoms. Negative symptoms can improve in parallel with positive symptoms in acute schizophrenia and it has been recommended that trials of pharmacological treatment of negative symptoms not be performed during the acute phase of the illness (126). Patients participating in the controlled studies mentioned were chronically ill and included those with no or few positive symptoms (164), as well as those with high levels of positive symptoms (155). Improvement in negative symptoms was found in all groups and occurred in the absence of change in positive symptoms, indicating that the effect of fluvoxamine on negative symptoms was not secondary to a change in positive symptoms and independent of their presence.

From this discussion it can be concluded that fluvoxamine-induced change was in primary negative symptoms.

Is the Effect of Fluvoxamine on Negative Symptoms Unique or Is It a Class Effect?

Effects of other SSRIs

The question of whether fluvoxamine differs from other SSRIs in its effect on negative symptoms remains to be tested directly. Currently, it is possible to compare only separate studies with limitations arising from methodological differences. A review of the studies examining the effect of SSRIs on negative symptoms has been published (61); here only controlled studies will be reviewed.

Six controlled studies examined the effect of SSRIs, other than fluvoxamine, in schizophrenia. Three studies (12,70,179) compared the effect of add-on fluoxetine and placebo in patients treated with typical antipsychotics; two showed significant effect and one showed no improvement. One study (30) examined the effect of adding fluoxetine to clozapine and found no improvement. Individual studies reported no effect of adding citalopram (152), or sertraline (111) to typical antipsychotics.

Spina et al. (179) added fluoxetine (20 mg/day) or placebo to conventional neuroleptics in 34 chronic schizophrenia inpatients over 12 weeks. Positive symptoms were low at baseline and patients with HAM-D scores > 20 were excluded. Extrapyramidal symptoms were measured with the SA scale, but results are not reported. Negative symptoms (SANS) were improved in the fluoxetine but not in the placebo group. Depressive symptoms (HAM-D) improved in fluoxetine but not in placebo-treated patients. Fluoxetine treatment did not influence positive symptoms.

Goff et al. (70) added fluoxetine 20 mg/day or placebo to 41 schizophrenia outpatients on stable depot neuroleptic treatment after a 2-week, placebo lead-in period. Patients with DSM-III-R depression were excluded and EPS were measured using the SA. Controlling for baseline scores, negative symptoms (measured with negative symptoms subscale of the BPRS) were significantly lower at week 6 in patients receiving fluoxetine ($n = 20$) compared with patients receiving placebo ($n = 21$). Measures of psychosis (BPRS psychotic symptoms), depression (HAM-D), general psychopathology (BPRS total), and EPS (SA) did not differ between groups. The improvement in negative symptoms increased steadily over the treatment period suggesting to the authors that more clinical improvement may have been achieved with longer treatment. Fluoxetine administration was associated with an increase in serum fluphenazine (mean = 65%; $n = 15$) and haloperidol concentrations (mean = 20%; $n = 3$).

Arango (12) studied 32 outpatients with schizophrenia (DSM-II or DSM-III-R) treated with typical antipsychotics (stable dose at least 1 month). Entry criteria included minimum positive (BPRS positive score ≥8) and negative (SANS score ≥20 or a score ≥2 on at least one global item) symptom levels. After a 2-week evaluation phase, add-on fluoxetine (mean dose = 36.2 mg; range 20 to 80 mg) was compared with placebo for 8 weeks. No significant change was noted in any of the clinical measures in either group. Blood concentrations of antipsychotics increased in the fluoxetine group by an average of 48%.

Buchanan et al. (30) added fluoxetine (mean maximum dose = 48.9 mg/day) or placebo in 33 schizophrenic outpatients who, despite adequate treatment with clozapine (mean dose = 457 mg/day), continued to exhibit persistent positive (BPRS positive symptoms score ≥8) or negative symptoms (SANS score ≥20 or a score ≥2 on one or more global item). They found no significant improvement in positive, negative, depressive, or obsessive-compulsive symptoms after 8 weeks of treatment.

Salokangas et al. (152) compared citalopram (40 mg/day) and placebo added to typical neuroleptics in 90 chronic schizophrenia (DSM-III-R) outpatients with PANSS scores higher than 50. A significant decrease in total PANSS was found in both groups after 12 weeks but there were no significant differences between them. The authors were under the impression that citalopram appeared to increase the subjective well being of patients. There were no significant differences in the occurrence of side effects in either group. Neuroleptic plasma levels were not altered after addition of citalopram.

Lee et al. (111) compared sertraline (50 mg/day; $n = 18$) or placebo, added to haloperidol treatment, for 8 weeks in 36 inpatients with chronic schizophrenia and found no significant change in positive, negative, or general psychopathology factors of the PANSS or CGI Scale. No significant side effects were noted. Sertraline addition did not alter plasma haloperidol or reduced haloperidol.

In conclusion, the available evidence suggests that fluoxetine can ameliorate negative symptoms and that this effect is not unique to fluvoxamine. The question of relative efficacy of drugs and whether this is also characteristic of all SSRIs awaits direct comparisons.

Fluvoxamine in Other Syndromes Associated with Schizophrenia

Obsessional symptoms in schizophrenia

Clinicians have noted the coexistence of obsessive-compulsive (OC) symptoms and schizophrenia since early descriptions of the illness (28). Recent research suggests that clinically significant OC symptomatology may be present in some 30–50% of patients with schizophrenia (23,27). Reported rates of diagnosable obsessive-compulsive disorder (OCD) in schizophrenia range from 8 (60) to 30% (24). The presence of obsessional symptoms in schizophrenia may be linked to poorer social and vocational function (62), earlier onset of illness, and greater utilization of health services (23).

Fluvoxamine for obsessional symptoms

The use of fluvoxamine in obsessive disorders has been reviewed extensively (34,67, 68,75,136). Most placebo-controlled studies (72,73,76) reported a response rate of 38 to 52% (0 to 18% for placebo) with one study (138) reporting a much higher value (81 vs. 19% for placebo) with fluvoxamine treatment in the range of 100 to 300 mg/day over 6 to 10 weeks. Obsessive-compulsive symptoms occur in a variety of psychiatric disorders, which may comprise an OC spectrum (91). Fluvoxamine has been investigated in the treatment of a number of spectrum disorders including eating disorders (16,65,66,95), pathological gambling (93,94), dysmorphic disorder (92,140), autistic disorder (120), trichotillomania (181), compulsive buying (26), and kleptomania (39,57). However, reports consist of case descriptions or open studies involving small numbers of patients with treatment periods limited to less than 12 weeks. No controlled studies in obsessive spectrum disorders have been reported.

Fluvoxamine for obsessional symptoms in schizophrenia

No double-blind, controlled studies examining the effect of fluvoxamine on obsessional symptoms in schizophrenia have been reported to date, and evidence is limited to case reports and a limited number of open trials with small numbers of subjects.

Poyurovsky et al. (144) described improvement in 2 out of 4 schizophrenia (DSM-III-R) patients, who developed OC symptoms during the course of clozapine treatment, approximately 4 to 5 weeks after addition of fluvoxamine (250 mg). Other schizophrenia symptoms also improved. Subsequently, the same group (145) reported improvement in the obsessions (but not compulsions) subscale of the Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) (74) in 10 stable chronic schizophrenia patients with OC symptoms after fluvoxamine (up to 150 mg/day) was added to treatment with typical or

atypical antipsychotics for 12 weeks. Improvement was noted also in positive and negative symptoms.

Reznik and Sirota (149) studied 30 inpatients treated with conventional neuroleptics who met DSM-IV criteria for schizophrenia and had prominent OC symptoms. Fourteen patients treated with fluvoxamine 100 to 200 mg/day for 8 weeks were compared with 16 patients who continued their previous neuroleptic therapy in an open-label design. The neuroleptic/fluvoxamine group showed greater reduction in Y-BOCS total scores and compulsions, pathological slowness and Pathological Doubtness subscales, than those treated with neuroleptics alone. Improvement in PANSS, Y-BOCS, and CGI scores was noted in both groups.

In conclusion, there is suggestive evidence from open-label studies that fluvoxamine improves obsessional symptoms in some schizophrenia patients. Controlled studies remain to be done. Since OC symptoms improved in unison with other schizophrenia symptoms, the specificity of the effect for OC symptoms remains to be determined.

Aggression

Aggression and impulse control impairments have been linked to serotonergic abnormalities in humans (133) and animal models (35). Investigations of the relationship between aggression and serotonergic abnormalities in schizophrenia patients have shown mixed results. Modai et al. (124) compared [^{3}H]paroxetine binding in blood platelets in 11 aggressive, 15 nonaggressive schizophrenia patients, 15 presently nonaggressive schizophrenic patients with homicidal history, and 15 healthy volunteers and found an association between current aggression among schizophrenia patients and high B_{max} values of [^{3}H]paroxetine binding in blood platelets. The authors concluded that this reflected state rather than trait aggression. However, Maguire et al. (117) found no relationship between aggressive behavior and peripheral serotonin function as measured by [^{3}H]paroxetine binding to platelet membranes in 40 aggressive and nonaggressive schizophrenia patients. Pindolol, a 5-HT_{1A} antagonist, has been reported to reduce violence in aggressive schizophrenia patients when added to antipsychotic treatment (36).

Fluvoxamine has been reported to improve aggression in subjects with autism (120), so there is ground for thinking that it may be useful in aggressive schizophrenia patients. However, to date no study, apart from a case report (161), has examined the effect of fluvoxamine on aggression in schizophrenia. Vartiainen et al. (192) reported a reduction of aggressive incidents during citalopram treatment in double-blind, cross-over study comparing citalopram (20 to 60 mg/day) and placebo, added to neuroleptic medication, in chronically violent schizophrenia inpatients over a 24-week treatment period.

Side Effects of Fluvoxamine in Combination Therapy

Fluvoxamine given alone is generally well tolerated. In a large series of postmarketing data. Wagner et al. (195) reported on tolerability in 34,587 predominantly depressed patients in 66 (usually uncontrolled) studies of fluvoxamine (dosage range = 50 to 300 mg/day; modal dose = 100 mg/day) and found more than one adverse event in about 40% of patients. Nausea was found to be the only common symptom, with an incidence rate of 16%. Approximately 2% of the fluvoxamine population reported at least one serious adverse event (per FDA criteria). Safety findings revealed a pharmacological adverse event profile similar to that seen with other serotonin reuptake inhibitors.

Similarly, prescription-event monitoring of 10,401 patients treated with fluvoxamine for up to 6 months found that gastrointestinal events were the most common (nausea was the only event reported in >10% of the subjects). Central nervous system adverse events reported included headache, dizziness, insomnia, and drowsiness/sedation with an incidence <3% (58). Adverse events associated with fluvoxamine administration are usually transient and mild to moderate in severity. Serious adverse events were reported in <3% of patients (195) and reported discontinuation rates due to adverse events ranged from 14.4 to 27.8% (58,195). Patients starting on fluvoxamine may experience an increase in anxiety and excitation agitation. This has been reported in some 1.5% of patients and has led to the recommendation to start with a low dose and gradually increase it over time (142). Serotonergic syndrome (resulting from excessive serotonergic activity) has been reported in 2 cases (18,112).

Data gathered in the course of controlled studies of fluvoxamine combined with typical antipsychotics have shown that the combination was well tolerated (155,164,166) and was not associated with more EPS or psychotic exacerbations than placebo, despite increases in blood levels of fluvoxamine. This is similar to studies of fluoxetine and other SSRIs combined with typical antipsychotics (12,70,11,152,178). Exacerbations of positive symptoms have been described in case reports (158) and noted during the course of open studies (143,158), but the unstable nature of the illness makes attribution of exacerbations to treatment difficult in such instances. A controlled study in patients with high levels of positive symptoms found no difference in exacerbations between fluvoxamine- and placebo-treated patients (166). Worsening of positive symptoms (increase in SAPS scores of >20% from baseline) was found in 13% of patients in the fluvoxamine group and 26.1% of patients in the placebo group. Likewise 8.7% of the fluvoxamine and 17.4% of the placebo group showed a worsening of >20% in BPRS total scores at the end of the study.

Fluvoxamine and clozapine

Tolerability data regarding combination with fluvoxamine and atypical antipsychotics is less robust than for typical antipsychotics and relies on small open studies and case reports. The combination of fluvoxamine and clozapine may present a greater risk of side effects because changes in blood concentrations of clozapine can be very large (see below). Several open studies (89,116,162,198) reported that the combination of fluvoxamine and clozapine was well tolerated despite elevations in blood concentrations of clozapine. Chong et al. have reported cases of adverse interactions with clozapine (40). Studies examining fluoxetine added to atypical antipsychotics reported that the combination was well tolerated (30,110). A single case of a fatal outcome in a patient treated with a combination of fluoxetine and clozapine has been reported (64).

Drug-Drug Interactions

Consistent with its action in inhibiting cytochrome enzymes, fluvoxamine can increase blood levels of typical antipsychotics (47). The steady-state serum concentrations of clozapine can be increased by a factor of up to 5 to10 (38,110,116,198). Fluvoxamine can also increase blood levels of olanzapine (31). Somewhat surprisingly, such rises are not usually accompanied by increased side effects (89,110,183,198), a finding also described in fluoxetine augmentation (30,37,178). Nonetheless, precautionary drug monitoring may

be advisable (183), particularly with clozapine where the risk of toxic (>1000 ng/mL) concentration may be 10-fold greater (25%) in combined treatment (37).

Mechanism of Action

The mechanism by which fluvoxamine ameliorates negative symptoms is unknown. Pharmacokinetic explanations are unlikely. Increases in blood concentrations of antipsychotics do not improve negative symptoms and may worsen them. There are as yet no studies relating antipsychotic blood levels and negative symptom response in patients treated with add-on fluvoxamine, so a pharmacokinetic explanation cannot be excluded for this combination. However, no correlation was found between clinical response and increased levels of typical antipsychotics following add-on fluoxetine (15,70).

Pharmacokinetic interaction may be useful in rapid metabolizers of clozapine who need high doses to reach therapeutic blood levels and consequently suffer marked side effects, such as sedation or hypersalivation. Adding fluvoxamine can reduce the dose of clozapine needed to reach therapeutic levels and, therefore, lessen side effects (116).

A possible pharmacodynamic mechanism is that fluvoxamine acts to increase dopamine levels in the prefrontal cortex (PFC). Negative symptoms are associated with dopaminergic hypoactivity in the PFC (84,196,197). Microanalysis studies have shown that haloperidol, which is not effective against negative symptoms, does not increase dopamine levels in PFC (115) and reduces dopamine turnover in the prefrontal cortex (PFC) of rats (86). In contrast, atypical antipsychotics, such as clozapine and olanzapine, which may improve negative symptoms, increase extracellular fluid dopamine levels in the medial prefrontal cortex of rats (115,151). This feature has been related to an ability of clozapine to stimulate the electrophysiological activity of the dopaminergic cell bodies in the ventral tegmental area (121). Since dopaminergic and serotonergic systems interact in the PFC and endogenous 5-HT can enhance dopamine release in the nigrostriatal pathway (200), it is possible that, when added to typical antipsychotics, fluvoxamine increases dopamine levels in the PFC, producing a pharmacological picture resembling that of atypical antipsychotics. A similar mechanism may explain the effect of fluvoxamine in patients who exhibit negative symptoms, despite treatment with atypical antipsychotics, as the increased extracellular fluid dopamine levels in the medial prefrontal cortex of rats found after acute clozapine administration (115) tend to fall on sustained (chronic) treatment (99). Fluoxetine has been shown to increase dopamine levels in the PFC of rats administered olanzapine (201).

Several studies examined potential biological markers of the treatment response to fluvoxamine augmentation but have not yielded definitive results. A reduction in platelet monoamine oxidase (MAO) activity was reported after 5 weeks of fluvoxamine augmentation treatment (165) and, as this paralleled the course of clinical improvement, raised the possibility that fluvoxamine may act by modifying MAO activity. However, chronic (up to 6 weeks) administration of fluvoxamine to rats showed no reduction in MAO-A and MAO-B activities in the brain regions examined (167). The effect of fluvoxamine augmentation on the secretion of melatonin, a pineal hormone closely linked to serotonin and known to be influenced by antidepressant drugs, was also examined. Morning melatonin levels increased after fluvoxamine (50 to 150 mg) was added to typical antipsychotics in 11 chronic schizophrenia patients. It peaked at 3 to 5 weeks and returned to baseline levels after 8 weeks (156). A subsequent overnight study showed that this reflected amplitude re-

duction and phase shift of the melatonin secretion curve (157). This may indicate the development of tolerance in the processes underlying melatonin secretion and may be relevant to the therapeutic action of fluvoxamine. Potential mechanisms may involve serotonergic-adrenergic interactions affecting the sensitivity of the β-adrenoceptors (49), desensitization of 5-HT_{1A} receptors (50,114), or alteration of intracellular serotonin availability and increase density of α_2-adrenoceptors (49). Fluvoxamine inhibits melatonin hydroxylation to 6-hydroxymelatonin and O-demethylation to N-acetyl serotonin *in vitro* (79). It can also affect metabolism of melatonin *in vivo* (173) and increase its bioavailability (78) after acute administration, but the relevance of this to long-term dynamic changes remains to be determined.

Some of the findings from combined treatment raise questions concerning the mechanism of action of atypical antipsychotic drugs. Current views consider serotonergic antagonism to be a key element in determining the advantageous clinical (including negative symptoms) and EPS profile of clozapine and other atypical antipsychotics compared with typical antipsychotics (122). The paradoxical finding that combining serotonergic agonists such as fluvoxamine or fluoxetine with clozapine, a serotonergic antagonist, does not diminish the effect of clozapine and indeed may be beneficial, raises the central role of 5-HT antagonism into question and demands further investigation.

CONCLUDING REMARKS

The available evidence (Table 1) indicates that fluvoxamine can improve primary negative symptoms in chronic schizophrenia patients treated with typical antipsychotics and suggests that it may also do so in patients treated with atypical antipsychotics (so far only published for clozapine). The combination is generally safe and well tolerated although, as antipsychotic drug concentrations may be elevated, attention to dose and drug monitoring should be considered appropriately. Combination with clozapine may require particular caution because of potential toxicity if serum clozapine levels rise steeply. The fluvoxamine doses effective in augmentation are lower than those usually used to treat depression.

To date fluvoxamine augmentation has been studied in chronically ill and severely impaired patients. An important goal of future studies will be to define which patient groups may benefit from fluvoxamine treatment. In particular, the efficacy and tolerability in patients with more acute illness requires further study.

There is evidence suggesting that fluvoxamine augmentation may be useful in obsessional symptoms associated with schizophrenia and indications that further study in other schizophrenia-associated syndromes, such as aggression, may bear fruit.

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