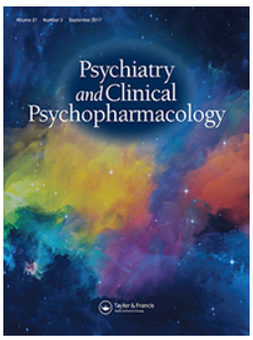

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Augmentation of aripiprazole by flupenthixol decanoate in poorly responsive schizophrenia: a randomized clinical study

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ABSTRACT

OBJECTIVE: According to some studies, while first-generation antipsychotics were associated with slightly better outcomes and lower costs in comparison with second-generation antipsychotics, atypical antipsychotics have become the most commonly used class of antipsychotic drugs in clinical practice. The objective of this study was to examine whether there could be any positive outcome if flupenthixol decanoate was added, as an adjuvant, to aripiprazole in poorly responsive cases of schizophrenia.

METHODS: Twenty-four male inpatients with diagnosis of schizophrenia, according to the DSM-5 diagnostic criteria, who had shown poor response to aripiprazole, were entered into an eight-week, parallel group, single-blind study for random assignment to either aripiprazole plus augmentative flupenthixol decanoate or current antipsychotic treatment 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 Scale (CGI-S), and the Simpson-Angus Scale (SAS).

RESULTS: According to the findings, the mean total scores of SAPS, SAI, and CGI-S in the augmented group decreased significantly in comparison with the aripiprazole group ($p < .01$, $p < .05$, $p < .01$, respectively), with around 19.55% decrement of SAPS in the augmented group. Conversely, the reduction in the mean total score of SANS was not significant in between-group analysis ($p > .05$). Also, the mean total score of SAS was significantly increased in the augmented group ($p < .01$). The effect-size analysis showed a large improvement with flupenthixol augmentation in terms of SAPS, SAI, and CGI-S scores.

CONCLUSIONS: While emergence of extra-pyramidal side effects should not be overlooked by clinicians, adding flupenthixol decanoate to aripiprazole may be beneficial for some cases of poorly responsive schizophrenia.

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Schizophrenia; aripiprazole; flupenthixol decanoate; poor response; treatment resistant

Introduction

The characteristic symptoms of schizophrenia involve a range of cognitive, behavioural, and emotional dysfunctions, but no single symptom is pathognomonic of the disorder. The diagnosis involves the recognition of a constellation of signs and symptoms associated with impaired occupational or social functioning. Individuals with the disorder will vary substantially on most features, as schizophrenia is a heterogeneous clinical syndrome. The onset of schizophrenia may be abrupt or insidious, but the majority of individuals manifest a slow and gradual development of a variety of clinically significant signs and symptoms [1]. During the past decade, there has been some progress in the pharmacotherapy of schizophrenia and schizoaffective disorder. Current evidence supports the use of various second-generation or atypical antipsychotic medications, although few of these agents have been associated with long-term efficacy and tolerability [2]. While first-generation antipsychotic (FGA) medications have shown the capacity to restrain the acute psychotic symptoms of schizophrenia and related psychotic disorders and prevent their recurrence, they were associated with high rates of neurological side effects (i.e. extra-pyramidal side effects and tardive dyskinesia) that could compromise the therapeutic effects of treatment and so have caused many patients to discontinue their usage and consequently increased the risk for relapse [2]. Dolder et al. have shown that though medication compliance ("adherence") was better with second-generation antipsychotics (SGAs) compared to the FGAs in patients with schizophrenia, poor compliance was considerable even among those receiving the SGAs [3]. Evidence suggests that SGAs affect a broader range of schizophrenia psychopathology and are generally better tolerated than FGAs. However, these claims have not been consistently confirmed by empirical data; so, researchers and clinicians differ in their attitudes concerning the comparative effectiveness of FGAs and SGAs [4,5]. Despite the lack of

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consensus, atypical antipsychotic drugs have become the most commonly used class of antipsychotic drugs in clinical practice [6–8]. However, according to one study, conventional drugs were associated with non-significantly better outcomes and lower costs in comparison with atypical drugs [9]. Also, according to another study, the one-year risk of readmission for patients treated with atypical antipsychotics was at least comparable to the one-year risk for patients receiving fluphenazine decanoate [10]. On the other hand, while compliance has generally been found to improve when patients are switched to depot antipsychotic medications [10], according to a number of surveys, aripiprazole may be helpful and well tolerated as well for a substantial number of antipsychotics-resistant patients with schizophrenia [11,12]. Aripiprazole is an atypical antipsychotic that has been found to improve positive and negative symptoms of schizophrenia with a favourable adverse-effect profile [13]. Based on the evidence reviewed, aripiprazole monotherapy appears to be effective and well tolerated in treating the positive, negative, and cognitive symptoms of schizophrenia and schizoaffective disorder [2]. Aripiprazole is a quinolinone derivative with a high affinity for dopamine D2 and D3 receptors, and serotonin 5-HT1A, 5-HT2A, and 5-HT2B receptors. The mechanism of action of aripiprazole is not yet known, but evidence suggests that its efficacy in the treatment of the positive and negative symptoms of schizophrenia and its lower propensity for extra-pyramidal symptoms (EPS) may be attributable to aripiprazole's partial agonist activity at dopamine D2 receptors. In general, while aripiprazole was associated with improvements in a broad range of symptom domains in the short-term treatment of schizophrenia and schizoaffective disorder [14], it was associated with a placebo-level incidence of EPS and EPS-related adverse events [15]. Flupenthixol is a non-sedating antipsychotic drug of the thioxanthene group. Its primary pharmacological action is dopamine blockade with high affinity for D1 and D2 receptors. While not approved in the U.S., its primary use is as a long-acting injection administered at two- to three-week intervals to patients with schizophrenia who have a poor compliance with prescription and suffer recurrent relapses of illness [16]. Flupenthixol has been used in combination with Zuclopenthixol in antipsychotics non-responsive schizophrenia patients [17] with some positive results. It appears that, monotherapy involving the atypical antipsychotics is not considered to be an effective therapy for a significant number of patients in clinical practice [18]. While there has been insufficient methodical appraisal, so far, regarding the joint effects of typical and atypical antipsychotics in poorly responsive schizophrenic patients, it is usual practice to prescribe a combination of conventional and atypical antipsychotics. Though antipsychotic polypharmacy continues currently, as it has over the past 30 years, evidence-based data to support this controversial management policy is still absent. Consequently clinicians are relying on their clinical practice, and may be intuition, to plan antipsychotic polypharmacy treatment protocols [19]. Justifications for combination treatment include an expansion of the range of receptor activity, or an increase in D2 receptor occupancy, with certain atypical agents [20]. Combinations of atypical antipsychotic drugs, too, are well tolerated and may be operative in the management of treatment-refractory schizophrenia and schizoaffective disorder [21]. Although some studies have found that in cases of treatment-refractory schizophrenia, where clozapine is supposed to be inappropriate, combination therapy with non-clozapine atypical antipsychotic drugs is an approach worthy of attention [22], primary case reports advise that aripiprazole combined with dopamine antagonists, with a high affinity for D2 and D3 receptors may worsen psychosis [22–24]. So it has been recommended by some researchers that, because of their lower D2 receptor affinity, clozapine and quetiapine might be a better choice for combined treatment with aripiprazole [24,25]. The main objective of the present study was to examine whether there could be any encouraging outcome if flupentixol decanoate is added, as an adjuvant, to aripiprazole in poorly responsive schizophrenia.

Methods

Twenty-four male inpatients with diagnosis of schizophrenia, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) [1], who had shown poor response to aripiprazole (Scale for Assessment of Positive Symptoms (SAPS) > 70 at baseline, with maximum dose of 30 mg daily for at least 4 weeks, as inclusion criteria) were entered into an 8-week, parallel group, single-blind study for random assignment to augmentative flupentixol decanoate plus their aripiprazole, or their current antipsychotic treatment, in a 1:1 ratio. All cases had been selected, as accessible sample, among the male patients with schizophrenia, who had been hospitalized in one of the chronic wards of the hospital (Figure 1). 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 Ethics Committee in *31 September 2014*. The assessor, a psychiatrist, was uninformed concerning the partition and the type of medications arranged for each group. These cases, according to the above-mentioned criteria, were randomly entered into one of the two matching groups simultaneously. The randomization was based on the number of beds, that is, even

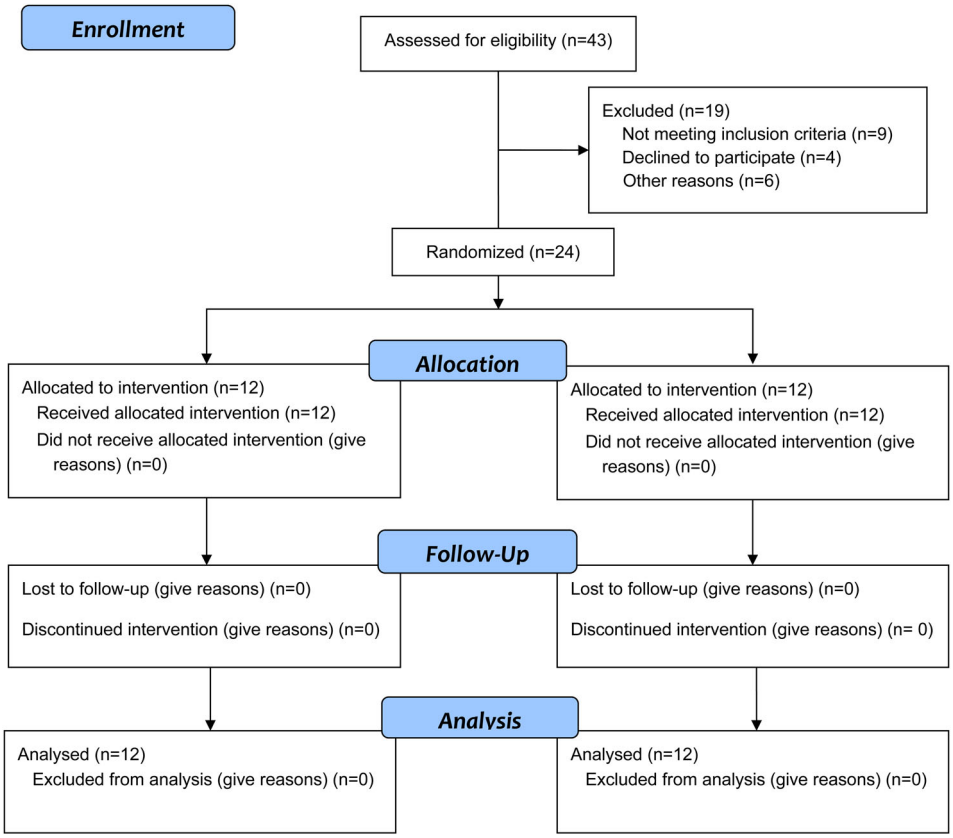

Figure 1. CONSORT flow diagram.

numbers into control group and odd numbers into target group. After baseline assessments, while the cases in the aripiprazole group ($n = 12$) continued their current antipsychotic up to the end of the trial (aripiprazole, 30 mg daily), in the target group ($n = 12$), flupenthixol decanoate was added to aripiprazole (30 mg daily). Flupenthixol decanoate was prescribed in the beginning (week 0) at a dosage of 10 mg/2 weeks IM (after initial titration in the first few days), and then increased to a maximum of 20 mg/2 weeks by week 4. The dose established by week 4 was held constant up to the end of the study. No other concurrent psychotropic medication or psycho-social intervention was allowed during the trial. Primary outcome measures of the study were changes in the mean total scores of the SAPS [26] and the Scale for Assessment of Negative Symptoms (SANS) [27] for appraisal of the positive and negative symptoms of schizophrenia, respectively. The secondary measures included the Schedule for Assessment of Insight (SAI) [28] and the Clinical Global Impressions-Severity Scale (CGI-S) [29] for further evaluation of clinical status; in addition, the Simpson-Angus Scale (SAS) [30] was used to scan for drug-induced side effects. The scoring of SAPS and SANS were carried out at the start of the study at baseline (week 0), and after that at the 2th, 4th, 6th and 8th 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 student's *t*-tests for continuous variables in order to assess the efficacy of the randomization procedure in ensuring homogeneity between the two treatment groups. Treatment efficacy was analysed by student's *t*-test, and repeated measures analysis of variance (ANOVA) comparing both groups over eight weeks with respect to SAPS and SANS. All secondary measures (SAS, SAI, and CGI-S) were analysed by *t*-test. Cohen's effect-size estimates were used when comparing baseline to endpoint changes in all 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. MedCalc Statistical Software (version 15.2) was used as statistical software tool for analysis.

Results

Intent-to-treat, last observation carried forward analysis for efficacy was based on data from an equal number of patients ($n = 12$) in both groups, since there were no dropouts in either group throughout the assessment. Given that all 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,

Table 1. Between-group comparison of primary outcome measures.

Group Scale – week	Aripiprazole Mean +/−SD	Aripiprazole + flupenthixol Mean +/−SD	*t*	*p*
SAPS-Baseline	86.63 ± 10.28	88.47 ± 8.91	−0.469	0.6440
SAPS-2nd	86.36 ± 9.22	87.58 ± 7.83	−0.349	0.7301
SAPS-4th	85.84 ± 6.27	85.29 ± 6.71	0.207	0.8376
SAPS-6th	84.88 ± 8.47	75.68 ± 5.19	3.208	0.0041
SAPS-8th	84.73 ± 7.61	73.17 ± 7.32	3.792	0.0010
SANS-Baseline	54.93 ± 6.37	57.36 ± 7.15	−0.879	0.3889
SANS-2nd	55.36 ± 5.78	56.62 ± 6.41	−0.506	0.6181
SANS-4th	56.19 ± 4.38	56.53 ± 5.11	−0.175	0.8627
SANS-6th	54.80 ± 5.26	50.47 ± 6.09	1.864	0.0757
SANS-8th	53.87 ± 4.02	50.13 ± 5.77	1.842	0.0789

Note: SAPS = scale for Assessment of Positive Symptoms and SANS = scale for Assessment of Negative Symptoms.

Table 2. Between-group analysis of secondary outcome measures.

Group Scale – week	Aripiprazole Mean ± SD	Aripiprazole + flupenthixol Mean ± SD	*t*	*p*
SAI-Baseline	3.14 ± 1.28	3.38 ± 0.91	−0.529	0.6018
SAI-8th	3.69 ± 0.23	4.41 ± 1.08	−2.259	0.0342
SAS-Baseline	2.63 ± 0.55	2.21 ± 1.26	1.058	0.3014
SAS-8th	3.26 ± 1.07	12.19 ± 2.41	−11.732	0.0000
CGI-S-Baseline	4.16 ± 1.12	4.23 ± 0.45	−0.201	0.8426
CGI-S-8th	3.99 ± 0.81	3.30 ± 0.12	2.919	0.0079

Note: SAI = scale for Assessment of Insight, SAS = Simpson-Angus Scale, and CGI-S = Clinical Global Impression (Severity) Scale.

there were no premature discontinuations in either group. Groups were originally analogous with respect to comparable demographic and diagnostic variables. In this regard, mean age of the patients in the aripiprazole and flupenthixol group was 33.69 ± 6.38 and 35.28 ± 5.16, respectively ($t = -0.671$, $p = 0.5090$), and mean age at onset was 20.73 ± 3.19 and 21.41 ± 4.04, correspondingly ($t = -0.458$, $p = 0.6517$). Duration of illness, as well, was 8.21 ± 5.37 and 7.39 ± 4.84, respectively ($t = 0.393$, $p = 0.6982$). Also, in terms of alcohol and substance abuse, family history of psychiatric disorders, other medical conditions, previous medications, marital status, and education levels, which could affect treatment responses, no significant differences were found between two groups ($p > .05$). According to the findings at the closing stages of the assessment, the mean total scores of SAPS, SAI, and CGI-S in the augmented group decreased significantly in comparison with the aripiprazole group ($p < .01$, $p < .05$, $p < .01$, respectively) (Tables 1 and 2). Decrement in mean total score of SAPS was approximately 19.55% in the augmented group, while it was around 2.19% in the other group (Table 1, Figure 2). In the intragroup analysis, as well, this decrement in SAPS was significant in the augmented group ($p < .01$), while it was not noticeable for the other group ($p > .05$) (Table 3). Repeated measures ANOVA showed significant changes of SAPS in the augmented group [F (4,55) = 34.7 $p < .000001$, SS = 2958.43 MSe = 21.32]. Split-plot (mixed) design ANOVA also showed substantial difference between the two groups [F (9,110) = 4.40 $p < .00006$, SS = 1231.47 MSe = 31.13]. On the other hand, while the mean total score of SANS decreased in the augmented group (12.60%), and the intragroup analysis showed significant changes in this regard ($p < .01$), it was not significant in between-group analysis ($p < .05$) (Tables 1 and 3, Figure 3). Similarly, repeated measures ANOVA wih respect to the SANS scores did not show any significant changes during the study in the augmented group [F (4,55) = 2.38 $p < .06$, SS = 124.17 MSe = 13.03], and split-plot (mixed) design ANOVA did not illustrate any considerable differences between the groups as well [F (9,110) = 1.42 $p < .19$, SS = 279.51 MSe = 21.94]. Furthermore, the mean total score of SAI improved significantly in the augmented group, in between-group ($p < .05$) (Table 2) and within-group analysis ($p < .01$) (Table 3). Likewise, regarding the mean total score of CGI-S, between-group and within-group analysis showed a significant improvement in the augmented group ($p < .01$ and p

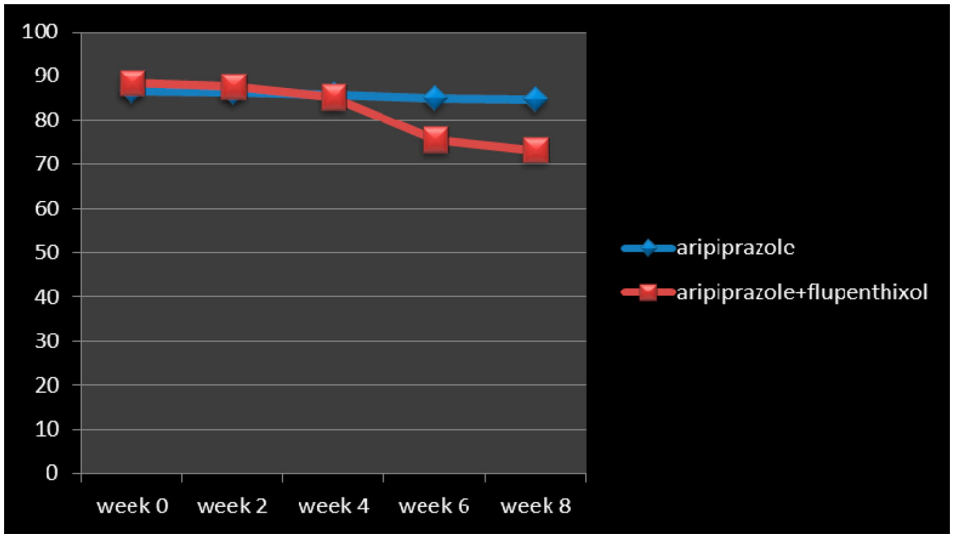

Figure 2. Changes of SAPS scores between baseline and week 8.

Table 3. Within-group analysis of primary and secondary outcome measures.

Week Scale – group	Baseline Mean ± SD	Week 8 Mean ± SD	*t*	*p*
SAPS – aripiprazole	86.63 ± 10.28	84.73 ± 7.61	0.515	0.6120
SAPS – aripiprazole + flupenthixol	88.47 ± 8.91	73.17 ± 7.32	4.596	0.0001
SANS-aripiprazole	54.93 ± 6.37	53.87 ± 4.02	0.487	0.6307
SANS – aripiprazole + flupenthixol	57.36 ± 7.15	50.13 ± 5.77	2.726	0.0123
SAI-aripiprazole	3.14 ± 1.28	3.69 ± 0.23	−1.465	0.1571
SAI – aripiprazole + flupenthixol	3.38 ± 0.91	4.41 ± 1.08	−2.526	0.0192
SAS - aripiprazole	2.63 ± 0.55	3.26 ± 1.07	−1.814	0.0833
SAS – aripiprazole + flupenthixol	2.21 ± 1.26	12.19 ± 2.41	−12.713	0.0000
CGI-S-aripiprazole	4.16 ± 1.12	3.99 ± 0.81	0.426	0.6742
CGI-S – aripiprazole + flupenthixol	4.23 ± 0.45	3.30 ± 0.12	6.917	0.0000

Note: SAPS = Scale for Assessment of Positive Symptoms; SANS = Scale for Assessment of Negative Symptoms; SAI = Scale for Assessment of Insight; SAS = Simpson-Angus Scale; and CGI-S = Clinical Global Impression (Severity) Scale.

< .01, respectively) (Tables 2 and 3). In contrast, the mean total score of SAS was significantly increased in the augmented group ($p = .0000$) (Table 3) and it was the same in between-group analysis ($p < .01$) (Table 2). This increment was observable in almost all of the SAS's sub-items, especially with respect to tremor, gait, and rigidity (elbow and wrist). Generally, 16.66% ($n = 2$) of the cases in the aripiprazole group and 58.33 ($n = 7$) of the patients in the target group needed anticholinergic drugs, at some point during the assessment, for amelioration of extra-pyramidal side effects due to prescribed antipsychotics. Moreover, since the sample size was small, the effect size (ES) was analysed for changes on SAPS, SAI, and CGI-S at the end of treatment, which indicated a large ($d = 0.8$ or $r = 0.3$), readily observable improvement with flupenthixol augmentation (1.87 & 0.68; −1.03 & −0.45, and 2.82 & 0.81, as Cohen's d and effect-size correlation r, respectively). *Post hoc* power analysis showed an intermediary power of 0.60 (n1 = 12, n2 = 12, ES = 0.8, alpha = 0.05, delta = 1.95, critical t [22] = 1.71) with respect to this trial, which changed to power = 0.83 in the frame of compromise power analyses (n1 = 12, n2 = 12, ES = 0.8, beta/alpha ratio = 1, delta = 2.11, critical t [22] = 0.99, alpha = 0.16).

Discussion

The predictors of course and outcome of schizophrenia are largely unexplained, and course and outcome may not be reliably predicted. The course appears to be favourable in about 20% of those with schizophrenia, and a few of patients are reported to recover completely [1]. Negative symptoms are more closely related to prognosis than are positive symptoms and tend to be the most persistent [31–34]. Despite the fact that it is a common clinical practice to prescribe a combination of antipsychotics in treatment-refractory schizophrenia, all antipsychotics are exclusively registered for use as monotherapy [20]. So, prescription of two or more antipsychotics at the same time, also called antipsychotic polypharmacy, has no experimental basis [20]. However, in the past years, antipsychotic polypharmacy with two conventional antipsychotics was regularly practised with reported frequencies ranging from almost 10–69% [18]. Similarly, a small number of studies from the U.S. and U.K. have focused on antipsychotic polypharmacy with atypical antipsychotics and reported frequencies ranging from 13% to 68% [18]. On the other hand, low-potent antipsychotics may be added to an atypical antipsychotic mainly because of their sedative, anxiolytic, and anticholinergic properties, rather than because of their antipsychotic properties. Even when the low-potent conventional antipsychotics are not included in the study, some analyses had found that antipsychotic polypharmacy was recommended in nearly 25% of the patients. The results of a European study indicated that 52.9% of

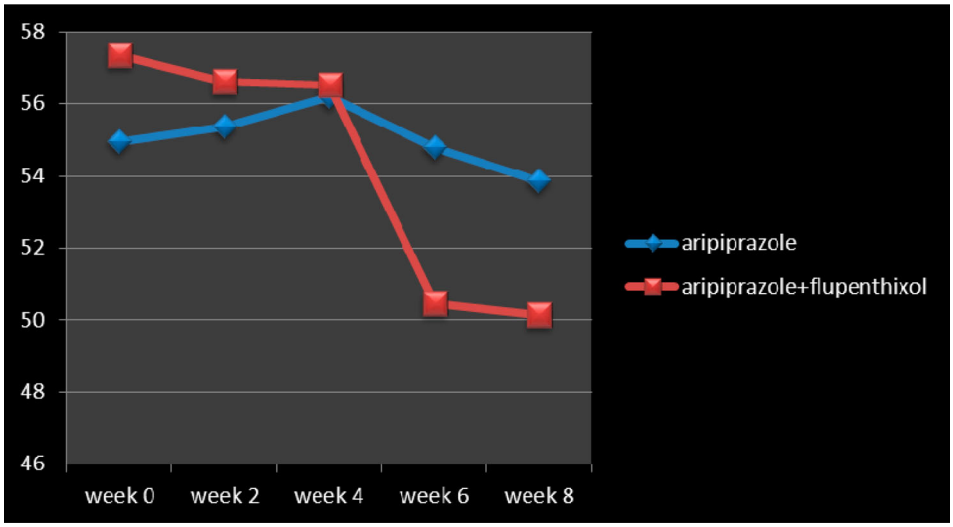

Figure 3. Changes of SANS scores between baseline and week 8.

the patients were not being treated in the way according to the psychiatric treatment guidelines and handbooks [19]. A number of theories for the relatively high rate of antipsychotic polypharmacy involving atypicals have been previously stated [18]. Firstly, it could be that the patients with an insufficient treatment response to one antipsychotic are treated with combinations of antipsychotics, including the atypical antipsychotic drugs. Nevertheless, there are scarcely any studies that show that antipsychotic polypharmacy is effective in patients who do not respond to one antipsychotic [20]. Secondly, it is also probable that antipsychotic polypharmacy is continued, even if the patient shows no improvement, for the reason that psychiatrists are uncertain to discontinue any medication in patients with persistent psychotic symptoms [18]. Thirdly, it could be that in some patients the recommended doses of the atypical antipsychotic medications are too low to be effective, and that adding a second antipsychotic is in fact a dose-increase tactic. In such cases, however, a higher dose of one particular atypical drug might be just as effective [18]. Fourthly, when switching between two antipsychotic drugs, it is common to titrate the first drug downwards, while at the same time titrating the second drug upwards (also known as cross-tapering). If the patient responds halfway through the titrating process, the clinician may decide to continue both antipsychotics, a situation referred to as "the cross-titration trap" [18]. According to our findings, flupenthixol decanoate brought about hopeful improvements in the aforementioned outcome measures when added to aripiprazole, despite small sample size and inadequate SANS outcomes. While according to an earlier study, regarding comparison of the efficacy and safety of aripiprazole versus fluphenazine decanoate in the treatment of patients, who met the diagnosis of schizophrenia or schizoaffective disorder, the aripiprazole group showed considerably better improvement in the Brief Psychiatric Rating Scale, the Positive and Negative Syndrome Scale, and CGI-S scores, and greater decrements of SAS and so it had shown superiority with regard to both efficacy and safety in comparison with fluphenazine decanoate [5]. Our findings are in agreement with that study regarding the extra-pyramidal side effects of flupenthixol decanoate , but practically poles apart concerning efficacy. The positive effect of combining flupenthixol decanoate with aripiprazole in our experiment slightly supports the argument of some earlier studies regarding the advantages of FGAs versus SGAs [7]. Essentially, long-acting depot injections of drugs such as flupenthixol decanoate are extensively used as a means of long-term maintenance treatment for schizophrenia, and according to a study there is no difference between flupenthixol decanoate and other depot antipsychotics regarding management of schizophrenia, especially when its prevention of relapse in standard dose is not different from higher dose [16]. Also, the results of this present assessment are consistent with the findings of an earlier study with respect to the augmentative effect of fluphenazine decanoate in patients who responded poorly to olanzapine [35]. In terms of benefits of using long-acting antipsychotics, it has been revealed that, for example, fluphenazine decanoate had valuable effects in reducing self-harm behaviours in outpatients with histories of multiple suicide attempts [36], which might be helpful in treating patients with schizophrenia. In addition, according to two Cochrane Databases of Systematic Reviews, while the use of depots continues to be based largely on clinical judgement, one long-term study showed that relapse was significantly reduced by fluphenazine decanoate [37,38]. Moreover, based on the existing results, in opposition to Adan-Manes et al. [22], Takeuchi et al. [23], and Letmaier et al. [24], no worsening of psychosis was evident by combination of aripiprazole with flupenthixol in the present assessment. While undetected poor aripiprazole adherence could be one potential reason for final results that show enhancement with flupenthixol decanoate, it surely is not the only one. Other possibilities, like constant or greater receptor blockade, as well, should be considered. Since flupenthixol decanoate, in addition to schizophrenia, has been indicated as well for depression, and bipolar disorder [39], so may be its use as an augmentative agent in poorly responsive schizoaffective cases, also, is advisable. On the other hand, while its negative outcome regarding SANS in between-group analysis might be due to intensification of secondary negative symptoms, which was consistent with the significant amplification of SAS, its significant improvement in within-group analysis, as well, could be due to efficient augmentation by flupenthixol decanoate, an implication that demands further consideration and additional exploration. Despite these interpretations, it could not be disregarded that strengthening of extra-pyramidal side effects by flupenthixol decanoate or similar antipsychotics may precipitate or increase the risk of other serious adverse effects such as tardive dyskinesia or neuroleptic malignant syndrome. On the other hand, though the recognized greater risk of tardive dyskinesia caused by conventional antipsychotics cannot be overlooked, possible metabolic side effects due to a higher dosage of aripiprazole or other SGAs [40,41], 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. Centorrino et al. [42] reports that the risk of adverse effects is 56% higher with antipsychotic polypharmacy. Furthermore, serious dangers of polypharmacy should not be ignored by clinicians. For instance, Waddington et al. [43] found that

antipsychotic polypharmacy is associated with increased mortality and reduced survival among patients with schizophrenia. In addition, newer outcome measures such as the Glasgow Antipsychotic Side-effect Scale must be taken into consideration for future assessments, which has been structured for detecting the side effects of SGAs and has shown to have good discriminatory power and construct validity, along with good test/re-test reliability [44]. Some of the limitations of this study could be summarized as follows: (1) small sample size; (2) no direct comparison between flupenthixol decanoate and aripiprazole regarding their individual therapeutic efficacy; (3) the short duration of the study; and (4) gender-based sampling.

Conclusions

While emergence of extra-pyramidal side effects should not be overlooked by clinicians, adding flupenthixol decanoate to aripiprazole may be beneficial for some cases of poorly responsive schizophrenia.

Disclosure statement

No potential conflict of interest was reported by the author.

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