

Rehabilitation of Schizophrenia : Adjunctive Therapy of Negative Symptoms

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ABSTRACT :

Negative symptoms in schizophrenia are among the important barriers against psychosocial rehabilitation of such patients. Adjunctive drugs can be used for reducing the severity of these symptoms. In this research we studied the efficacy of Clomipramine, Alprazolam, Citalopram, Bromocriptine, Fluoxetine, Nortriptyline, Maprotiline and Fluvoxamine, in this regard.

After a primary prevalence survey regarding Negative symptoms, 170 schizophrenic patients were divided into three different groups, and then the aforesaid adjuvant drugs were examined in three double-blind clinical controlled trials. Estimation of negative symptoms by "SANS" were done at the beginning of each trial for the first time and then three weeks later, after prescription of drugs in lower dosage and finally at the end of sixth week, means three weeks after doubling the dosages. The data were analyzed by z and chi-square (X^2 -test) formula.

Clomipramine, Alprazolam, Citalopram, Nortriptyline and Maprotiline could reduce the severity of negative symptoms. Their effectiveness in comparing with placebo was statistically remarkable. No important side effect or worsening of positive symptoms was seen in our samples during aforesaid trials.

Conservative usage of adjuvant drugs can be an advantageous means for making rehabilitative programs more efficacious than before.

Introduction :

Negative symptoms in schizophrenia as one of the major criteria in addition to other ones in DSM TV-TR, include six presentation as follows: 1)Restricted up to flat affect 2)Apathy 3)Alogia 4)Anhedonia 5)Avolition 6)Asociality (1,2). According to Carpenter existence of at least two of these symptoms or more for duration not less than twelve month is enough for diagnosis of deficit syndrome, as a subtype of schizophrenia (3). In DSM IV-IR, too, negative symptoms in addition to one of the positive symptoms (delusion, hallucination, disorganized speech, and disorganized behavior) for duration of at least one month is enough for diagnosis of acute phase. Anxiety, suspiciousness, mental retardation, depression, Parkinsonism and lack of environmental stimulants can result in secondary negative symptoms or reinforcement of primary ones. The importance of negative symptoms can be deduced also from the hidden firm barrier which is constructed by them between patients and others around them. Inaccessibility to patients which is resulted from such cluster of symptoms, after suppression of positive

symptoms, can make different psychosocial interventions, which are employed in the framework of community psychiatry, futile. This phenomenon especially in developing or nondeveloped countries can result easily to a kind of pessimistic and doubtful standpoints regarding the goals and efficiency of rehabilitation of such patients. Therefore if reducing the severity

among Iranian schizophrenic patients and 2) the effectiveness of adjunctive drugs on severity of such symptoms.

Method and materials :

RAZI psychiatric hospital, located in south of Tehran, the largest psychiatric

| Inclusion criteria | Exclusion criteria |
|--------------------|--|
| Schizophrenia | 1-Depression 2-Schizoaffective 3-Mental retardation 4-Bipolar disorders 5-Neurological disorders 6-Using atypical antipsychotics 7-Using antidepressants or lithium 8-Medical complications 9-Unstable, irritable, aggressive patients 10-Duration less than one year 11-Parkinsonism 12-Medical deafness or muteness |

Table 1- Inclusion and Exclusion criteria

of negative symptoms by pharmacological strategies can facilitate the attainment of short and long term goals of rehabilitation, this will support the application of such programs with respect to the cost-effect economical points of view, which as a guarantee is not many times less important than academic or humanistic benefits. So there has been done a survey regarding 1) the prevalence of negative symptoms

hospital in middle East, and the first established center for handling psychiatric patients since last century in IRAN, had been chosen as our field for research. In summer of 2003, among one thousand and two hundred (1200) patients who were admitted there, 2/3 of them in long-term wards and 1/3 in short-term ones, 270 patients with diagnosis of schizophrenia, according to the DSM IV-TR criteria, had

been chosen randomly for a survey regarding to the prevalence of negative symptoms and their severity. In this regard some of the patients had been excluded due to some intervening factors (table 1). This cluster of symptoms had been estimated and registered by Scale for Assessment of Negative Symptoms (SANS) (4). After determining this prevalence, they had been divided to three different groups .

Group A (n = 40) for a Clinical Controlled Trial (CCT) regarding the effectiveness of Clomipramine , Alprazolam , and Citalopram on reducing the severity of negative symptoms , Groups B (n = 100) with a similar approach with respect to the moderating effect of Bromocriptine , Fluoxetine and Nortriptyline , and finally group C (n = 30) regarding similar effects of Fluvoxamine and Maprotiline. In every group and at the beginning of the related trials , before addition any adjunctive drug , a new estimation of the negative symptoms by SANS had been performed as the baseline and then the adjunctive drugs had been added to the patient's current treatments , including typical antipsychotics (one of the Chlorpromazine , haloperidol , Perphenazine Trifluoperazine or Fluphenazine decanoate) . Each drug in each group was started with its lower dose and then at the end of the third week after beginning adjunctive treatments , again another estimating 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 and their changing had been registered . Overallly 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 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 put forwarded by their nurses, social workers, psychologists and occupational therapists had provided the necessary resources for this research .

$$1-z = \frac{\frac{x_1}{n_1} - \frac{x_2}{n_2}}{\sqrt{p(1-p)\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}, p = \frac{x_1 + x_2}{n_1 + n_2}, \alpha = 0.05,$$

$$|z| > z_{1-\frac{\alpha}{2}} = (0.975) = 1.96$$

Results:

The prevalence of negative symptoms among schizophrenic patients were remarkable . Almost no patient was free from negative symptom , and no specific or similar pattern could be found among them. Although some of the patients had similar severity in all of their negative symptoms , but many of them had discrete symptoms with different severity . The prevalence of Affecting Blunting , Alogia , Avolition-Apathy , Anhedonia-Asociality and finally Attention Deficit among this sample (n=270) were : %96/28 (n=260) , %94/80 (n=156) , %99.62 (n=269) , %98.88 (n=267) and %99.25 (n=268) respectively .

| Severity Negative Symptoms | Normal | | Mild Grade 1,2,3 SANS | | Severe Grade 4 , 5 SANS | |
|----------------------------------|--------|-------|-----------------------------|--------|-------------------------------|--------|
| | | | | | | |
| Affective Blunting | 10 | %3.72 | 160 | %59.25 | 100 | %37.03 |
| Alogia | 14 | %5.20 | 155 | %57.40 | 101 | %37.40 |
| Avolition-Apathy | 1 | %0.38 | 171 | %63.33 | 98 | %36.29 |
| Anhedonia-Isolation | 3 | %1.12 | 144 | %53.33 | 123 | %45.55 |
| Attention Deficit | 2 | %0.75 | 115 | %42.59 | 153 | %56.66 |

Table 2 - Prevalence of Negative symptoms among 270 schizophrenic patients in RAZI Psychiatric Hospital

(Table 2) . The age of these patients were between 24-68 years (mean = 43.6) and the duration of their residency in hospital was between 2.5-28 years (mean=17.83) and all of them were male. Then we selected forty (40) patients among them , as group A , for performing the first trial with Citalopram, Alprazolam Clomipramine and placebo, after dividing them into four subgroup, with every subgroup containing ten patients. The starting dose was 20mg, 0/75 mg , and 25 respectively for Citalopram , Alprazolam and Clomipramine which were doubled after three weeks .

The whole of trial had been done accord-

ing to the aforesaid processes in method and material's section . According to the resulted data , Citalopram ($p < 0/001$) , Alprazolam ($p < 0/01$) and Clomipramine ($p < 0/01$) were more effective than placebo in reducing the severity of negative symptoms. This different was not large between them themselves ($p < 0.25$) . Generally this reduction in severity was restricted to 20% from baseline, and only in Clomipramine group 40% reduction was seen in Alogia and Attention Deficit in two separate patients respectively. There was not any relation between response to adjunctive drugs and the severity.

| Negative Symptoms Drugs | Affecting Blunting | | Alogia | | Avolition Apathy | | Anhedonia Asociality | | Attention Deficit | | Total | |
|----------------------------|--------------------|---------|---------------|---------|------------------|---------|----------------------|---------|-------------------|---------|----------------|---------|
| | 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% | $\frac{8}{10}$ | 80% |
| Alprazolam 0.75-1.5 mg | 3 | 30% | 3 | 30% | 4 | 4% | 2 | 20% | 2 | 20% | $\frac{5}{10}$ | 50% |
| Clomipramine 25-50 mg | 4 | 40% | 2 | 20% | 1 | 10% | 3 | 30% | 3 | 30% | $\frac{5}{10}$ | 50% |
| Placebo | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | $\frac{0}{10}$ | 0% |

Table 3- Improvement of Negative symptoms by adjunctive drugs in schizophrenic patients .

| Negative Symptoms Drug | Baseline severity of symptoms (SANS) | | | | Beginning of Response to Dosage | | | | | | Maximum reduction of severity | | | |
|---------------------------|--------------------------------------|--------|------------|--------|---------------------------------|--------|--------|--------|--------|--------|-------------------------------|--------|------|--------|
| | Mild 1,2,3 | | Severe 4,5 | | Lower | | Higher | | Linear | | 20%≤ | | >20% | |
| Citalopram | 14 | 70% | 6 | 30% | 3 | 15% | 16 | 80% | 1 | 5% | 20 | 100% | 0 | 0% |
| Alprazolam | 8 | 61.53% | 5 | 38.46% | 4 | 30.75% | 9 | 69.23% | 0 | 0% | 13 | 100% | 0 | 0% |
| Clomipramine | 6 | 42.85% | 8 | 57.14% | 5 | 35.71% | 7 | 50% | 2 | 14.28% | 12 | 85.71% | 2 | 14.28% |
| Placebo | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |

Table 4-Characteristics of improved Negative symptoms in each subgroup

| Drugs \ Negative Symptoms | Number of negative symptoms with positive response | | | | | | | | | |
|---------------------------|--|---------|---------------|---------|---------------|---------|---------------|---------|---------------|---------|
| | 1 | | 2 | | 3 | | 4 | | 5 | |
| | No of patient | Percent | No of patient | Percent | No of patient | Percent | No of patient | Percent | No of patient | Percent |
| Citalopram | 1 | 10% | 4 | 40% | 0 | 0% | 2 | 20% | 1 | 10% |
| Alprazolam | 1 | 10% | 2 | 20% | 0 | 0% | 1 | 10% | 1 | 10% |
| Clomipramine | 1 | 10% | 2 | 20% | 0 | 0% | 1 | 10% | 1 | 10% |
| Placebo | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |

Table 5- Number of improved Negative symptoms in each subgroup

These reductions were discrete and there was not uniform decreasing in all of such symptoms in every patient. Patients who had received placebo did not show any benefit. Only one patient in every subgroup except placebo, showed 20% reduction in severity of all of their negative symptoms. Affective Blunting showed the most and Anhedonia-Asociality the least response in this group. (Table 3,4,5).

In second trial we selected another one hundred (100) patients and divided them into four subgroups . Here we started Bromocripme , Fluoxetine , and Nortriptyline with dosage , of 2.5 mg , 20 mg and 25 mg respectively for the first three subgroups and placebo for the last subgroup .

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 . After three weeks the aforesaid dosages doubled. 37.5% (n=9), 44% (n=11) , 62.5% (n=15) , and 8% (n=20) of patients in subgroups showed 20% reduction in the severity of some of their negative symptoms under the influence of placebo , Bromocriptine , Fluoxetine and Nortriptyline respectively . Only in three patients in the Nortriptyline subgroup and one patient in the Bromocriptine subgroup there was shown 40% improvement of their negative symptoms . Overallly these reductions were taken place discretely among five clusters of such symptoms. There was no difference between mild or severe symptoms regarding their response to the adjunctive drugs .

| Drugs | Affecting Blunting | | Alogia | | Avolition Apathy | | Anhedonia Asociality | | Attention Deficit | | Total | |
|------------------------|--------------------|---------|---------------|---------|------------------|---------|----------------------|---------|-------------------|---------|-----------------|---------|
| | No of patient | Percent | No of patient | Percent | No of patient | Percent | No of patient | Percent | No of patient | Percent | No of patient | Percent |
| Bromocriptine 2.5-5 mg | 3 | 12% | 5 | 20% | 3 | 12% | 3 | 12% | 6 | 24% | $\frac{11}{25}$ | 44% |
| Fluoxetine 20-40 mg | 4 | 16.6% | 4 | 16.6% | 7 | 29.1% | 2 | 8.3% | 10 | 41.6% | $\frac{15}{24}$ | 62.5% |
| Nortriptyline 25-50 mg | 6 | 24% | 9 | 36% | 8 | 32% | 9 | 36% | 10 | 40% | $\frac{20}{25}$ | 80% |
| Placebo | 2 | 8.3% | 6 | 25% | 1 | 4.1% | 4 | 16.6% | 6 | 25% | $\frac{9}{24}$ | 37.5% |

Table 6 - Improvement of Negative symptoms by adjunctive drugs in schizophrenic patients

| Drug | Baseline severity of symptoms (SANS) | | | | Beginning of response to Dosage | | | | | | Maximum reduction of severity | | | |
|---------------|--------------------------------------|--------|------------|--------|---------------------------------|--------|--------|--------|--------|-------|-------------------------------|--------|------|-------|
| | Mild 1,2,3 | | Severe 4,5 | | Lower | | Higher | | Linear | | 20%≤ | | >20% | |
| Bromocriptine | 10 | 50% | 10 | 50% | 12 | 60% | 7 | 35% | 1 | 5% | 19 | 95% | 1 | 5% |
| Fluoxetine | 11 | 40.74% | 16 | 59.25% | 20 | 74.07% | 7 | 25.92% | 0 | 0% | 27 | 100% | 0 | 0% |
| Nortriptyline | 22 | 52.38% | 20 | 47.61% | 29 | 69.04% | 10 | 23.8% | 3 | 7.14% | 39 | 92.85% | 3 | 7.14% |
| Placebo | 8 | 42.10% | 11 | 52.89% | 13 | 68.42% | 6 | 31.57% | 0 | 0% | 19 | 100% | 0 | 0% |

Table 7 - Characteristics of improved Negative symptoms in each subgroup

| Drugs | Negative Symptoms | Number of negative symptoms with positive response | | | | | | | | | |
|---------------|-------------------|--|---------|---------------|---------|---------------|---------|---------------|---------|---------------|---------|
| | | 1 | | 2 | | 3 | | 4 | | 5 | |
| | | No of patient | Percent | No of patient | Percent | No of patient | Percent | No of patient | Percent | No of patient | Percent |
| Bromocriptine | | 4 | 37.37% | 6 | 54.54% | 0 | 0% | 1 | 9.09% | 0 | 0% |
| Fluoxetine | | 6 | 40% | 6 | 40% | 3 | 20% | 0 | 0% | 0 | 0% |
| Nortriptyline | | 4 | 20% | 12 | 70% | 3 | 15% | 0 | 0% | 1 | 5% |
| Placebo | | 4 | 44.6% | 2 | 22.2% | 1 | 11.1% | 2 | 22.2% | 0 | 0% |

Table 8 - Number of improved Negative symptoms in each subgroup

In comparing with placebo , Nortriptyline was the most effective ($P<0.005$) and then Fluoxetine ($p<0.1$) and the last one was Bromocriptine ($p<0.75$) . Attention Deficit in comparing with other negative symptoms responded more frequently to the adjunctive drugs and Affecting Blunting less than others . Only in one patient in the Nortriptyline subgroup all of the negative symptoms showed improvement . (Table 6, 7, 8) .

In the third trial, another thirty (30) patients were divided into three subgroups and 25

mg Maprotiline , 50 mg Fluvoxamine , and placebo were added as adjunctive drugs to their current antipsychotic drugs respectively . After three weeks these dosages doubled . %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 . (table 8,9,10) . This effect was remarkable for Maprotiline in comparing with placebo ($p<0/01$) , and it was greater for Fluvoxamine too ($p<0/1$) .

| Drugs | Improved Negative Symptoms | Affective Blunting | | Alogia | | Avolition Apathy | | Anhedonia Asociality | | Attention Deficit | | Total | |
|-----------------------|----------------------------|--------------------|-----------|----------------|-----------|------------------|-----------|----------------------|-----------|-------------------|-----------|----------------|-----------|
| | | 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% | $\frac{8}{10}$ | 80% |
| Fluvoxamine 50-100 mg | | 5 | 50% | 3 | 30% | 1 | 10% | 3 | 30% | 1 | 10% | $\frac{6}{10}$ | 60% |
| Placebo | | 0 | 0% | 2 | 20% | 0 | 0% | 1 | 10% | 0 | 0% | $\frac{2}{10}$ | 20% |

Table 9 - Improvement of Negative symptoms by adjunctive drugs in Schizophrenic patients

| Drug | Negative Symptoms | | Baseline severity of symptoms (SANS) | | Beginning of response to Dosage | | | | | | Maximum reduction of severity | | |
|-------------|-------------------|--------|--------------------------------------|--------|---------------------------------|--------|--------|--------|--------|----|-------------------------------|------|---|
| | Mild 1,2,3 | | Severe 4,5 | | Lower | | Higher | | Linear | | 20%≤ | >20% | |
| Maprotiline | 3 | 18.75% | 13 | 81.25% | 5 | 31.25% | 11 | 68.75% | 0 | 0% | 16 | 100% | 0 |
| Fluvoxamine | 3 | 23% | 10 | 76.9% | 3 | 23.07% | 10 | 76.23% | 0 | 0% | 13 | 100% | 0 |
| Placebo | 0 | 0% | 3 | 100% | 0 | 0% | 3 | 100% | 0 | 0% | 3 | 100% | 0 |

Table 10- Characteristics of improved Negative Symptoms in each subgroup

| Drugs | Negative Symptoms | | Number of negative symptoms with positive response | | | | | | | | | |
|-------------|-------------------|---------|--|---------|----------------|---------|----------------|---------|----------------|---------|----------------|---------|
| | | | 1 | | 2 | | 3 | | 4 | | 5 | |
| | No of patients | Percent | No of patients | Percent | No of patients | Percent | No of patients | Percent | No of patients | Percent | No of patients | Percent |
| Maprotiline | 3 | 30% | 2 | 20% | 1 | 10% | 2 | 20% | 0 | 0% | | |
| Fluvoxamine | 2 | 20% | 2 | 20% | 1 | 10% | 1 | 10% | 0 | 0% | | |
| Placebo | 1 | 10% | 1 | 10% | 0 | 0% | 0 | 0% | 0 | 0% | | |

Table 11 -Number of improved Negative symptoms in each subgroup

In this sample severe symptoms responded more than mild ones to adjunctive drugs and in %79.41 of cases this improvement was started with higher dosages . There was not any patient with improvement in all of his Negative symptoms , and generally these reductions had been taken place discretely , like the previous trials . (Table 9, 10, 11)

Discussion:

Effectiveness of adjunctive drugs in reducing the severity of Negative symptoms is interesting. In the previous studies by LindenMayer (1990-1993) , positive effects of Clomipramine had been mentioned (5) . Also some improvement by Alprazolam (1.5-5 mg) was seen (7) . Our findings are in harmony with aforesaid results . Clomipramine showed more efficacies with respect to Affective Blunting and Alprazolam had a better effect on Avolition - Apathy . But regarding to Citalopram, Silver (2001) had reported negative results , like Sertraline , and the other studies had focused more on it's positive effects on the treatment of depressive schizophrenic patients . But here the higher efficacy of Citalopram in comparing with Clomipramine and Alprazolam in this sample and trial is interesting , since its side effects and pharmacokinetic interactions in comparing with tricyclics and Benzodiazepines are more safe and tolerable . On the other side , in regard to Bromocriptine , wolf (1992) had found positive results in one study (in combination with neuroleptics) and negative results in other two studies (without neuroleptics) (6) .

Leviminzi (1991) , too , had similar findings , like the first study . Wolf also report-

ed remarkable positive effects of Bromocriptine on Anergia (one of the items in BPRS) . But according to our findings , the most effect of Bromocriptine was on Attention Deficit and then on Alogia (two items in SANS) . King (1978) and Cutlaz (1992) also reported positive effects of Bromocriptine, But without neuroleptics (5) . Regarding to the effectiveness of Fluoxetine, its positive effects had been reported by Silver (1992) , Coff (1991) and LindenMayer (5) . According to our findings Fluoxetine was more effective than placebo in reducing the severity of negative symptoms and its most effect was on Avolition - Apathy, and its least effect was on Anhedonia - Asociability . With respect to Nortriptyline , which had the most positive effect is our second trial , although there was positive reports about Imipramine (Siris , 1990) , Mianserin (Mizoky x , 1992) and Amitriptyline (Prusof , 1989) , but we did not find any research regarding the effectiveness of Nortriptyline on negative symptoms (5,6,7) . According to our findings , Nortriptyline was remarkably more effective than placebo ($p<0.005$) and other compared drugs in its group and it's most effectiveness in this sample was on Attention Deficit . Regarding Maprotiline and Fluvoxamine , our findings were similar to Yamagami (1989) and Silver (1992) respectively (5) . The most effect of Maprotiline was on Alogia and Anhedonia - Asociability , and regarding fluvoxamine , it was on Affective Blunting . Neither of patients in our three aforesaid trials had suffered any important side effects of adjunctive drugs and none of them had showed any worsening of positive symptoms , due to appropriate antipsychotic coverage prior to trials. Maybe longer duration and higher dosage of adjunctive

drugs could result in better response in this regard .

Conclusion :

Conservative prescription of adjunctive drugs can be a useful strategy for making schizophrenic patients more prone to psychosocial interventions and in consequence increasing the effectiveness of rehabilitative programs .

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