ORIGINAL ARTICLE

An Open Label Study on Amisulpride In Augmentation with Atypical Antipsychotics in Treatment Resistant Schizophrenia and Schizoaffective Disorders

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Abstract: The authors report an open label study in treatment resistant patients of schizophrenia, schizoaffective disorders. The patients who were earlier being treated with atypical antipsychotics, were put on combination of amisulpride and atypical antipsychotics and efficacy, safety of combination was assessed. A study of 6 weeks duration was conducted on 30 outdoor patients (9 women, 21 men). The mean dose of amisulpride used was from 250.00 mg/day ± 91.65. SAPS, SANS, CGI-S scales were applied. 4 patients dropped out of study. Remaining 26 patients completed 6 weeks duration. There was significant improvement in negative symptoms, positive symptoms especially in old chronic schizophrenics. Only two patients developed extrapyramidal symptoms. The dose of amisulpride used in both patients was 200 mg/day. The combination of amisulpride with atypical antipsychotics is a promising option in patients who are resistant to treatment.

INTRODUCTION

Despite the various treatment options for schizophrenia, about 30% of patients have partial or no response to pharmacotherapy. Clozapine is drug of choice in patients who are treatment resistant, with clozapine 40-70% of patients show adequate response or slow clinical improvement. This problem of treatment resistance is a big problem. Clinicians have considered various approaches to solve this problem. Usual approaches include switching treatment resistant patients from a classic neuroleptic drug to an atypical antipsychotic or to any alternative typical agent, the use of electroconvulsive therapy. Other options are adding another psychotrophic drug such as a benzodiazepine, lithium, an anticonvulsant or combining high and low potency medications.

Antidepressants combination as a treatment of resistant depression is widely used and is effective, but regarding resistant schizophrenia, polypharmacy is still controversial. Since the development and introduction of atypical antipsychotics into routine clinical management, the use of antipsychotic drug combinations to treat schizophrenia has appeared to gain new impetus. The newer atypical antipsychotics exhibit more novel neuroreceptor profiles, which lead to the hypothesis that combination with either typical or atypical antipsychotic medications would provide a more efficacious profile. There are studies reporting efficacy of contribution of antipsychotics in treatment resistant schizophrenia. In daily clinical practice upto a quarter of patients are taking two drugs. We cannot predict beforehand which medication regimen or drug combination will be effective.
Every antipsychotic has its own affinities for different receptors. For example, clozapine has high affinities for 5-HT2a, 5-HT2c, 5-HT7, M1-M5, alpha 1 and alpha 2–adrenergic, muscarinic, histaminic H1 receptors and dopamine D1, D3 (relatively weak), and D4 receptors. Risperidone’s affinity is related mainly to 5HT2, dopamine D2, norepinephrine alpha 1. Olanzapine affinity is very close to that of clozapine—high affinity for 5HT2a, 5HT7, M1-M5, H1 receptors.

In contrast, amisulpride, another atypical antipsychotic, possesses a unique pharmacological profile and is characterized by a selective interaction with dopamine D2/D3 receptors. Moreover, amisulpride is supposed to ameliorate negative symptoms at low dose. This drug does not lead to weight gain and is associated with fewer extrapyramidal side effects as compared to conventional neuroleptics.

Furthermore, several recent studies have demonstrated that a combination of amisulpride and olanzapine or clozapine may be useful in treatment resistant schizophrenic patients.

The aim of present study was to investigate whether amisulpride was effective as add on treatment with other atypical antipsychotics in management of treatment resistant patients of schizophrenia, schizoaffective disorders.

METHODS

In this open label study, we examined the clinical records of resistant patients suffering from schizophrenia and schizoaffective disorders. These patients had persisting positive negative symptoms and they were already on treatment with atypical antipsychotics (clozapine, olanzapine, risperidone) as monotherapy or polypharmacy. Total 30 outdoor patients were included for trial (9 women, 21 men). Age group ranged from 18-65 years. Patients suffering from organic mental disease, epilepsy, pregnant females, lactating mothers, patients having history of substance abuse were excluded from trial. 4 patients dropped out of study and 26 completed the 6 weeks duration. Out of these patients, many patients had marked deterioration during course of illness and completely dependent for financial support on others. The following data were extracted from the medical records: age, gender, ICD-10 diagnosis, time of onset of illness, previous treatment history, rationale for combination therapy and side effects. Before conduction of clinical trial, informed written consent was taken from patients and relatives of patients. Thorough clinical and psychiatric examination of all patients was conducted before inclusion in clinical trial. Summarised data are provided in Table 1.

As there had been no significant improvement in persisting positive and negative symptoms with treatment which was already going on, improvement was assessed on basis of impairment in social, occupational, interpersonal functioning as per information collected from their family members. It was decided to shift them to amisulpride. Amisulpride was added to ongoing treatment with a starting dose of 50-100 mg/day (depending on predominance of negative and positive symptoms) and its dose was increased by 50-100 mg every week if clinical state was not improved. After an improvement of symptoms, an attempt was made to reduce the dosage of earlier medication. Maximum dose of amisulpride reached was up to 400mg/day only. Dose of amisulpride was chosen according to collaborating centre for drug statistics methodology recommendations. Study was conducted for total duration of 6 weeks. Patients were followed up every week. Clinical improvement was evaluated with scale for assessment for positive symptoms (SAPS), scale for assessment of negative symptoms (SANS) and clinical global impressions – severity of illness scale (CGI-S).
RESULTS
Total 26 patients completed the 6 weeks duration of trial. Among them were 19 males and 7 female patients. Mean age was 31.42 years ± 11.16 ranging between 18 and 65 years. Following the ICD-10 classification, 21 patients were suffering from schizophrenia (F20.0), 5 were having schizoaffective disorder (F25.0). Patients were treated with the combination of amisulpride (dose 50-400 mg/day, mean dose 250.00 mg ± 91.65), and clozapine (mean dose 300 mg, 6 patients), or olanzapine (mean dose 22.25 mg, 10 patients) or risperidone (mean dose 5.6 mg, 10 patients). Only two patients developed side effects, dose of amisulpride in these patients was 200 mg per day. 1 developed parkinsonism and another developed trismus.

Mean baseline score on SAPS scale was 35.77 ± 16.54 which reduced to endpoint mean score of 4.69 ± 9.98 at completion of 6 weeks. Whereas on SANS scale, baseline mean score was 103.73 ± 20.55 which decreased to endpoint score of 23.12 ± 25.73 at 6 weeks.

The therapeutic effect was retrospectively evaluated according to differences between the clinical assessment before combination therapy and after 6 weeks of treatment.

Disappearance or persistence of only a few psychotic symptoms with full resocialisation (+++) was considered as major improvement; partial improvement of some psychotic and negative symptoms (+) was defined as marked improvement; clinically marginal changes were considered as minor improvement (+); no change (0), or deterioration of mental state (-).

The mental state of 25 patients treated with combination improved. 10 patients, (38.46%) had marked improvement and 1 patient (3.8%) had mild improvement. Only one patient showed no change in his mental state. In 14 patients (53.84%), there was an amelioration of positive and negative symptoms including improvement of daily functioning. No patient demonstrated worsening of mental symptoms.

DISCUSSION
Resistance or nonresponsiveness to antipsychotic treatment is a significant problem in management of schizophrenic patients. Failure of at least 2 antipsychotic drugs in adequate dose and duration of treatment is generally required to consider a patient refractory to treatment, although some researchers believe that the length of an adequate drug trial is difficult to define.

Ideally, combination of psychotropic drugs should be offered in only those cases in whom monotherapy with different classes of typical antipsychotics or atypical antipsychotics was ineffective. In clinical practice, different combinations of psychotropic drugs are used only for a relatively small group of patients who have failed with conventional methods of psychopharmacotherapy and are resistant to atypical antipsychotics.

For example, Munro et al treated 33 schizophrenic patients resistant to clozapine with combination of clozapine and amisulpride in an open label nonrandomized study. The authors concluded that coadministration of amisulpride in patients who are partially or nonresponsive to clozapine may lead to a substantial improvement in positive and negative symptoms without side effects.

The mechanisms underlying the combined action of antipsychotics remain unclear. Amisulpride is considered a highly selective dopamine D2/D3 receptor antagonist that binds preferentially to receptors in mesolimbic system, it probably supplements the relatively broad receptors interactions of other antipsychotics, resulting in synergistic therapeutic potency without increasing the side effects. Bergemann et al reported about the elevation
effect of amisulpride as a result of combination with clozapine.

In our study, it was observed that majority of patients were either very much or much improved as a result of combined treatment. Tolerability was good; only two patients developed extrapyramidal symptoms. There was improvement in both positive and negative symptoms along with improvement in overall cognitive status of patients. Of male patients have started earning money to support their family members. In these patients, improvement is remarkable. Others patients are also able to look after themselves. only one patient has not shown any improvement. Out of side effects with this combination observed are trismus in one patient and parkinsonism in another patient. Except for these no other side effect was noticed.

Our study demonstrates that addition of amisulpride to previous antipsychotic medicine may benefit a subgroup of chronic schizophrenic patients nonresponsive or partially responsive to clozapine or other atypical antipsychotics. Our results coincide with data of previous publications regarding coadministration of amisulpride with olanzapine and clozapine.

One more commonly cited problem in discussions about polypharmacy is the cost of such treatment. Of course, the combination of 2 atypical antipsychotics is expensive, but prolongation of hospitalization is also expensive. The opportunity to reduce the length of stay by this combination therapeutic approach may reduce total cost of whole treatment significantly. Polypharmacy for bipolar disorders is considered as an acceptable and modern approach. The use of the antipsychotic combinations for the management of treatment resistant patients may prove to be equally optimal.

The results of our study show that there are treatment resistant schizophrenic patients, who may be successfully managed with a combination of amisulpride and other antipsychotic medications with few side effects. However, Further prospective, systematic, controlled, randomized and double blind clinical studies including only nonresponding schizophrenic patients are needed.

REFERENCES


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