

Effects of Bromocriptine on Negative Symptoms of Schizophrenia: A Double Blind Clinical Trial

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Received May 15, 2002; Revised July 11, 2002; Accepted July 16, 2002

This paper is available online at <http://ijpt.iums.ac.ir>

ABSTRACT

Negative symptoms are still a major obstacle in the recovery of schizophrenic patients. Many attempts to develop novel drugs affecting negative symptoms of schizophrenia have yielded insignificant results. This study evaluates the effects of bromocriptine, a dopamine agonist, on negative symptoms of schizophrenia utilizing a placebo-controlled crossover double-blind clinical trial. **Methodology:** To eliminate interfering factors, only patients with significant negative symptoms who did not have signs of depression, drug side effects, active psychosis, significant somatic diseases, substance abuse, or contraindications for bromocriptine were included. Among 61 patients, only 14 fulfilled inclusion criteria, two of them refrained from taking part. Patients were randomly divided into test and placebo groups and were treated for 13 weeks; for 6 weeks the test group received bromocriptine and the other received placebo, followed by a one week wash-out period during which both groups received placebo, after that groups were exchanged. Subjects were treated with 15 milligrams of bromocriptine and tested with Positive and Negative Syndrome Scale (PANSS), which is a standard test for measuring positive and negative symptoms of schizophrenia. Data analyzed using Wilcoxon sign-rank test. **Conclusions:** This trial showed that addition of bromocriptine to antipsychotic drugs did not increase the risk of psychosis and reduced negative symptoms of schizophrenia.

Keywords: *schizophrenia, negative symptoms, dopamine agonist, bromocriptine*

Schizophrenia is considered one of the most important psychiatric disorders as the disorder disrupts patient's performance, as well as continuously affecting patient's family who have to cope with and care for the patient for many years. As a result, the disorder not only imposes significant psychological stresses on the family, but also treatment-costs puts a great financial burden on them. Hence, treatment of schizophrenia must be comprehensive and appropriate such that in addition to remission of symptoms, caregivers also experience little psychological and financial stress [1]. One of the most important therapeutic approaches to schizophrenia has been the use of antipsychotic drugs; the success rates were high enough that their use has grown significantly during last fifty years. Classic antipsychotics have significant effects on delusions and hallucinations, and little effects on other symptoms.

In the 1980, Crow differentiated two types of schizophrenic symptoms on the basis of neurobiological observations [2]: type I (positive symptoms) which Crow believed were caused by an increase in the activity of dopaminergic system; and type II (negative symptoms) are caused by structural brain abnormalities.

During 1980s, many studies confirmed validity of classification of schizophrenia into positive and negative domains. In spite of Crow's assumption that the cause of negative symptoms was cellular destructions, Opler et al, showed that although negative symptoms are distinct from positive symptoms, they might be caused by biochemical processes rather than pure anatomical lesions [2].

If negative symptoms are irreversible, then there is no point in trying to alleviate them. However, if they are reversible, then search for neuropsychological aspects of, and pharmacological strategies to treat them must be followed aggressively.

The progress in drug therapy achieved to date has mainly focused on the antipsychotic effects of these drugs. In most clinical studies, attention has focused on the hallucinations and thought disorders and as a target for develop of new drugs, and as a domain needing independent considerations, negative symptoms have received little attention. 'Blunted affect, poverty of speech, thought blocking, poor grooming, lack of motivation, and anhedonia are the most common negative symptoms [1, 2]. Studies conducted on the treatment of

negative symptoms have mainly added the drug of interest to the neuroleptic regimen; most of them were open and uncontrolled.

One possible therapeutic approach is the use of dopamine agonists. The rationale for this approach is the assumption that dopamine activities are reduced in mesocortical tracts [4]. Dopamine agonists, dopamine re-uptake inhibitors, and dopamine precursors were used for this purpose.

Trials in this area were productive. But most of them were case-studies and few of them were adequately controlled [2, 5]. This study with a double-blind design, and controlling many possible confounding variables, evaluates the effects of bromocriptine, a dopamine agonist, on negative symptoms and compares them with those of placebo.

METHODOLOGY

The present study employs a double-blind clinical intervention design, using placebo, as well as crossing over patients between experimental and control groups.

All of the participants were chosen from a pool of patients at the follow-up unit of Shahid Esmaili psychiatric center. In this unit, schizophrenic patients were treated with depot antipsychotics for several years. A rigid inclusion criteria were adopted to minimize possible confounding variables:

1. Prominent negative symptoms, judged by ratings higher than 61 obtained from Negative subscale of PANSS (Positive and Negative Syndrome Scale).
2. Absence of frank depression, judged by clinical interview and ratings lower than 65 on Depression subscale of PANSS.
3. Absence of neuroleptic side effects on the basis of clinical evaluation.
4. Absence of active psychosis, i.e. hallucinations and delusions with significant behavioral effects, as reflected by ratings of 65 or lower on Positive subscale of PANSS.
5. Absence of debilitating physical illness, determined by past medical records and history taken from patients' families, which might resemble the negative symptoms of schizophrenia (e.g. Parkinson's disease).
6. Absence of a history of substance abuse one month prior to the study (except for nicotine and caffeine).
7. Treatment with stable antipsychotic regimen equivalent to 200 to 1000 milligrams per day of chlorpromazine during six months prior to the study, and a stable dose of anticholinergic drugs equivalent to 4 to 8 milligrams per day of trihexyphenidyl.
8. No treatment with antidepressants (i.e. tricyclics, monoamine oxides inhibitors, serotonin specific re-uptake inhibitors), antihypertensive drugs (co-administration with bromocriptine is contra-indicated), lithium, and ergot alkaloid drugs at the time of study.

9. Absence of documented history of diseases in which bromocriptine must be used with caution; i.e. liver disease, ischemic heart disease, or heart failure.

According to the above-mentioned criteria, only 14 patients out of 60 qualified for the study and two refrained from taking part. Average age of volunteers was 39.9 years, which were randomly divided into two groups of 6 volunteers. Groups were randomly divided to controls and tests. Preparations used were bromocriptine and its placebo formulated by its producer in Iran (Pars Minoo Industries). Bromocriptine was administered at 5 mg three times a day (morning, noon and evening) after food. Evaluation was performed using PANSS test and its structured clinical interview, SCL-PANSS, which were developed by Kay et al. Various studies have confirmed the reliability of this test [6, 7, 8].

PANSS test is a 33 item tool, which covers 5 major scales, namely, Positive, negative, composite, general and complementary psychopathology and a minor scale, risk of hostility, which are independently scored.

Informed consent was obtained from relatives of each subject and treatment was started randomly with bromocriptine or placebo. The study was conducted in two 6-week stages with a one-week period in between. During the first six weeks, group I received placebo while group 2 received bromocriptine. For one week (wash out period) both groups received placebo and then groups were exchanged for another 6 weeks.

During the study, subjects were examined by a psychiatrist and a psychologist to assess the possible presence of drug side effects (beginning and end of 3rd, 6th, 7th, 10th and 13th week). Before the beginning of the study, the families of the subjects were provided with a leaflet including information on the drug and its administration. PANSS test was performed at the beginning and end of each 6 weeks period.

Information regarding status of each subject was obtained from a single person in charge of looking after the patient during the study. All subjects continued their antipsychotic and anticholinergic medications as prior to the study.

Obtained data were compared as T scores (standard scores obtained from PANSS test) and were analyzed using two different approaches. In first approach, scores of the test and placebo groups were compared in the first and second 6-week stages (a comparison of drug and placebo). In the second approach, in order to increase the sample size, averages of the scores of each group, only when given drug not placebo, were compared with the scores of the same group before starting of study. In this approach, the placebo scores were not calculated.

Statistical analysis was performed using SPSS software and due to the small number of samples, Wilcoxon's non parametric sign-rank test was utilized. In Wilcoxon's method, the 'ranks' not 'means' are compared thus standard deviation is not calculated and not stated in the study.

RESULTS

Twelve patients participated in the study; 9 men and 3 women with an average age of 39.9 years (25-55 years). All patients were unemployed, 2 married, 1 divorced and 9 single. Mean duration of disorder was 17.9 years (8-33 years). Patients were averagely hospitalized 3.9 times (1-10 times) while none of them were hospitalized one year prior to the study. Eleven patients were receiving fluphenazine decanoate and one received chlorpromazine. All patients were taking oral antipsychotic preparations such as chlorpromazine, perphenazine and thiothixene. Average daily antipsychotic (oral and parenteral) dose was 683 mg (200-1000 mg/day) in addition to 4-6mg trihexyphenidyl or biperidine. 4 subjects took diazepam 10mg/day. 1 patient was excluded from the study at the end of the second week due to the occurrence of drug side effects.

Table 1. Average I score of PANSS test prior to study.

Parameter	Group 1	Group 2	Significant
Negative scale	71.3	66.5	NS*
Positive scale	48.3	47.5	NS
Combined scale	34.3	36.8	NS

* Non Significant.

Table 1 shows average positive, negative and combined T scores of PANSS test: the two groups showed no difference prior to beginning of the study indicating true random distribution.

Table 2 shows data obtained from comparison of positive and negative scores as well as comparison of data before and after the study. No significant difference was detected in negative scale scores before and after treatment. In the second approach, in which both groups were considered as one group and their data compared before and after the study, a significant difference was noted. Positive scale showed significant differences in neither approach while combined scale depicted significant difference between the two groups in the second 6-week stage as well as compared to pre-study data using the second approach.

DISCUSSION

Data obtained point out a significant difference between the two groups in the second approach of comparison ($p = 0.02$). It is noteworthy to mention that placebo shows some level of therapeutic effect and on the other hand, patients in the second group had not taken their medications adequately as indicated by the number of returned medications. It appears that the above-mentioned points and the small number of subjects explain the ineffectiveness of therapy in the 1st comparison

approach. However, by increasing the sample number in the second comparison approach, the difference became significant. Results of this study are compatible with those published by Davis et al., Angrist et al., Von Knorring and Boronow using oral or parenteral amphetamine [2, 4, 5]. In a study conducted by Gattaz et al., using bromocriptine and placebo (2-3 mg/day) for three weeks utilizing Brief Psychiatric Rating Scale (BPRS) no significant difference was observed regardless of some improvements in the status of the patients.

The insignificance of results may be due to the insufficient dose of bromocriptine or short treatment course. Levi-Minzi showed considerable improvement in the negative symptoms by administration of higher bromocriptine doses (10-20 mg/day), which was persistent in long term as well [9, 10].

It is also shown in this study that bromocriptine does not affect positive symptoms. In other words, bromocriptine does not exacerbate psychosis. This is in accordance with results published by Perovich et al. and Levi-Minzi et al. [10, 11].

Data in composite subscale of PANSS are rather interesting. The difference between the means of 'T' scores in combined scale was significant in the second 6-week stage and in total comparison. It can be inferred that combined scale is a more sensitive tool since it is compiled from two sets of data. On the other hand, according to our data, positive scales were non significant in both approaches meaning that decreased combined score is due to lower negative scale scores not increased positive scores.

From this study and similar research, it is assumed that addition of a precursor or dopamine agonist to a neuroleptic drug regimen not only does not increase the risk of worsening psychosis but also decreases the negative syndromes in some patients.

Despite suggestions made by Meltzer, recommending administration of dopamine agonists parallel to antipsychotic agents, it is believed that further controlled studies are needed to assess the long-term effects and possible side effects of these agents.

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Table 2. Companion of average I scores of PANSS test between the two groups during the 1st and 2nd six-weeks (1st approach) and between all patients before and after treatment with bromocriptine (2nd approach). M₁: average score of group 1. M₂: average score of group 2. M_p: average score of all subject prior to study. M_i: average score of all subjects during treatment C_t: all patients before and after treatment.

	1 st six-weeks			2 nd six-weeks			C _t		
	M ₁ (n = 6)	M ₂ (n = 6)	p	M ₁ (n = 6)	M ₂ (n = 5)	p	M _p (n = 12)	M _i (n = 11)	p
Negative scale	58.3	65.0	NS*	50.2	59.2	NS	66.8	58.3	0.02
Positive scale	44.9	47.7	NS	50.0	45.3	NS	47.9	48.7	NS
Combined scale	39.3	38.5	NS	50.2	38.0	0.01	35.6	43.8	0.02

* Non Significant.

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