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Comparison of Clozapine-Amisulpride and Clozapine-Quetiapine Combinations for Patients With Schizophrenia Who Are Partially Responsive to Clozapine: A Single-Blind Randomized Study

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ABSTRACT

Schizophrenia is a devastating psychiatric disorder. Clozapine has long been the gold standard for treatment of patients with treatment-resistant schizophrenia; however, some patients are only partially responsive to clozapine treatment. Augmentation of clozapine treatment might enhance its effectiveness in partial responders, but only a few studies have investigated possible augmentation strategies. This study compared the effectiveness and tolerability of the combination of amisulpride and clozapine with the combination of quetiapine and clozapine in patients who were only partially responsive to clozapine monotherapy. Fifty-six treatment-resistant patients who were partially responsive to clozapine were randomly assigned to receive amisulpride or quetiapine along with an ongoing stable dose of clozapine. Fifty patients completed the study. Patients were evaluated at baseline and at the first, third, sixth, and eighth weeks. Efficacy measures consisted of the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Scale for the Assessment of Positive Symptoms (SAPS), and the Clinical Global Impression (CGI) scale. Tolerability and adverse effects were assessed with the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale and the Simpson Angus Scale (SAS). A substantial improvement occurred in both groups by the end of the eighth week; however, the improvement associated with amisulpride was

1037

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significantly greater than that seen with quetiapine. This difference was noted as early as the third week of follow-up in terms of CGI scores, and by the sixth week with regard to BPRS, SANS, and SAPS scores. Both drugs were well tolerated, as measured by UKU and SAS. Improvement favoring clozapine+amisulpride could be attributed to the selective D2/D3 binding property of amisulpride, which had an additional effect in improving symptoms of schizophrenia. The authors concluded that amisulpride seems to be effective and well tolerated for augmentation purposes in clozapine-resistant patients.

Keywords: schizophrenia; augmentation; clozapine; amisulpride; quetiapine; efficacy; tolerability; BPRS; SANS; SAPS

INTRODUCTION

Schizophrenia is a devastating psychiatric disorder. Its lifetime prevalence is known to be 1% to 1.5%. Recurrent psychotic attacks may result in functional impairment and a poor outcome. The aim of treatment, therefore, is to relieve these attacks and to prevent further attacks. This can only be achieved if patients take the prescribed medication, which should be effective and have tolerable adverse effects. Despite the effectiveness of antipsychotic medications in the treatment of patients with schizophrenia, 30% to 50% of patients who receive adequate treatment with typical antipsychotic drugs have significant persistent symptoms.[1-5] Of these treatment-resistant individuals, 40% to 70% do respond to clozapine,[6] but for the remaining patients, treatment options are very limited. Thus, treatment-resistant psychosis is an important and difficult problem.

In many studies, criteria for treatment-resistant schizophrenia have included (1) resistant positive psychotic symptoms (at least 2 of 4 positive symptom items on the Brief Psychiatric Rating Scale [BPRS] should be rated at >4 points; clinical severity of the disorder should be at least moderate [>45 points on the 18-item BPRS; Clinical Global Impression [CGI] score should be >4 points]), (2) poor social and occupational functioning over the past 5 y, and (3) inadequate response to at least 2 different treatment options (lack of a ≥20% decrease in BPRS scores in spite of antipsychotic use for an adequate time and at an appropriate dose).[2,7,8]

Clozapine has long been the gold standard in the treatment of schizophrenic patients who are unresponsive to other psychopharmacologic treatment regimens. It has a low affinity for dopamine D2, exhibits selective antagonism for 5-HT_2, which increases available dopamine, and demonstrates antagonism on adrenergic α_1- and muscarinic receptors; therefore, it decreases both positive and negative symptoms of schizophrenia, thus improving patient quality of life.[9] Good clinical improvement has been attained by treatment-resistant patients who received clozapine. Yet, some patients who are on clozapine treatment are only partially responsive. Augmentation of clozapine treatment with another antipsychotic might offer improved effectiveness among partial responders.

For augmentation purposes, several clozapine adjunctive agents have been used to enhance the antipsychotic efficacy of clozapine.[10-12] Various antidepressants such as fluoxetine and fluvoxamine,[13,14] mood stabilizing agents like lithium,[15] novel anticonvulsants such as lamotrigine,[16] and several other agents like glycine[17] and

mazindol[18] have been tried as clozapine adjuncts to address resistant positive, negative, or cognitive symptoms. For most of these compounds, evidence regarding effectiveness has been derived from open-label trials and case studies; therefore, the results are confounding.

Conventional or novel atypical antipsychotics are among the most commonly used adjunctive agents. Augmentation with amisulpride in a controlled, randomized trial resulted in a 50% improvement in positive and negative symptoms among clozapine partial responders within a few weeks.[19] Risperidone has also been tried for augmentation purposes, but the results have been controversial.[20-22] Amisulpride, which has a unique pharmacologic profile, is characterized by selective interaction with dopamine D2/D3 receptors.[23,24] Augmentation with amisulpride in an open, nonrandomized study in 28 patients who were partially resistant to clozapine led to substantial improvement in positive and negative symptoms without worsening of the adverse effect burden.[25] Other studies have shown the beneficial effects of amisulpride and clozapine given in combination.[26,27]

To date, quetiapine, another atypical antipsychotic agent that is similar to clozapine in receptor profile but does not cause severe adverse effects, has not been studied in clinical trials for augmentation purposes in clozapine-resistant patients. Its structural similarity to clozapine, however, warrants investigation of its potential augmentative action, at least in patients in whom clozapine cannot be titrated to maximum doses because of its limiting adverse effects, including seizures and anticholinergic and cardiovascular adverse effects. To date, no study has compared the efficacy of amisulpride with that of quetiapine when used as an adjunctive agent in clozapine-resistant patients.

This study was conducted to compare the effectiveness and tolerability of the combination of amisulpride and clozapine with the combination of quetiapine and clozapine in patients who were only partially responsive to clozapine monotherapy.

METHODS

Patients

Inpatients and outpatients who continued to experience psychotic symptoms despite adequate treatment with clozapine were eligible to participate in this trial. Study participants were recruited from a large population of university hospital inpatients and outpatients from January 2004 to March 2005. Thorough records of psychiatric history and prior antipsychotic drug therapy for all patients were made available to investigators. Inclusion criteria were as follows: (1) a DSM-IV *(Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)*[28] diagnosis of schizophrenia; (2) age between 18 and 50 y; (3) partial response to at least a 12-wk trial of 400 to 600 mg/d of clozapine (partial response was defined as persistent psychotic symptoms, as evidenced by a total score >45 on the BPRS [on which each of 18 items is scored from 1 to 7] or a rating of moderately ill [>4] on at least 2 of the 4 BPRS positive symptom items [hallucinatory behavior, conceptual disorganization, unusual thought content, and suspiciousness]); and (4) voluntary participation in the study with signed informed consent.

Patients with comorbid substance abuse, organic mental disorders, epilepsy, mental retardation, and severe physical illness were excluded from the study.

Study Procedures

All patients who were partially responsive to clozapine treatment who were willing to participate in the study were assessed by the first author. Patients were studied by the second author for random assignment after inclusion criteria had been met. To be included in the 8-wk follow-up study, patients had to have remained on a stable dose of clozapine for at least 4 wk. Patients who were not on a stable clozapine dose for at least 4 wk were randomly assigned only after this period was completed. After completing 4 wk of stable clozapine treatment, patients were randomly assigned by the second author to the clozapine and amisulpride group or the clozapine and quetiapine group. Drug follow-up was performed by the second author, and all tests were administered by the first author. The first author, who was the rater, remained blinded to the medication throughout the study. All patients were fully informed about the benefits, risks, and potential adverse effects associated with participation in this study, and all signed an informed consent document. Patients remained in their current living arrangements with no study-related modifications made to their daily routines beyond regularly scheduled clinical rating sessions. Patients were evaluated at baseline and at the first, third, sixth, and eighth weeks. Baseline doses of clozapine were established by the second author and remained stable throughout the study. The final maximum doses to be titrated were 900 mg/d for quetiapine and 600 mg/d for amisulpride at the end of the second week. Patients judged by the second author to be unable to tolerate the dose escalation schedule because of adverse effects (other than clinical symptoms of schizophrenia) were maintained at their maximum tolerated dose for the remainder of the study.

Patient Assessments

Systematic evaluations of psychopathology and adverse events were completed at baseline and at the first, third, sixth, and eighth weeks. Assessments were performed primarily by the first author—a senior research fellow who had been blinded to treatment assignment and was not directly involved in patient care.

Efficacy evaluations included (1) the BPRS[29,30]; (2) the Scale for the Assessment of Negative Symptoms (SANS), which assessed negative symptoms of schizophrenia[31]; (3) the Scale for the Assessment of Positive Symptoms (SAPS), which measured positive symptoms of schizophrenia[31]; and (4) the CGI.[32] Tolerability and adverse effects were assessed with the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale,[33] a 52-item scale that measures adverse effects and tolerability related to psychotropic medication, and the Simpson Angus Scale (SAS),[34] which measures movement disorders related to the use of psychotropic drugs. Results of a full biochemistry test panel, a urinalysis, and hematologic studies were obtained before patients were randomly assigned and again at the end of the study.

Statistical Analysis

The primary objective was to test the hypothesis of differential clinical efficacy between the clozapine with amisulpride group and the clozapine with quetiapine group. A priori planned comparisons used between-group repeated measures analysis of variance based on group (the 2 treatment groups) and time (first, third, sixth, and eighth weeks) as main effects. Specific 2-group comparisons across time consisted of

BPRS total scores, SANS total scores, SAPS total scores, CGI improvement scores, SAS scores, and UKU scores.

Within-group differences were computed with the use of paired sample *t* tests. Between-group differences on baseline measures such as test scores and demographic variables were determined by independent sample *t* test or χ^2 test, when appropriate. All significance tests were performed, and 2-tailed probabilities with an alpha level of .05 were used.

RESULTS

Fifty-six patients who were partially responsive to clozapine treatment entered the trial and were randomly assigned in equal numbers to receive clozapine combined with amisulpride or quetiapine. Six patients (5 from the clozapine+quetiapine group and 1 from the clozapine+amisulpride group) discontinued the study protocol within the first 2 wk. Reasons for discontinuation of combination treatment in the clozapine+quetiapine group consisted of exacerbation of psychotic symptoms in 4 patients and an unwillingness to continue treatment because of lack of efficacy in 1 patient. One patient in the clozapine+amisulpride group was missed in follow-up after the second week; therefore, this patient was also excluded from the analysis. A total of 50 patients (23 from the clozapine+quetiapine group and 27 from the clozapine+amisulpride group) who were able to complete the 8-wk follow-up were assessed for statistical analysis. Background characteristics of patients in the 2 groups were similar (Table).

Demographic and Clinical Characteristics of Study Patients

Characteristics	Augmentation Groups: Clozapine+Amisulpride (n=27)		Clozapine+Quetiapine (n=23)		Analysis
	n	%	n	%	χ^2 *(P)*
Sex					
Male	12	44.4	9	39.1	.704
Female	15	55.6	14	60.9	.704
	Mean	**SD**	**Mean**	**SD**	***t* test *(P)***
Age, y	37.29	8.17	7.30	8.18	.997
Initial clozapine dose, mg/d	550.00	127.09	536.95	125.42	.718
Age at first hospitalization, y	23.07	5.58	22.60	5.65	.778
Duration of illness, y	15.66	6.98	15.69	6.90	.988
Initial BPRS score	50.55	3.59	48.69	3.00	.056
Initial CGI severity score	5.18	0.55	5.04	0.63	.406
Initial SAPS score	64.70	7.86	60.17	11.04	.098
Initial SANS score	58.92	8.03	59.60	3.81	.711
Initial UKU score	17.88	6.17	18.43	5.36	.742
Initial SAS score	2.18	0.68	2.04	0.70	.474

Mean doses of the drugs added to clozapine were 437.03 mg/d (standard deviation [SD]=104.32) for amisulpride and 595.65 mg/d (SD=125.21) for quetiapine. These doses are equivalent to 437.03 mg/d chlorpromazine for amisulpride and 446.73 mg/d chlorpromazine for quetiapine[35]; resultant test score values were similar in terms of chlorpromazine equivalent doses (t=0.357; df=48; P=.723).

A comparison of final test scores within groups with reference to baseline scores yielded a significant reduction in BPRS (t=9.84; df=26; P=.0001), SAPS (t=7.694; df=26; P=.0001), and SANS (t=7.214; df=26; P=.0001) scores and improvement in CGI (t=9.603; df=26; P=.0001) scores by the end of the eighth week of follow-up in the clozapine+amisulpride group. Adverse effects measured by the UKU (t=2.964; df=26; P=.006) were significantly higher than baseline scores at the end of the eighth week in the clozapine+amisulpride group; however, this significant increase in adverse effects was not visible in SAS scores (t=1.586; df=26; P=.125) reported at the end of the eighth week.

In the clozapine+quetiapine group, at the end of the eighth week, there were statistically significant reductions in BPRS (t=2.148; df=22; P=.043) and SANS (t=3.656; df=22; P=.001) scores compared with baseline. In terms of SAPS scores, no change in positive symptoms was seen by the end of the eighth week compared with baseline scores (t=0.335; df=22; P=.741). Improvement as measured by CGI was statistically significant at the end of the eighth week compared with baseline (t=2.554; df=22; P=.018). No statistically significant difference in adverse effects was seen in UKU (t=1.283; df=22; P=.213) and SAS (t=1.817; df=22; P=.083) scores at the end of the eighth week compared with baseline.

A comparison of the reduction in BPRS, SANS, and SAPS scores between groups favored the clozapine+amisulpride group. As seen in Figure 1, the reduction in BPRS scores in the clozapine+amisulpride group was greater than that reported in the clozapine+quetiapine group (F=8.59; df=4; P<.001). This difference resulted from differences in measurements obtained during the sixth (t=2.157; P=.036) and eighth weeks (t=3.046; P=.004).

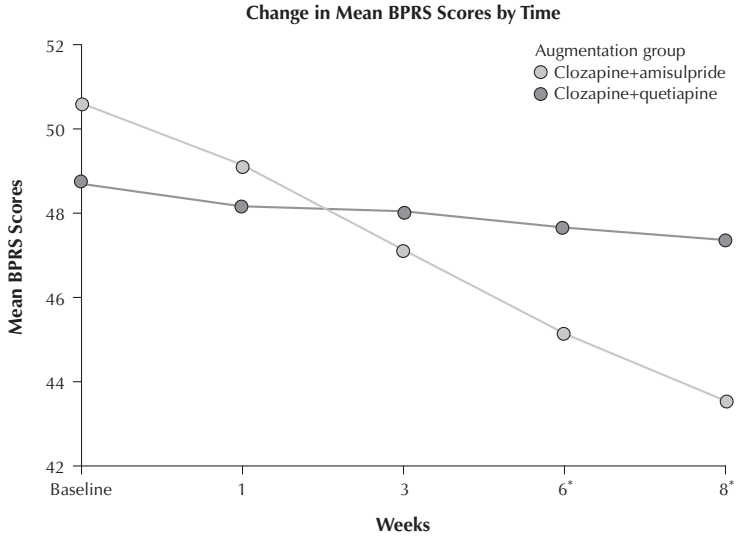
The reduction in SAPS scores in the clozapine+amisulpride group was greater than that observed in the clozapine+quetiapine group (F=7.79; df=4; P<.001) (Fig 2). This difference resulted from differences in measures attained during the sixth (t=2.032; P=.048) and eighth weeks (t=3.010; P=.004).

The reduction in SANS scores in the clozapine+amisulpride group was greater than that noted in the clozapine+quetiapine group (F=4.74; df=4; P=.003) (Fig 3). This difference resulted from differences in measures during the sixth (t=2.028; P=.048) and eighth weeks (t=2.455; P=.018).

Improvement in CGI scores in the clozapine+amisulpride group was greater than in the clozapine+quetiapine group (F=3.806; df=4; P=.01) (Fig 4). This difference resulted from differences reported in measures taken during the third (t=3.213; P=.002), sixth (t=3.958; P<.001), and eighth weeks (t=3.848; P<.001).

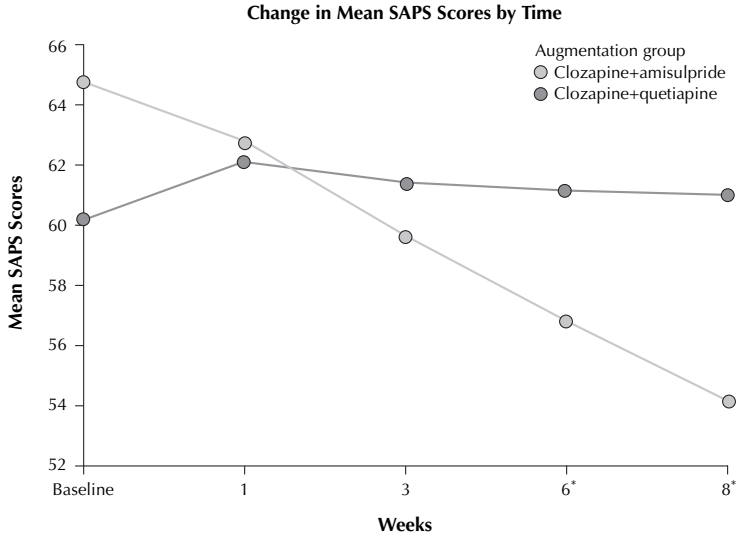
A comparison of total adverse effects between the 2 augmentation regimens measured by UKU (F=1.544; df=4; P=.206) and SAS (F=2.132; df=4; P=.092) revealed similar tolerability in the clozapine+amisulpride and clozapine+quetiapine groups.

Fig 1. Mean BPRS scores of patients over the study period.



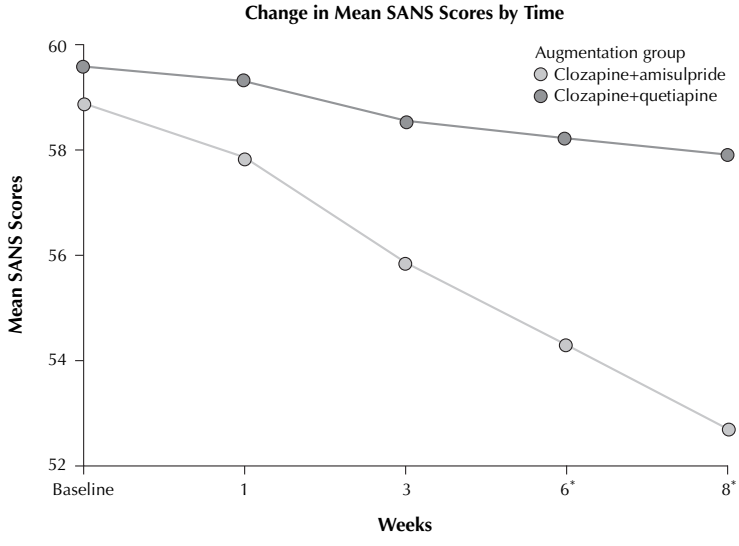
*Significantly greater score reduction at the sixth and eighth weeks in the clozapine+amisulpride group compared with the clozapine+quetiapine group, per analysis of variance (ANOVA) (F=8.59; df=4; *P*<.001).

Fig 2. Mean SAPS scores of patients over the study period.



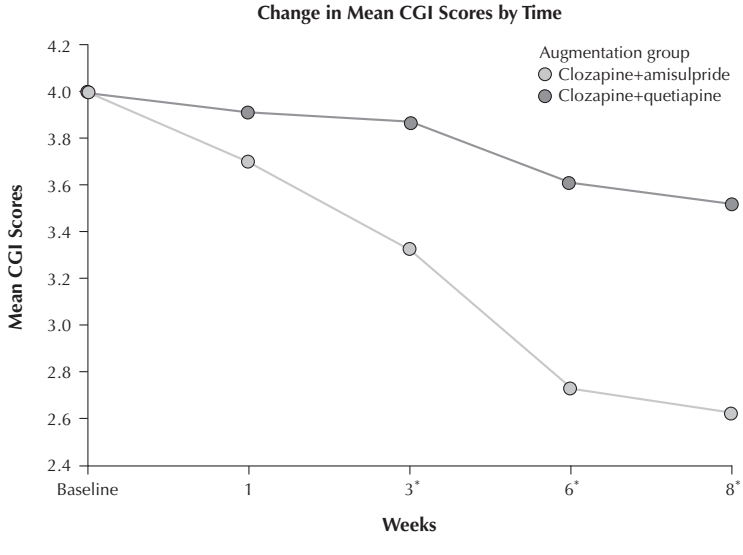
*Significantly greater score reduction at the sixth and eighth weeks in the clozapine+amisulpride group compared with the clozapine+quetiapine group, per ANOVA (F=7.79; df=4; *P*<.001).

Fig 3. Mean SANS scores of patients over the study period.



*Significantly greater score reduction at the sixth and eighth weeks in the clozapine+amisulpride group compared with the clozapine+quetiapine group, per ANOVA (F=4.74; df=4; *P*=.003).

Fig 4. Improvement over the study period as measured by patients' mean CGI scores.



*Significantly greater improvement in scores at the third, sixth, and eighth weeks in the clozapine+amisulpride group compared with the clozapine+quetiapine group, per ANOVA (F=3.806; df=4; *P*=.01).

DISCUSSION

The demographic and clinical characteristics of the 50 patients who were partially responsive to clozapine reveal that the randomly constituted clozapine+amisulpride and clozapine+quetiapine groups were homogenous in terms of baseline severity scores, age, sex, duration of illness, and clozapine doses taken. The average clozapine dose was 550 mg/d for the clozapine+amisulpride group and 536.95 mg/d for the clozapine+quetiapine group. These doses of clozapine are similar to those used in most augmentation studies in which clozapine was given.[21,25] Chlorpromazine doses were similar to those of the 2 adjuvant drugs, which reduced the confusion regarding doses of adjuvant drugs.

There was a substantial improvement in both groups by the end of the eighth week with regard to within-group changes in measures. Amisulpride, with its selective D2/D3 receptor binding property, has the potential to produce extrapyramidal adverse effects, especially at higher doses. In the clozapine+amisulpride group, by the end of the eighth week, total adverse effects measured by the UKU were greater than baseline scores, but this increase in adverse effects was not related to emergence of extrapyramidal adverse effects because no significant change in SAS scores was observed. Moreover, a between-group comparison of changes in scores revealed similar tolerability and adverse effects with the 2 augmentation strategies. Also, augmentation of clozapine with amisulpride did not result in a worsening of adverse effects, although higher doses of amisulpride were used.[25]

The efficacy of clozapine augmented with amisulpride was superior to that of clozapine combined with quetiapine in this randomized, single-blind trial of 50 patients with schizophrenia who were partially responsive to clozapine monotherapy. The superior beneficial effects of clozapine+amisulpride treatment compared with the clozapine+quetiapine combination were notable in mean BPRS, SANS, and SAPS total scores; this outcome began during the sixth week and continued throughout the study. In other words, amisulpride adjuvant to clozapine is an effective augmentation strategy that is superior to clozapine+quetiapine in improving both negative and positive symptoms of schizophrenia. In addition, improvement as measured by CGI was greater in the clozapine+amisulpride group than in the clozapine+quetiapine group. This difference between the 2 augmentation groups began during the third week and continued through the end of the study. Both augmentation strategies were well tolerated, as measured by UKU and SAS, and no differences between groups were reported in terms of adverse effects and tolerability; however, 4 patients in the clozapine+quetiapine group discontinued combination treatment within the first 2 wk because of worsening symptoms. These patients were excluded from the analysis because they were unable to complete the study. The reason for the worsening symptoms is unknown and needs clarification. Although chance may be a factor in the exacerbation of symptoms noted in 4 patients in the clozapine+quetiapine group, beyond its lesser efficacy, the reliability of the clozapine+quetiapine augmentation strategy is questionable, unless and until it is proven otherwise.

Other important issues involve the causes of improvements observed. Amisulpride selectively blocks dopamine D2 and dopamine D3 receptors and has no affinity for any other known receptors. Clozapine and quetiapine share a similar receptor binding profile with higher affinity for serotonin 5-HT_2. Therefore, the superior efficacy of amisulpride combined with clozapine may be attributed to

the complementary receptor profiles of the 2 drugs. The dopamine-specific, limbic selective mode of action of amisulpride makes it a suitable and effective drug for augmentation of clozapine in that the limited dopamine blockade achieved by clozapine is selectively enhanced by amisulpride. Augmentation with quetiapine, however, which has a receptor binding profile similar to that of clozapine, did not result in improved symptoms of schizophrenia. Adjuvant quetiapine might be regarded simply as an increase in the dose of clozapine. Some improvement was seen in the clozapine+quetiapine group at the eighth week, compared with baseline (revealing that some patients benefited from this augmentation), so this combination may be used in patients for whom the dose of clozapine may not be titrated to higher doses because of its adverse effects. The improvement seen in the quetiapine group, however, seems similar to that reported in the placebo group in placebo-controlled trials[21]; therefore, other factors, such as level of patient participation in the study and the benefits of weekly clinic visits, may contribute to this improvement.

In addition, the time taken to respond to clozapine for some individuals was reportedly as long as 2 y.[3] Therefore, some late responders may not have been included in this study. On the other hand, this improvement may have been an artifact of the fluctuating course of schizophrenia and the tendency of extreme observations to regress toward the mean over time.

To date, few trials, including randomized controlled trials and open-label studies, have addressed the benefits of augmentation strategies in patients who were partially responsive to clozapine.[21,25,36] To our knowledge, this is the first single-blind, randomized trial of clozapine augmented with 2 different atypical antipsychotics. Stern et al[37] reviewed 13 published trials of antipsychotic augmentation and reported that the likelihood of a positive result occurring by chance was 63%. These authors concluded that augmentation trials require 40 to 100 patients, depending on the number and variability of outcome measures, effect size, and duration of follow-up (which ranges from 4 to 12 wk).

The study reported here had many strengths, including acceptable sample size, an appropriate period of observation, and the use of efficacy measures that can be used for comparison in future studies. Also, our finding of a significant treatment/time interaction suggests that studies based on a short (ie, 4-wk) period of observation are likely to produce unreliable results.

The present study had some limitations, including the lack of a double-blind design. Nevertheless, the findings reported here must be regarded as preliminary. Although random assignment and single-blinding are important strengths of the current study, definitive conclusions about the superior efficacy of clozapine combined with amisulpride over that of clozapine combined with quetiapine await future investigation with larger sample sizes. The long-term effects of this combination remain unknown; therefore, although this treatment approach seems to be effective and tolerable, it should be provided with caution.

The risks of antipsychotic polypharmacy have not been well studied, and information about long-term risks is particularly sparse. The short-term risks in this study seem acceptable, however, and, considering the devastating nature of schizophrenia, augmentation strategies are essential for the treatment of patients who are only partially responsive to clozapine. Future studies of antipsychotic combinations should include long-term observation of patients for potential toxic effects, hemato-

logic effects, movement disorders, tardive dyskinesia, and pharmacodynamic interactions between drugs.

The observations reported here, although preliminary, suggest that augmentation with amisulpride may benefit patients who are partially responsive or nonresponsive to clozapine monotherapy. This study population represents both inpatients and those who have recovered sufficiently to live in community settings, but it is not clear whether the findings can be equally applied to both types of patients. Clozapine augmentation with amisulpride appears to be well tolerated and safe, at least over 8 wk of treatment, and superior in efficacy to augmentation with quetiapine, but clinicians should approach this augmentation strategy with caution because polypharmacy is associated with potential risks that have not been systematically studied in prospective trials. Exacerbation of the symptoms of schizophrenia in the quetiapine group is a complication of polypharmacy for which clarification is needed. Additional larger, controlled trials must be completed before firm clinical recommendations can be made about clozapine augmentation strategies.

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