Augmentation of Olanzapine by Fluphenazine Decanoate in Poorly Responsive Schizophrenia

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Abstract

Introduction: Evidence suggests that atypical antipsychotics affect a broader range of schizophrenic psychopathology and are generally better tolerated than conventional antipsychotics. Therefore, they have become the most commonly used class of antipsychotic drugs in clinical practice. But poor compliance and resistance is noteworthy even among those receiving atypical drugs. The objective of this study was to examine whether there could be any encouraging outcome if fluphenazine decanoate was added, as an adjuvant, to olanzapine in poorly responsive cases of schizophrenia. **Method:** Twenty-eight female inpatients with a diagnosis of schizophrenia, according to the Structured Clinical Interview for DSM Disorders' diagnostic criteria, who had shown poor response to olanzapine, were entered into a twelve-week, parallel group, double-blind study for random assignment to either fluphenazine decanoate or placebo in a 1:1 ratio. Primary outcome measures of the study were changes in the mean total scores of the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS). The secondary measures were the Schedule for Assessment of Insight (SAI), the Clinical Global Impressions-Severity of Illness (CGI-S) and the Simpson-Angus Scale (SAS). Treatment efficacy was analyzed by t-test, split-plot (mixed) and repeated measures analysis of variance (ANOVA) comparing both groups over twelve weeks. All secondary measures (SAS, SAI, and CGI-S) were analyzed by t-test. **Results:** According to the findings, the mean total scores of SAPS ($P<0.01$), SAI ($P<0.0001$) and CGI-S ($P<0.03$) in the "fluphenazine plus olanzapine" group were decreased significantly in comparison with the "placebo plus olanzapine group." In spite of an increase in mean total score of SANS in the target group, there was no significant difference in this regard at the study's conclusion ($P<0.09$). The mean total score of SAS was also increased significantly in the augmented group ($P<0.0001$). Effect size (ES) analyses for changes in SAPS, SAI and CGI-S at the end of treatment indicated a large improvement with the fluphenazine augmentation. **Conclusions:** Adding fluphenazine decanoate to olanzapine may improve some cases of poorly responsive schizophrenia. However, it is essential that consideration be given to the emergence of extrapyramidal side effects and the strengthening of negative symptoms due to fluphenazine, and the probable pharmacokinetic interaction between the two drugs.

Key Words: Olanzapine, Fluphenazine Decanoate, Poorly Responsive Schizophrenia

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Introduction

First-generation antipsychotic medications have shown the capacity to restrain the acute psychotic symptoms of schizophrenia and related psychotic disorders and prevent their recurrence (1, 2). In addition, antipsychotic drugs were associated with high rates of neurological side effects (i.e., extrapyramidal side effects and tardive dyskinesia) that could compromise the therapeutic effects of treatment and caused many patients to discontinue their use, thus increasing the risk for relapse (1, 2). Dolder et al. have recently

Clinical Implications

Adding fluphenazine decanoate to olanzapine may improve some cases of poorly responsive schizophrenia. However, it is essential that consideration be given to the emergence of extrapyramidal side effects and the strengthening of negative symptoms due to fluphenazine, and the probable pharmacokinetic interaction between the two drugs. Obvious study limitations suggest that our findings are only exploratory and in need of additional verification.

shown that medication compliance ("adherence") was better with atypical than typical antipsychotics in schizophrenic patients, but poor compliance was considerable even among those receiving the atypical drugs (3). Evidence suggests that atypical antipsychotics affect a broader range of schizophrenic psychopathology and are generally better tolerated than conventional antipsychotics. However, these claims have not been consistently confirmed by empirical data; thus, researchers and clinicians differ in their attitudes concerning the comparative effectiveness of first- and second-generation antipsychotics (SGAs) (4, 5). Despite the lack of consensus, atypical antipsychotic drugs have become the most commonly used class of antipsychotic drugs in clinical practice (4-9).

However, according to one study, conventional drugs were associated with nonsignificantly better outcomes and lower costs in comparison with atypical drugs (10). Also, according to another study, the one-year risk of readmission for patients treated with SGAs was at least comparable to the one-year risk for patients receiving fluphenazine decanoate (11, 12). It is important to note that compliance has generally been found to improve when patients are switched to depot agents (13, 14). According to a number of surveys, olanzapine may be helpful and well tolerated as well for a substantial number of neuroleptic-resistant schizophrenic patients (15-18). Although resistance against SGAs usually justifies resorting to older typical antipsychotics or clozapine (1, 2), there has been no methodical appraisal regarding the joint effects of atypical and conventional antipsychotics in poorly responsive schizophrenic patients to date. So, the objective of this study was to examine whether there could be any encouraging outcome if fluphenazine decanoate were added, as an adjuvant, to olanzapine in poorly responsive cases of schizophrenia.

Methods

Twenty-eight female inpatients with a diagnosis of schizophrenia, according to the Structured Clinical Interview for DSM Disorders' diagnostic criteria (code: 295.xx), who had shown poor response to olanzapine (less than 25% decrement in total SAPS score while it was no less than 70 at baseline, with maximum dose of 25 mg daily for at least four weeks as inclusion criteria) were entered into a twelve-week, parallel group, double-blind study for random assignment to extra fluphenazine decanoate or placebo in a 1:1 ratio. Since the field of research was restricted to the chronic female district of the psychiatric hospital, all of the samples were selected among chronic female schizophrenic patients. After a complete description of the study to the subjects, written informed consent was obtained from either the participant or a legal guardian or representative. In addition, the entire procedure was approved by the University's related ethical committee. The placebo had been arranged in the shape of comparable vials, like the target drug, containing distilled water to make patients blind with respect to the procedure. The evaluators, as well, were unaware concerning the partition and the type of medications arranged for each group. These cases, according to the above-mentioned criteria, were randomly entered in one of the two matching contemporaneous groups, alternately one patient after the other (one into the experiment group and the next into the control group, in sequence and back-to-back). After baseline assessments, the cases in the control group (N=14) were prescribed placebo while continuing their current antipsychotic up to the end of the trial (olanzapine, with dose range of 15–25 mg daily, that was fixed throughout the study, with an ultimate mean dose of 21.96±5.03). Alternatively, in the target group (N=14), fluphenazine decanoate was added to olanzapine (with the same dose range and a final mean dose of 22.38±4.97). It was prescribed in the beginning (week zero) at a dosage of 6.25 mg/2 weeks IM, and then individually increased by 6.25 mg increments, as needed or tolerated, in biweekly intervals, to a maximum of 25 mg/2 weeks by week eight. The dose established by week eight was held constant up to the end of the study (final mean dose of 17.42±6.07 mg/2 weeks). No other concurrent psychotropic medication or psychosocial intervention was allowed during the trial. Olanzapine adherence was assessed through close observation that was managed by a skilled staff to monitor the possibility of noncompliance.

Primary outcome measures of the study were changes in the mean total scores of the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS) for appraisal of the positive and negative symptoms of schizophrenia, respectively. The secondary measures included the Schedule for Assessment of

Table 1 Baseline Demographic and Disorder Characteristics of Participants in a Clinical Trial Comparing "Olanzapine+Placebo" with "Olanzapine+Fluphenazine Decanoate"

Variable	Olanzapine+placebo (N=14)	Olanzapine+fluphenazine decanoate (N=14)	X2	df	t	P value
Mean age, y	35.78±5.58	37.33±4.61		26	0.80	0.43
Mean age at onset, y	25.87±4.72	26.39±3.34		26	0.36	0.73
Mean duration of illness, y	6.73±2.12	7.68±2.76		26	1.02	0.31
No. of married patients	N=10	N=8	0.12	1		0.72
Mean dosage of olanzapine	21.96±5.03	22.38±4.97		26	0.22	0.82

Insight (SAI) and the Clinical Global Impressions-Severity of Illness (CGI-S) for further evaluation of clinical status; in addition, the Simpson-Angus Scale (SAS) was used to scan for drug-induced side effects. The estimations of SAPS and SANS were carried out at the start of the study at baseline, and after that at the fourth, eighth, and twelfth week. The secondary scales were scored only at the beginning and the end of the study.

Statistical Analysis

Patients were compared on baseline characteristics using chi-square tests for categorical variables and t-tests for continuous variables in order to assess the efficacy of the randomization procedure in ensuring homogeneity between the two treatment groups. The primary analysis was carried out according to the intention-to-treat, last observation carried forward (LOCF) approach. Treatment efficacy was analyzed by t-test, split-plot (mixed) and repeated measures analysis of variance (ANOVA) comparing both groups over twelve weeks with regard to SAPS and SANS. All secondary measures (SAS, SAI, and CGI-S) were analyzed by t-test. Cohen effect-size estimates were used when comparing baseline to endpoint changes in all of the scores. All tests of hypotheses were tested at a two-sided alpha level of 0.05. Power analysis was also calculated at the end of the trial.

Results

Intent-to-treat, last observation carried forward (LOCF) analysis for efficacy was based on data from an equal number of patients (N=14) in both groups, since there were no dropouts in either group throughout the assessment. Given that all of the patients were hospitalized throughout the study in the chronic district of the hospital, the absence of serious adverse effects in the patients, and, moreover, the short duration of trial, there was no premature discontinuation in either patient group. Groups were originally analogous with respect to comparable demographic and diagnostic variables, as well as the dosages of olanzapine (Table 1). According to the findings at the closing stages of the assessment, the mean total scores of SAPS, SAI and CGI-S in the fluphenazine group decreased significantly in comparison with the control group (Table 2). Decrement in mean total scores of SAPS was approximately 17.9% in the experiment group and 6.83% in the control group (P<0.01) (Table 2). In the intragroup analysis, as well, this decrement was significant in the augmented group (P<0.0001), while it was not significant for the control group (P<0.06) (Table 3). Repeated measures analysis of variance (ANOVA) showed significant change as regards the experiment group (F [3, 39]=34.0, P<0.000001, SS=2014.63, MSe=19.76) and nonsignificant change concerning the control group (F [3, 39]=5.05, P<0.06722, SS=46.67, MSe=22.88). Split-plot (mixed) design ANOVA also showed considerable divergence between the two groups (F [3, 52]=9.16, P<0.000057, SS=349.92, MSe=12.73).

Conversely, the mean total score of SANS was increased in the augmented group (2.56%) and decreased in the control group (5.9%), but this difference was not significant (P<0.09) (Table 2). In this regard, intragroup analysis, as well, showed no significant changes in the control group (P<0.07) and experiment group (P<0.49) (Table 3).

Interestingly, repeated measures analysis of variance (ANOVA) concerning the experiment and control groups showed nonsignificant changes during the study (F [3, 39]=0.437, P<0.728023, SS=46.17, MSe=35.25) and (F [3, 39]=1.50, P<0.230495, SS=93.94, MSe=20.92), respectively, and split-plot (mixed) design ANOVA also did not illustrate

Table 2 Between-Group Analysis of Primary and Secondary Outcome Measures throughout Study

Measure	Olanzapine+placebo (N=14)	Olanzapine+fluphenazine (N=14)	t	P	df	95% CI
SAPS Baseline	85.79±9.04	89.13±3.58	1.28	0.21	26	-2.00 to 8.68
SAPS-4th week	81.95±6.27	79.26±6.93	1.06	0.29	26	-7.80 to 2.46
SAPS-8th week	79.48±8.39	73.83±4.08	2.25	0.03	26	0.52 to 10.77
SAPS-12th week	79.93±6.57	73.17±7.32	2.57	0.01	26	1.35 to 12.16
SANS Baseline	66.93±7.48	63.47±8.16	1.17	0.25	26	-9.54 to 2.62
SANS-4th week	63.29±3.29	65.93±5.28	1.58	0.12	26	-0.77 to 6.05
SANS-8th week	62.71±3.31	65.12±3.81	1.78	0.08	26	-0.36 to 5.18
SANS-12th week	62.97±3.09	65.14±3.62	1.70	0.09	26	-0.44 to 4.78
SAI Baseline	3.03±1.17	3.27±0.89	0.61	0.54	26	-0.56 to 1.04
SAI-12th week	3.59±0.12	4.20±1.07	6.00	0.00	26	2.25 to 4.48
SAS Baseline	4.72±0.64	4.11±1.31	1.56	0.12	26	-1.41 to 0.19
SAS-12th week	4.76±1.07	13.39±2.54	11.71	0.00	26	7.11 to 10.14
CGI-S Baseline	4.13±1.02	4.16±0.39	0.10	0.91	26	-0.57 to 0.63
CGI-S-12th week	3.97±0.73	3.48±0.43	2.16	0.03	26	0.02 to 0.95

SAPS=Scale for Assessment of Positive Symptoms, SANS=Scale for Assessment of Negative Symptoms, SAI=Schedule for Assessment of Insight, SAS=Simpson-Angus Scale, CGI-S=Clinical Global Impressions-Severity of Illness

any considerable variation between them (F [3, 52]=1.76, P<0.166026, SS=126.35, MSe=23.91).

Furthermore, the mean total score of SAI also improved significantly in the augmented group, which was considerably better than its counterpart (P<0.00) (Table 2). In intragroup analysis, as well, this improvement was significant in the fluphenazine group (P<0.01) but not remarkable in the control group (P<0.08) (Table 3). The CGI-S also improved significantly in the target group in comparison with the control group (P<0.03) (Table 2). Intragroup analysis as well showed noteworthy enhancement in the augmented group (P<0.0001) and slight alteration in the control group (P<0.63) (Table 3). In contrast, the mean total score of SAS was significantly increased in the augmented group (P<0.0001) (Table 2). This increment was seen among 42.85% (N=6) of the patients in the augmented group, and in almost all of the SAS's subitems, especially with respect to gait, rigidity (elbow, wrist) and tremor.

Moreover, since the sample size was small, the effect size (ES) was analyzed for changes on SAPS, SAI and CGI-S at the end of treatment, which indicated a large ("d≥0.8"), readily observable improvement with fluphenazine decanoate augmentation (2.76 and 0.81; 0.94 and 0.42, and 1.65 and 0.63, as Cohen's d and effect-size correlation r, respectively) (Table 3). Although some insignificant changes in weight or metabolic indices were evident in both group of patients (due to olanzapine), neither was problematical during the present study.

Post hoc power analysis showed a power=0.68 (n1=14, n2=14, ES=0.8, alpha=0.05, delta=2.11, critical t[26]=1.70) with respect to this trial, which changed to power=0.85 in the frame of compromise power analyses (n1=14, n2=14, ES=0.8, beta/alpha ratio=1, delta=2.11, critical t[26]=1.01, alpha=0.14).

Discussion

According to our findings, fluphenazine brought about hopeful improvements in the aforementioned outcome measures when added to olanzapine, despite the fact that such a combination was not so "remarkable" given the small sample size and the disappointing SANS results. In an earlier study, the efficacy and safety of olanzapine had been compared with fluphenazine in the treatment of patients who met the diagnosis of schizophrenia or schizoaffective disorder (5). According to the findings of that study, the olanzapine group showed considerably better improvement in the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS) and CGI-Severity scores, and greater decrement of SAS. In that study, olanzapine had shown superiority with regard to both efficacy and safety in comparison with fluphenazine (5). Our findings are in agreement with this study regarding the extrapyramidal side effects of

Table 3 Intragroup Analysis of Different Measures at Baseline and 12th Week, plus Effect-Size Analysis

Measure	Baseline	12th Week	t	P value	95% CI	Cohen's d	Effect-size r
SAPS OL+placebo	85.79±9.04	79.93±6.57	1.96	0.06	-11.99 to 0.27		
SAPS OL+FL	89.13±3.58	73.7±7.32	7.32	0.00	20.43 to 11.48	2.76	0.81
SANS OL+placebo	66.93±7.48	62.97±3.09	1.83	0.07	-8.40 to 0.48		
SANS OL+FL	63.47±8.16	65.14±3.62	0.70	0.49	-3.23 to 6.57	0.26	0.13
SAI OL+placebo	3.03±1.17	3.59±0.12	1.78	0.08	-0.08 to 1.20		
SAI OL+FL	3.27±0.89	4.20±1.07	2.50	0.01	0.16 to 1.69	0.94	0.42
SAS OL+placebo	4.72±0.64	4.76±1.07	0.12	0.90	-0.64 to 0.72		
SAS OL+FL	4.11±1.31	13.39±2.54	12.15	0.00	7.71 to 10.85	4.59	0.91
CGI-S OL+placebo	4.13±1.02	3.97±0.73	0.47	0.637	-0.84 to 0.52		
CGI-S OL+FL	4.16±0.39	3.48±0.43	4.38	0.00	0.36 to 0.99	1.65	0.63

SAPS=Scale for Assessment of Positive Symptoms, SANS=Scale for Assessment of Negative Symptoms, SAI=Schedule for Assessment of Insight, SAS=Simpson-Angus Scale, CGI-S=Clinical Global Impressions-Severity of Illness, OL=olanzapine, FL=fluphenazine decanoate

fluphenazine, but are not precisely compatible concerning efficacy. The positive effect of combining fluphenazine decanoate with olanzapine in our experiment slightly supports the argument of some earlier studies regarding the advantages of conventional antipsychotics vis-à-vis SGAs (9, 10).

In addition, fluphenazine decanoate has shown some valuable effects in reducing self-harm behaviors in outpatients with histories of multiple suicide attempts (19), which might be helpful in treating patients with schizophrenia. According to two Cochrane Database of Systematic Reviews, while the use of depots, like fluphenazine, continues to be based largely on clinical judgment, one long-term study found that relapse was significantly reduced by fluphenazine; and, moreover, movement disorders were significantly less for people receiving fluphenazine decanoate as compared with oral neuroleptics (20, 21). The above viewpoints, although not absolute, do to some extent promote using fluphenazine decanoate as a plausible helpful adjuvant to olanzapine in poorly responsive cases. While undetected poor olanzapine adherence could be one potential reason for the results supporting enhancement with fluphenazine depot, it surely is not the only one. Other possibilities, like continuous receptor blockade, also should be considered. Although the recognized greater risk of tardive dyskinesia caused by conventional antipsychotics cannot be overlooked, possible metabolic side effects due to a higher dosage of olanzapine (22, 23), which may be prescribed by clinicians in cases of treatment resistance, also need to be considered. In addition, since both of these drugs are substrates of cytochrome P450 2D6, possible pharmacokinetic interaction between them must be noted.

Lastly, obvious study limitations suggest that our findings are only exploratory and in need of additional verification. Weaknesses of this study could be summarized as follows: 1) small sample size; 2) no direct comparison between fluphenazine decanoate and olanzapine regarding their individual therapeutic efficacy; 3) the short duration of the study; and, 4) gender-based sampling.

Conclusions

Adding fluphenazine decanoate to olanzapine may improve some cases of poorly responsive schizophrenia. However, both the emergence of extrapyramidal side effects and the strengthening of negative symptoms due to fluphenazine, and probable pharmacokinetic interaction between fluphenazine and olanzapine, are critical issues that need to be considered.

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