Add-on Fluvoxamine Improves Primary Negative Symptoms: Evidence for Specificity From Response Analysis of Individual Symptoms

by Henry Silver, Nelson Aharon, and Alla Kaplan

Abstract

Establishing that treatment for negative symptoms improves primary features of schizophrenia rather than similar symptoms of other etiology is an important clinical issue. Primary negative symptoms may also differ among themselves in the propensity to respond to a given treatment. In this study, we examined the response of negative symptoms to add-on fluvoxamine by analyzing discrete symptoms independently and controlling for potential confounding variables. Data from two published controlled studies comparing fluvoxamine to placebo were pooled for the analysis. Eleven of sixteen Scale for the Assessment of Negative Symptoms items tested, including key negative symptoms such as affective flattening and alogia, improved. The improvement was not related to baseline levels of depressive, extrapyramidal, and positive symptoms or to changes in the symptom scores during the study. The findings support the view that fluvoxamine augmentation can improve primary negative symptoms in chronic schizophrenia patients.

Keywords: Side effects, SSRI, fluvoxamine, negative symptoms, response analysis, schizophrenia, augmentation treatment.


The poor response of negative symptoms of schizophrenia to current treatments underlines the need for more effective agents. Recently, several controlled trials found that adding the selective serotonin reuptake inhibitors (SSRIs) fluvoxamine (Silver and Nassar 1992; Silver and Shumiglakov 1998; Silver et al. 2000; Silver 2001) and fluoxetine (Spina et al. 1993, 1994, 1998; Goff et al. 1995) to antipsychotic treatment can improve negative symptoms, suggesting a potential new treatment direction. Establishing that such treatments are specific for primary negative symptoms and not a result of changes in similar (secondary) phenomena with other causes, in particular depressive, extrapyramidal, and positive symptoms, requires particular attention. Furthermore, negative symptoms may differ in their propensity to respond to a given treatment. Total scores of scales such as the Scale for the Assessment of Negative Symptoms (SANS) or global assessments show redundancy (Czobor et al. 1991; Welham et al. 1999) when used to assess negative symptoms and may not detect differential symptom changes. Studying response at the level of individual negative symptoms can overcome this limitation and identify the profile of responding and nonresponding symptoms.

Here we report the results of a symptom response analysis using data from 2 independent studies to achieve the statistical power needed. The studies (Silver and Nassar 1992; Silver et al. 2000) examined the effect of add-on fluvoxamine on negative symptoms in medicated patients with stable chronic schizophrenia and controlled for potential confounding variables.

We hypothesized that fluvoxamine-related improvement would be observed in negative symptoms identified in the literature as primary and would be independent of depressive, extrapyramidal, and positive symptoms.

Methods

The two studies, fully described elsewhere (Silver and Nassar 1992 [study 1]; Silver et al. 2000 [study 2]), used similar inclusion criteria and treatment protocols. Participants were inpatients suffering from chronic schizophrenia (DSM-III-R) with scores of at least moderate on one of the global ratings of affective flattening, alogia, or avolition on the SANS (Andreasen 1984) after long-term, stable treatment with typical antipsychotics (mean dose in chlorpromazine equivalents 1194, standard deviation [SD] 990 mg). Participants included 38 male and 45 female patients with mean age 42.2 (SD 10.3) years who had been ill for 19.2 (SD 9.7) years. Significant clinical depression, organic brain damage, and history of alcohol or drug abuse

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or acute exacerbation of symptoms were exclusion criteria. To reduce possible contamination from secondary symptoms, the entry criteria also required that levels of depressive and extrapyramidal symptoms be low. This was reflected in low scores on scales of depressive (study 1: Hamilton Depressive Rating Scale, mean score 7.7; study 2: Montgomery-Asperg Depression Scale, mean score 9.6) and extrapyramidal (Simpson-Angus Rating Scale for Extrapyramidal Side Effects [SA] [Simpson and Angus 1970]: study 1, mean 3.6; study 2, mean 1.0) symptoms at baseline. The enduring nature of the negative symptoms was not formally assessed with "deficit" criteria (Strauss et al. 1974; Carpenter et al. 1988) at entry, but examination of case notes and consultation with staff and family members who had known the patients for long periods confirmed that negative symptoms were long-standing and persistent. The studies differed on the requirement for concomitant presence of positive symptoms; in study 1, patients with prominent positive symptoms were excluded, while in study 2 a score of at least moderate on a global scale of the Schedule for the Assessment of Positive Symptoms (SAPS) (Andreasen 1983) was required. This was reflected in the mean baseline SAPS scores (study 1: fluvoxamine 2.3 [SD 4.5], placebo 1.1 [SD 0.9]; study 2: fluvoxamine 51.9 [SD 21.03], placebo 39.17 [SD 16.57]). Fluvoxamine (50 mg, n = 24, or 100 mg/day, n = 59) or placebo was added, in a double-blind manner, to ongoing antipsychotic treatment, which was kept constant.

Clinical state was assessed weekly using the SANS, the SAPS, the SA, and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962). Depressive symptoms were assessed with the Hamilton Depression Scale (HAM-D; Hamilton 1960) in study 1 and the BPRS depressive factor in study 2. For this study we used the depressive measure derived from the BPRS (BPRS-Dep) consisting of the mean of three items: depressed mood, guilt, and anxiety. The BPRS-Dep shows good correlation with the HAM-D in schizophrenia patients (Welham et al. 1999).

All participants provided written informed consent after receiving a clear explanation of the study procedures, and the studies were approved by the local ethics committee.

Statistics. The endpoint measures were SANS item scores after 6 weeks of treatment. In some cases, the endpoint data were missing, and the last-observation-carried-forward method was used provided that patients had completed at least 3 weeks of treatment. Treatment effect was tested using analysis of covariance (ANCOVA) with endpoint score as the dependent variable, treatment condition (fluvoxamine/placebo) as the independent variable, and baseline depressive (BPRS-Dep), extrapyramidal (SA), and positive (SAPS) symptom scores as covariates. The items inappropriate affect and blocking, the global assessment items, and the attention subsection of the SANS, all of which differ from the other negative symptoms (Andreasen et al. 1995), were excluded.

Changes in the scores (Δ) were calculated by subtracting endpoint from baseline values for each scale. Correlations analyses utilized Pearson's r. Two tailed significance was used throughout. Analyses utilized the SPSS for Windows version 10 program (SPSS Inc 2000).

Results

Table 1 shows SANS item scores before and after treatment and the results of ANCOVA analysis with positive, depressive, and extrapyramidal symptoms as covariates. Eleven symptoms showed significant improvement: decreased spontaneous movement, paucity of gestures, poverty of speech, increased latency of response, grooming/hygiene, poverty of amount of speech, physical anergia, recreational interests, facial expression, lack of vocal inflections, and intimacy. Five items did not respond: poor eye contact, affective nonresponsiveness, impersistence at work, sexual activity, and relating with friends.

To exclude a possible error due to multiple comparisons, a reanalysis using a Bonferroni correction was performed. After this correction (table 1), six items showed significant treatment-related improvement: decreased spontaneous movement, paucity of gestures, poverty of speech, grooming/hygiene, poverty of amount of speech, and physical anergia.

Next we examined whether change in the confound variables could explain improvement in negative symptoms by performing an ANCOVA analysis using the endpoint SANS item score as the dependent variable and adding change in depressive, extrapyramidal, and positive symptoms scores as covariates. The results were the same as for the analysis using baseline values as covariates except for 4 items. The affective nonresponsiveness item, which did not reach significance in the previous analysis, showed significant improvement (F = 6.11, p ≤ 0.02) when changes in confounding symptoms were the covariates. The items poor eye contact (F = 3.43, p = 0.07), increased latency of response (F = 3.38, p = 0.07), and relating with friends (F = 3.22, p = 0.07) showed a reduction in significance of the treatment effect to borderline levels when changes in confounding variables were covariates.

We also examined whether negative symptoms improved in patients with no depressive symptoms by using ANCOVA with SANS item score as the dependent variable and the baseline scores and SAPS and SA scores as covariates in a subgroup of patients with baseline BPRS-Dep = 0 (n = 36). The results were similar to those...
### Table 1. Response of individual SANS items to fluvoxamine treatment

<table>
<thead>
<tr>
<th>Items</th>
<th>Fluvoxamine Baseline</th>
<th>Fluvoxamine Posttreatment</th>
<th>Placebo Baseline</th>
<th>Placebo Posttreatment</th>
<th>ANCOVA</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Facial expression</td>
<td>3.3</td>
<td>1.0</td>
<td>2.5</td>
<td>1.2</td>
<td>2.40</td>
<td>0.7</td>
</tr>
<tr>
<td>Decreased spontaneous movement</td>
<td>2.4</td>
<td>1.2</td>
<td>1.4</td>
<td>1.5</td>
<td>41.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Paucity of gestures</td>
<td>2.6</td>
<td>1.3</td>
<td>2.0</td>
<td>1.3</td>
<td>23.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Poor eye contact</td>
<td>2.4</td>
<td>1.5</td>
<td>1.2</td>
<td>1.3</td>
<td>51.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Affective nonresponsiveness</td>
<td>3.0</td>
<td>1.1</td>
<td>2.5</td>
<td>1.4</td>
<td>16.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Lack of vocal inflections</td>
<td>3.0</td>
<td>1.0</td>
<td>2.3</td>
<td>1.2</td>
<td>23.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Poverty of speech</td>
<td>2.4</td>
<td>1.5</td>
<td>1.1</td>
<td>1.4</td>
<td>53.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Poverty of amount of speech</td>
<td>3.0</td>
<td>1.1</td>
<td>2.1</td>
<td>1.6</td>
<td>30.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Increased latency of response</td>
<td>1.2</td>
<td>1.2</td>
<td>0.7</td>
<td>1.0</td>
<td>43.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Grooming/hygiene</td>
<td>2.4</td>
<td>1.4</td>
<td>1.3</td>
<td>1.4</td>
<td>46.9</td>
<td>1.9</td>
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<tr>
<td>Impersistence at work</td>
<td>2.6</td>
<td>1.7</td>
<td>1.8</td>
<td>1.7</td>
<td>30.0</td>
<td>2.4</td>
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<tr>
<td>Physical anergia</td>
<td>2.2</td>
<td>1.6</td>
<td>1.7</td>
<td>1.6</td>
<td>22.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Recreational interests</td>
<td>3.6</td>
<td>0.9</td>
<td>3.0</td>
<td>1.5</td>
<td>16.7</td>
<td>3.3</td>
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<tr>
<td>Sexual activity</td>
<td>3.9</td>
<td>1.1</td>
<td>3.7</td>
<td>1.2</td>
<td>4.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Intimacy</td>
<td>3.6</td>
<td>0.8</td>
<td>3.4</td>
<td>0.9</td>
<td>5.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Relating with friends</td>
<td>3.6</td>
<td>0.7</td>
<td>3.4</td>
<td>0.9</td>
<td>6.3</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Note.—ANCOVA = analysis of covariance; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation.

1 Fluvoxamine baseline n = 45, end n = 38, all dropouts before 3 weeks of treatment; placebo baseline n = 38, end n = 37, only dropout was after > 3 weeks of treatment, n = 38.

2 Mean of improvement in individual participants (slight difference from percentage of improvement in mean values).
in the whole study population, with significant improvement \((p < 0.05)\) in the items decreased spontaneous movement, paucity of gestures, poor eye contact, affective non-responsiveness, lack of vocal inflections, poverty of speech, poverty of amount of speech, increased latency of response, and grooming/hygiene.

Positive (SAPS total) and extrapyramidal (SA total) scores showed no significant change with treatment (table 2). Depressive symptoms (BPRS-Dep) showed statistically significant improvement when all the patients were analyzed. However, the mean baseline scores were low, and an analysis of a subgroup of patients with at least mild levels of depressive symptoms at baseline (BPRS-Dep score > 1, \(n = 18\)) showed no significant improvement \((p > 0.38)\).

Change in negative symptoms \((\Delta \text{SANS})\) showed no significant correlation with change in depressive \((\Delta \text{BPRS-Dep})\), \(r = 0.2, p = 0.2\), fluvoxamine group; \(r = 0.3, p = 0.6\), placebo group) or positive \((\Delta \text{SAPS}, r = 0.05, p = 0.77\), fluvoxamine group; \(r = 0.24, p = 0.17\), placebo group) symptoms.

To examine possible confound from combining two studies, ANCOVA using the SANS endpoint score as the dependent variable, treatment as an independent variable, and study number (study 1/study 2) as a second independent variable and baseline SANS score as covariant was performed. No significant treatment by study number interaction \((df = 1,70; F = 1.73; p = 0.19)\) was found.

**Discussion**

Fluvoxamine treatment was associated with improvement in 11 of the 16 SANS items examined after the effects of the major confounds extrapyramidal, depressive, and positive symptoms were controlled. The responding items included unchanging facial expressions, a component of the affective flattening category, and poverty of speech and poverty of content of speech, components of alogia. Affective flattening and alogia are universally agreed to be key negative symptoms and appear in all negative symptom scales (Fenton and McGlashan 1992). They are independent of medication status (Kelley et al. 1999) and persist for many years (Herbener and Harrow 2001).

The responding symptoms came from the affective flattening, alogia, anhedonia, and avolition subgroups of the SANS, so this classification did not predict differential response. Likewise, the response pattern did not resemble the various factors identified in factor analytic studies that demonstrated heterogeneous structures of the negative dimension (Strauss et al. 1974; Mueser et al. 1994; Toomey et al. 1997; Peralta et al. 2000; but see Andreasen et al. 1995).

Indeed, we could identify no characteristic that clearly distinguished between responding and nonre-
sponding symptoms, but there was some indication that symptom complexity may be important. Some SANS items measure simple, directly observable behaviors such as motor responses, changes in facial expression, or body movements, while others assess complex interactive behaviors such as interpersonal relationships or work performance as reported by the patient and others. Most of the symptoms in the former group improved, but only two (recreational interests and intimacy) of the latter did so. This may reflect multiple etiologies of complex behaviors, difficulties in assessment, or slower response to treatment. Further study is needed to determine whether such a distinction is useful.

The demonstration that negative symptom improvement was independent of both baseline levels and of change in depressive, extrapyramidal, and positive symptoms supported our hypothesis that the change was in primary features of the illness. Our findings thus provide evidence that fluvoxamine improves primary symptoms both by excluding effects of the major confounding variables and by showing that key symptoms such as affective flattening and alogia improved. It cannot be excluded, however, that some factors not readily detected by our instruments contributed to the findings.

Furthermore, because of the selective nature of the study population, caution is required in generalizing our findings to other schizophrenia patients, particularly when drug side effects and depressive symptoms are prominent. The effect of longer treatment periods, which may differentially affect symptoms, also needs further investigation. Future studies should consider potential differences in symptom response patterns to distinct agents as significant variables. To study this issue, assessment tools with suitable levels of resolution to detect such differences should be used.

References


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