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Augmentation of Clozapine With Amisulpride in Patients With Treatment-Resistant Schizophrenia An Open Clinical Study

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Abstract

Background: Therapeutic options for patients with treatment-resistant schizophrenia are limited. In such cases, a combination of atypical antipsychotic drugs is an often used strategy. We tested the hypothesis that the combination of amisulpride and clozapine would lead to long-term improvement in this patient group.
Objective: 15 patients with treatment-resistant schizophrenia participated in this open clinical trial and received a combination of amisulpride and clozapine. Patients had to have remained on a stable dose of clozapine for at least 6 months in order to ensure a reasonable opportunity to respond to clozapine monotherapy. Clinical status was evaluated at baseline, and 3, 6 and 12 months' follow-up, using the Brief Psychiatric Rating Scale (BPRS).
Results: All patients completed 12 months' combination treatment. The mental state of 11 patients (73.3%) was improved and there was a significant reduction in the mean BPRS score over the 12 months of combination treatment. The augmentation of amisulpride in clozapine treated patients did not result in a corresponding increase in side effects. The combination allowed a mean reduction of 12.8% of the daily clozapine dose.
Conclusions: The combined application of clozapine and amisulpride follows a neurobiological rationale and appears to be safe and well tolerated, without increasing the risk of side effects (German J Psychiatry 2006; 9: 17-21).

Keywords: Treatment-resistant schizophrenia, antipsychotic drugs, combination therapy, clozapine, amisulpride

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Introduction

Typical and atypical antipsychotic drugs exhibit inadequate or poor response in 20%-40% of patients with schizophrenia (Hellewell 1999). Clozapine remains the "gold standard" for schizophrenic patients with treatment-resistant symptoms. However, a considerable number of patients treated with clozapine are still nonresponsive or only partially responsive. The combined application of antipsychotic drugs is an established step in the cascade of treatment strategies of treatment-resistant schizophrenia (Lerner et al. 2004, 2005). An overview of the literature suggests that combinations with clozapine and a second atypical antipsychotic were mostly beneficial in the described patients (Josiassen et al. 2005, Zink et al. 2004 a). Clozapine shows a unique receptor profile with high affinities for D_4, 5-HT_{2A}, 5-HT_{2C}, mAch (M_1 and M_4), α_1, H_1 receptors and relatively low affinities for D_1, D_2, D_3, D_5, 5-HT_{1A}, 5-HT_3, α_2, mAch (M_2) receptors.

Amisulpride is another atypical antipsychotic and selectively blocks dopamine D_2 and D_3 receptors (Leucht 2004). The preferential blockade of mesolimbic rather than nigrostriatal

dopaminergic transmission, the preferential blockade of dopamine D_2 autoreceptors rather than postsynaptic receptors and the preferential blockade of dopamine D_3 receptors in the limbic areas have been proposed as explanations for the atypical activity of amisulpride (Schoemaker et al. 1997). In placebo-controlled studies, amisulpride was shown to be effective in improving the positive and negative symptoms in patients with schizophrenia or schizoaffective disorder (Moeller et al. 1997, 2000). Compared with clozapine, amisulpride has greater affinity for D_2 receptors. Only a small part of amisulpride is metabolized in the liver through de-ethylation and oxidation. Up to 75% is renally eliminated in the urine as the parent compound (Rosenzweig et al. 2002).

A few recent studies have demonstrated that a combination of amisulpride and clozapine may be useful in treatment-resistant schizophrenia (Munro et al. 2004, Kaempf et al. 2003). We performed the present open clinical trial aiming to test the hypothesis that the combination regimen would be well tolerated and lead to a long-term improvement in the mental state of patients with treatment-resistant schizophrenia.

Patients and Methods

Outpatients or inpatients unresponsive or partially responsive to adequate clozapine monotherapy were eligible to participate in this prospective open clinical trial. All patients met ICD-10 (DSM-IV) criteria for schizophrenia. Patients had to have remained on a stable dose of clozapine for at least 6 months in order to ensure a reasonable opportunity to respond to clozapine monotherapy. Records of psychiatric history and prior antipsychotic drug therapy were available for all patients. Patients with persistent psychotic symptoms, as evidenced by a total score of at least 25 on the Brief Psychiatric Rating Scale (BPRS), were classified as partial responders or nonresponders (Overall et al. 1961). All patients were fully informed about the benefits, risks and potential adverse effects of polypharmacy. They all gave verbal consent to the combination treatment on an open-label voluntary basis. Demographic and clinical details were recorded at baseline: gender, age, ethnicity, dose of clozapine, serum clozapine levels, routine blood tests, ECG, EEG, side effects, time of onset, number of hospitalizations and pharmacological background (documented treatment failure after the minimum of two antipsychotics given before clozapine treatment started). In the trial, all authors took part in the clinical examination and evaluation of clinical state. At baseline interview mental state was rated using the BPRS. Follow-up evaluations, using the same rating scale as at baseline, were undertaken 3, 6 and 12 months from the start date of amisulpride. Serum clozapine levels, EEG and ECG were repeated at follow-up. Side effects were documented as reported spontaneously by the patients and directly queried by the psychiatrist. Treatment response was defined as a reduction in total BPRS score of greater than 20%. After a patient reached stabilization on treatment with the medication, clozapine was reduced until the patient began to show symptoms of worsening of psychosis. Data analysis was carried out using SPSS for windows (version 12.0) statistical package. Because of the small sample size and the use of ordinal scales, non parametric statistical procedures (Kruskal-Wallis test, Wilcoxon signed rank test, Mann-Whitney U-test) were used for testing the hypothesis. The between-subject term was the individual patient ID and the repeated term was the time point (baseline, 3, 6 and 12 months' follow-up). Tests were two-tailed and $P < 0.05$ considered significant.

Table 1. Baseline demographic and clinical data of 15 patients with treatment refractory schizophrenia

Age mean (years)	38,4 (SD 10.1, range 21 – 54)
Gender	
Female	4 (26.7%)
Male	11 (73.3%)
Diagnosis (ICD-10 / DSM-IV)	
F 20.0 / 295.2	13 (86,6 %)
F 20.1 / 295.1	1 (6,7 %)
F 20.3 / 295.9	1 (6,7 %)
Age at symptom onset, mean (years)	20,7 (SD 3.9, range 17 – 28)
Number of hospitalizations, mean	11,2 (SD 6.7, range 5 – 21)
Patient status at baseline	
Inpatient	9 (60.0%)
Outpatient	6 (40.0%)
Clozapine dose, mean (mg/day)	560.0 (SD 110.1, range 400 - 800)

Results

Fifteen schizophrenic (meeting ICD-10/DSM-IV-criteria) patients (4 women and 11 men, age between 21 and 54 years, mean 38.4 ± 10.1 years) with persistent psychotic symptoms were treated with the combination of clozapine and amisulpride. Among these were 9 inpatients and 6 outpatients (status at baseline). Table 1 shows the sociodemographic and clinical characteristics of the patients, which underline the fact that the indication for combination therapy was restricted to severe cases. Every patient in this group had been unsuccessfully treated with at least 2 typical and/or 2 atypical antipsychotic drugs as monotherapy before. In some cases they had not responded to six ore more different antipsychotic drugs. ECT was also applied to three of the patients. Moreover, they had continued to show substantial psychotic symptoms despite having received optimal treatment with clozapine as monotherapy. In numerous patients the clozapine monotherapy led to several side effects (Table 3). All patients completed 12 months of combination treatment. At baseline the patients were treated with 560.0 ± 110.1 mg clozapine daily (range 400 mg/d to 800 mg/d). The mean serum clozapine levels (0.63 mg/l) at baseline were above the recommended minimum level (0.35 mg/l). They did not vary significantly over time (mean serum clozapine level at 12 months' follow-up 0.59 mg/l). At 12 months' follow-up

Figure 1. BPRS Positive Symptom Subscale Scores at baseline and 12 months' follow-up. Error bars represent Standard Deviations

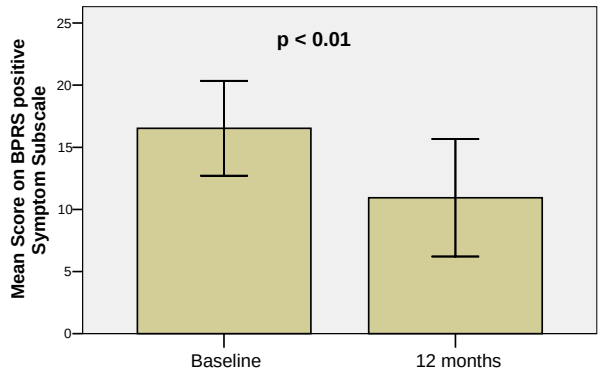

Table 2. Mean drug dosages (mg/day) from baseline, 3, 6 and 12 months' follow-up

	Amisulpride	Clozapine
Baseline	0	560.0 (SD 110.1, range 400-800)
3 Months	593.3 (SD 122.3, range 350-800)	538.3 (SD 85.0, range 400-700)
6 Months	606.7 (SD 110.0, range 350-800)	511.7 (SD 71.9, range 400-675)
12 Months	600.0 (SD 100.0, range 350 - 750)	488.4 (SD 63.6, range 400 - 600)

the patients were treated with 488.4 ± 63.6 mg clozapine (range 400 mg/d to 600 mg/d) and 600.0 ± 100.0 mg amisulpride (range 350 mg/d to 750 mg/d) daily (Table 2). As seen in Figure 1, the total BPRS scores decreased significantly from baseline to 12 months' follow-up. Score reductions from baseline to 3 months' follow-up were greater than during the following treatment period. Using the predetermined response criteria (20% or greater reduction in BPRS total score) 10 (66.7%) of the 15 patients had responded after 3 months of combination treatment.

At 6 and 12 months' follow-up, 11 (73.3%) of the 15 patients had responded to the treatment regimen. The mean improvement of the total BPRS score over the 12 months was 33.4% (mean BPRS score reduction at 12 months 11.9 ± 5.0, range 5 to 23). As seen in Figure 2, scores on the BPRS positive symptom subscale decreased significantly from baseline to 12 months' follow-up (mean BPRS positive symptom subscale reduction at 12 months 5.7 ± 4.1, range 0 to 13). In terms of negative symptoms, we found no significant decrease on the mean BPRS negative symptom subscale. The combination allowed a mean reduction of 12.8% of the daily clozapine dose over time (Table 2). The co-administration of amisulpride in clozapine treated patients did not result in a corresponding increase in side effects over the 12-month period (Table 3). The regimen provided a modest weight loss in two patients and three other patients reported reduced hypersalivation. One patient reported reduced sedation (daytime fatigue). We found no significant ECG or EEG changes. Table 4 presents demographic and clinical data of treatment-responders and non-responders. Interestingly, however, most treatment non-responders were women and the daily amisulpride and clozapine dosages were lower than in the treatment responders.

Discussion

Our study demonstrates that the combination of clozapine and amisulpride represents a useful treatment option in patients who are partially or nonresponsive to clozapine monotherapy. Improvement of psychopathological state could be achieved. We did not observe the occurrence of persisting new side effects or unfavourable drug interactions. The combination of clozapine and amisulpride appears to be safe and well tolerated.

Antipsychotic polypharmacy occurs frequently within clinical practice, with rates ranging from 5-18% in outpatients and up to 50% or more in inpatients (Wang et al. 2000). This practice has been criticized as unjustified, too expensive and based on insufficiently performed clinical trials (Ananth et al. 2004, Stahl et al. 2004). Treatment resistance is difficult to define, and the criteria remain controversial. Treatment failure of at least two antipsychotic trials of adequate dose

Figure 2. BPRS Total Symptom Scores Over the Study Period. Error Bars Represent Standard Deviations

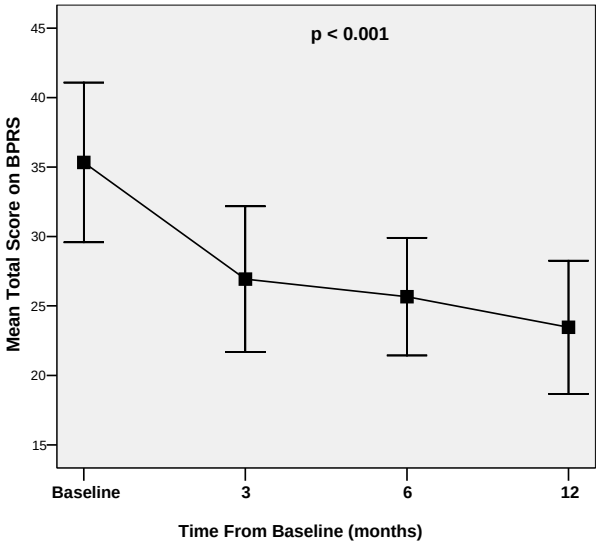

Table 3. Side effects before and during combination treatment

	Before combination treatment (n=15)	During combination treatment (n=15)
Weight gain > 5kg	10 (66.7%)	No further weight gain²
Hypersalivation	7 (46.7%)	4 (26.7%)
Sedation (daytime fatigue)	4 (26.7%)	3 (20.0%)
EEG changes	3 (20.0%)	3 (20.0%)
Blood changes¹	3 (20.0%)	3 (20.0%)

¹ elevated liver enzymes
² In 2 patients the combination led to modest weight loss (-1.4 kg and -2.0 kg)

Abbreviations: EEG, electroencephalogram

and duration of treatment is generally required to consider a patient treatment refractory (Kane 1999). Most randomized studies in the literature have a duration of only 4 to 8 weeks. However, it is increasingly acknowledged that the time taken to respond to clozapine for some individuals may be up to or beyond a year (Meltzer 1989). In particular, time to response may be longer for patients with past episodes, as each successive episode may increase the time to remission (Lieberman et al. 1996). In purchase to these results, combination therapies should be considered only if the treatment duration with clozapine monotherapy was 6 to 12 months. The combined application of antipsychotic drugs in treatment-resistant schizophrenia is a common strategy, but these polypharmacy usage patterns are in contrast with most published treatment guidelines (Lehman et al. 2004, Gaebel and Falkai 2003, Miller et al. 2004) and should be limited to severe cases only if monotherapy, with different classes of FGAs or SGAs in sufficient doses over an adequate time period, has proved ineffective. There are 4 double-blind, placebo-controlled studies available in the literature (Josiassen et al. 2005, Shiloh et al. 1997, Anil Yagcioglu et al. 2005, Potter et al. 1989), but most investigations are performed in an open, uncontrolled design and deal with small series of patients (Zink and Dressing 2005).

Risperidone is, to date, the most extensively documented clozapine augmentation agent. A double-blind study (Josiassen et al. 2005) and two uncontrolled prospective treatment studies (Henderson et al. 1996, Taylor et al. 2001) found improvement with the combination, without a significant increase in side effects. In contrast Yagcioglu et al (2005) and DeGroot et al (2001) have reported no benefit. In a controlled trial clozapine combination with chlorpromazine was not superior to clozapine monotherapy (Potter et al. 1989).

The combination of sulpiride or amisulpride (relatively selective D_2-antagonists) with clozapine showed promising effects in different studies (Zink et al. 2004 a, Shiloh et al. 1997, Munro et al. 2004, Kaempf et al. 2003). The authors reported a significant benefit in terms of improvement of psychopathological state and side effects. Furthermore, Zink et al (2004 a) demonstrated that the daily clozapine doses could be reduced, and lower individual drug doses could be used in combination therapy compared with monotherapy. Other investigators have reported on combination of amisulpride and olanzapine, risperidone and amisulpride or ziprasidone and amisulpride (Zink et al 2004 b, Lerner et al. 2005). Case reports and a small patient series have suggested promise for clozapine augmentation with pimozide (Friedman et al. 1997) and olanzapine (Gupta et al. 1998).

Kaye (2003) performed an open clinical trial with ziprasidone augmentation of clozapine in 11 patients treated with high dose clozapine monotherapy. The regimen provided a significant benefit in terms of weight loss, improved initiation and motivation, reduced apathy, improved cognitive functioning and improved lipid profiles. Our group found similar effects in a study on 9 patients besides the reduction of the daily clozapine dose (Ziegenbein et al. 2005).

The mechanisms underlying the combined action of antipsychotics still remain unclear. Most authors suggest that the additive pharmacokinetic effect on dopamine D_2/D_3 receptors might be the most important synergistic mechanism to explain the favourable therapeutic outcome of combining amisulpride with clozapine or olanzapine (Zink et al. 2004 b, Friedman et al. 1997, Leucht 2004, Kaempf et al. 2005). Some studies suggest that risperidone increases plasma concentrations of clozapine (Tyson et al. 1995) and Bergemann et al (2004) reported that clozapine leads to a moderate increase in amisulpride plasma concentrations. However, McCarthy et al (1995) report on the risperidone effect, stating pharmacokinetic interactions are not the basis for symptom reduction.

We believe that the efficacy of the combination treatment with amisulpride and clozapine may be attributed to the synergistic receptor profiles of the 2 substances, rather than a pharmacokinetic phenomenon. The relatively weak dopamine D_2-antagonist properties of clozapine, might be enhanced by amisulpride, which provides high-potency D_2-blockade. Positron emission tomographic data demonstrate that dopamine D_2 receptor occupancy of 70% is necessary for therapeutic benefits, whereas occupancy greater than 80% is associated with extrapyramidal symptoms (Nordstorm et al. 1995, Kapur et al. 2000). A newer neuroimaging study by Matthiasson et al. (2000) showed that in patients receiving clozapine monotherapy the mean D_2 receptor occupancy in the basal ganglia was 46%, increasing to a mean of 76% after the addition of amisulpride. In contrast to clozapine, amisulpride shows a low protein binding and only a small part is metabolized to inactive metabolites in the liver. Therefore pharmacokinetic interactions such as increasing the metabolism of clozapine via cytochrome P450 seem unlikely, since the clearance of amisulpride is largely due to urinary excretion (Rosenzweig et al. 2002). The stability of serum clozapine levels of our patients over the investigation period suggests that the benefit of amisulpride is not dependent upon raising serum clozapine levels and pharmacokinetic interaction. The dosages of the combination therapy in the group of nonresponsive patients should be changed and we will perform another follow-up.

Table 4. Demographic and clinical data of treatment responders and non-responders at baseline and 12 months' follow-up

	Treatment responders	Treatment non-responders
Age mean (years)	39.1 (SD 10.5, range 21–54)	36.5 (SD 14.0, range 24–51)
Gender		
Female	1	3
Male	10	1
Diagnosis (ICD-10 / DSM-IV)		
F 20.0 / 295.2	10	3
F 20.1 / 295.1	0	1
F 20.3 / 295.9	1	0
Clozapine dose, mean (mg/day)		
12 months' follow-up	502.3 (SD 51.8, range 425 - 600)	449.8 (SD 84.3, range 400–575)
baseline	570.5 (SD 81.3, range 475 - 750)	531.3 (SD 181.7, range 400–800)
Amisulpride dose, mean (mg/day)	631.8 (SD 78.3, range 500 - 750)	512.5 (SD 110.9, range 350–600)
BPRS total score		
12 months' follow-up	20.6 (SD 2.7, range 17 - 25)	31.3 (SD 4.9, range 25–37)
baseline	34.6 (SD 5.7, range 28–48)	37.5 (SD 6.3, range 30–45)
BPRS positive symptom subscale		
12 months' follow-up	8.8 (SD 3.2, range 4–24)	16.8 (SD 3.1, range 14–21)
baseline	16.1 (SD 4.0, range 11–48)	17.8 (SD 3.5, range 14–22)

Our observations suggest that combination treatment with amisulpride and clozapine may be of long-term benefit for patients who are partially or nonresponsive to clozapine monotherapy. Improvement of psychopathological state and side effects could be achieved. This may increase patients' compliance, preventing exacerbations and subsequent hospitalizations. The combination of clozapine with amisulpride has cost implications as drug costs may rise, but prolongation of hospitalization is still more expensive.

The risks of antipsychotic polypharmacy have not been well studied, and information about long-term risks is particularly sparse. For risk/benefit evaluation future double-blind randomized trials of antipsychotic combinations with larger sample sizes should include long-term observation of patients for potential toxic effects, particularly metabolic effects, hematologic effects, movement disorders and tardive dyskinesia. These trials are required before firm clinical recommendations can be made about combination or augmentation strategies.

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