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Research Article

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Deficit Syndrome of Schizophrenia: TCAs against SSRIs

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Abstract

Introduction: Negative symptoms are among the important barriers against psychosocial rehabilitation of schizophrenic patients. Adjunctive drugs can be used for reducing the severity of these symptoms. In this study, we compared the helpfulness of Tricyclic antidepressants (TCAs) vs. Specific serotonin reuptake inhibitors (SSRIs) as regards their efficacy on reducing the severity of such symptoms.

Materials and Method: One hundred and thirty five schizophrenic patients were divided into three different groups and the efficacy of TCAs (clomipramine, nortriptyline, maprotiline) and SSRIs (flouxetine, citalopram, fluvoxamine), as adjuvant drugs, were examined in three different double-blind clinical controlled trials. Estimation of negative symptoms by Scale for Assessment of Negative Symptoms (SANS) was performed at baseline, week 3 and week 6. The data were analyzed by z and chi-square (X^2-test) formula.

Results: Clomipramine and Nortriptyline could reduce the severity of negative symptoms in some cases to a greater degree than SSRIs (40% versus 20% reduction from baseline). Generally, larger quantity of patients gained benefit from TCAs (73.33%) vis-à-vis SSRIs (65.90%). No important side effect or worsening of positive symptoms was evident in our samples throughout the aforesaid trials.

Conclusion: In severe cases of deficit syndrome, TCAs seem to be superior to SSRIs for amelioration of negative symptoms.

Negative symptoms in schizophrenia include: 1) Restricted up to flat affect 2) Apathy 3) Alogia 4) Anhedonia 5) Avolition 6) Asociality [1,2]. In DSM-5, negative symptoms in addition to one of the core positive symptoms (delusion, hallucination, disorganized speech) for duration of at least one month is enough for diagnosis of acute phase of schizophrenia. Anxiety, suspiciousness, mental retardation, depression, parkinsonism and lack of environmental stimulants can result in secondary negative symptoms or reinforcement of the primary ones [1,3]. The importance of negative symptoms can be deduced also from the hidden firm barrier that is constructed by them between patient and the surroundings. Aloofness of the patient as well may easily make different psychosocial interventions futile. Therefore amelioration of the severity of negative symptoms by pharmacological strategies may facilitate the attainment of short-term and long-term goals of rehabilitation [3]. So in this regard a series of studies had been accomplished for clinical appraisal of the effectiveness of adjunctive drugs, and also a comparison between their efficacies.

Method and Materials

One hundred and thirty five male inpatients, as accessible sample, from chronic wards of Razi Psychiatric Hospital, who were diagnosed as schizophrenic, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision criteria (DSM-IV-TR), and after complete description of the method and attaining the signed informed permission, had been divided into three different groups. While, the evaluation had been approved, in advance, by Academy's Medical Principles Comity, group A (n=30) designated for a clinically controlled comparison between clomipramine and citalopram regarding amelioration of negative symptoms, group B (n=75) with a similar approach with respect to comparison of fluoxetine with nortriptyline, and finally group C (n=30) for comparison of fluvoxamine with maprotiline. In every group and after baseline estimation of negative symptoms by SANS [4], as the primary outcome measure, the abovementioned adjunctive drugs had been added to the patient's current treatments, including typical antipsychotics (one of the Chlorpromazine, haloperidol, Perphenazine, Trifluperazine or Fluphenazine decanoate).

Each drug in each group was started in its minimal dosage and then at the end of the third week another estimation of negative symptoms by SANS had been performed. Then the dosage of the aforesaid drugs had been doubled and after another three weeks the final severity of negative symptoms had been registrated. Overally grade 1, 2 and 3 were regarded as non-severe (mild) symptoms and grade 4 and 5 as severe. At the end, data had been analyzed by Z and chi-square (X2-test) formula. All of the aforesaid controlled trials had been done in a double-blind fashion and by the same team. Interview with the patients and their relatives, and also observations and remarks of nurses, social workers, psychologists and occupational therapists had provided the necessary resources for this research.

Results

While analysis for efficacy was based on data from comparable number of patients in related parallel groups, they were originally analogous with respect to comparable demographic and diagnostic variables. In keeping with the findings and in the first group, citalopram and clomipramine were significantly more effective than placebo with respect to amelioration of negative symptoms (p=0.001 and p=0.01, respectively), while between-group analysis did not show any significant difference among them (p=0.25) [4]. This improvement was restricted up to 20%, from baseline, and only in the clomipramine group, something around 40% reduction was seen in two patients in Alogia and Attention Deficit. In general, there was not any apparent relationship between response to adjunctive drugs and the severity of negative symptoms.

Also, amelioration had taken place discretely and there was not uniform decreasing in all of the negative symptoms in every individual patient. Patients who had received placebo did not show any significant benefit. In this group, Affective Blunting showed the most and Anhedonia-Asociality the least response (Table 1).

Negative Symptoms	Affecting Blunting		Alogia		Avolition Apathy		Anhedonia Asociality		Attention Deficit		Total	
Drugs	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent
Citalopram 20-40 mg	5	50%	4	40%	4	40%	3	30%	4	40%	8/10	80%
Clomipramine 25-50 mg	4	40%	2	20%	1	10%	3	30%	3	30%	5/10	50%
Placebo	0	0%	0	0%	0	0%	0	0%	0	0%	0/10	0%

Table 1: *Improvement of negative symptoms by adjunctive drugs (first trial).*

In second group, one patient in the Fluoxetine subgroup, due to his inclination and one in the placebo subgroup due to cardiac infarction were omitted from this trial. According to the findings 37.5% (n=9), 62.5% (n=15), and 80% (n=20) of the patients showed around 20% reduction in the severity of some of their negative symptoms under the influence of placebo, fluoxetine and nortriptyline, respectively [5]. Three patients in the nortriptyline subgroup showed around 40% improvement of some of their negative symptoms. Overally these reductions, also, were taken place discretely amid five clusters of those symptoms. There was no difference between mild or severe symptoms regarding their response to the adjunctive drugs. Nortriptyline was significantly more effective than placebo

(P=0.005). But it was not so regarding fluoxetine (p=0.1). Attention Deficit in comparison with other negative symptoms responded better to the adjunctive drugs and Affecting Blunting responded less than others. Only in one patient in the nortriptyline subgroup all of the negative symptoms showed improvement (Table 2) [6].

Negative Symptoms	Affecting Blunting		Alogia		Avolition Apathy		Anhedonia Asociality		Attention Deficit		Total	
Drugs	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent
Fluoxetine 20-40 mg	4	16.6%	4	16.6%	7	29.1%	2	8.3%	10	41.6%	15/24	62.5%
Nortriptyline 25-50 mg	6	24%	9	36%	8	32%	9	36%	10	40%	20/25	80%
Placebo	2	8.3%	6	25%	1	4.1%	4	16.6%	6	25%	9/24	37.5%

Table 2: *Improvement of Negative symptoms by adjunctive drugs (second trial).*

In third trial and according to the findings, %80 (n=8), 60% (n=6), and 20% (n=2) of patients showed 20% improvement in some of their negative symptoms under the influence of maprotiline, fluvoxamine and placebo, respectively [7, 8]. This effect was significant with respect to maprotiline (p=0.01), but not so regarding fluvoxamine (p=0.1) (Table 3). In this trial, severe symptoms responded better than mild ones to adjunctive drugs. Like the previous trials, and some other trials [9], these reductions had been taken place discretely.

Improved Negative Symptoms	Affective Blunting		Alogia		Avolition Apathy		Anhedonia Asociality		Attention Deficit		Total	
Drugs	No of patients	Present %	No of patients	Percent %	No of patients	Percent %	No of patients	Percent %	No of patients	Percent	No of patients	Percent %
Maprotiline 25-50 mg	3	30%	5	50%	0	0%	5	50%	3	30%	8/10	80%
Fluvoxamine 50-100 mg	5	50%	3	30%	1	10%	3	30%	1	10%	6/10	60%
Placebo	0	0%	2	20%	0	0%	1	10%	0	0%	2/10	20%

Table 3: *Improvement of negative symptoms by adjunctive drugs (third trial).*

Discussion

Helpfulness of adjunctive drugs in reducing the severity of negative symptoms is attention-grabbing. In first trial, while both of citalopram and clomipramine were effective, reduction of severity of negative symptoms up to 40% in two patients was evident only with clomipramine.

Also in the second trial, only nortriptyline showed significant ameliorating effect on negative symptoms. Once more, it was only the nortriptyline in comparison with fluoxetine that could reduce the severity of negative symptoms up to 40% in three patients. In the third trial, also, only maprotiline had significant ameliorating effect on target symptoms. So, TCAs improved negative symptoms almost in 73.33% (n=33) of the cases, while this range for SSRIs was around 65.90% (n=29). Superior and more powerful effect of TCAs in comparison with SSRIs in our study is in harmony with recently increasing comparable result in literature regarding its stronger effect on severe or melancholic major depressive disorder [10].

Modulating effect of dopamine afferents on sensitivity of cortical post-synaptic beta-adrenergic receptors, influence of noradrenergic neurons in controlling the sensitivity of cortical D1 receptors and inhibition of cortical transmission at D1 receptor via stimulation of cortical alpha1-adrenergic receptors [11], and the relationship between serum level of nor-epinephrine and negative symptoms (their direct relationship in acute phase of the illness and reverse one in chronic phase) demonstrate the interplay between noradrenergic transmission and presentation of negative symptoms in schizophrenia [12,13].

The nor-epinephrine re-uptake blocking effect of TCAs (especially nortriptyline and maprotiline in comparing with clomipramine) in addition to their 5HT re-uptake blocking effect (especially clomipramine and, to a lesser extend, nortriptyline) at least theoretically make them more powerful than SSRIs, which only block re-uptake of 5HT. Due to appropriate antipsychotic coverage, there was no aggravation of positive symptoms during the assessments, and also due to minimum dosages of the adjunctive drugs, none of the cases had suffered any important side effects. Maybe longer duration of assessment and higher dosages of adjunctive drugs could result in better outcome in this regard. Limited sample size and the relatively subjective observational measurements could be known as the weaknesses of the present study.

Conclusion

In severe cases of deficit syndrome, TCAs seem to be superior to SSRIs for amelioration of negative symptoms.

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