

# Amisulpride in Addition to Clozapine: A Retrospective Study Indicates Improved Efficacy and Good Tolerability

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## Abstract

*Background:* The common practice of augmenting the efficacy of clozapine by addition of amisulpride has some empirical and theoretical support, but has not been thoroughly investigated.

*Objective:* We report on 14 patients (8 inpatients, 6 outpatients) with a mean age of 34.4 years (SD 8.6), who had received a combined clozapine/amisulpride treatment. 8 patients were suffering from schizophrenia (ICD-10 F20.0), 6 from a schizoaffective disorder (ICD-10 F20.5). All patients had received clozapine at a dosage of  $338 \pm 177$  mg for at least 4 weeks, amisulpride was added at a dosage of  $514 \pm 235$  mg, and combined treatment lasted for  $20 \pm 22$  weeks.

*Results:* The mean CGI score (severity of illness item) decreased from  $5.6 \pm 0.5$  to  $3.9 \pm 1.0$  ( $p < .01$ ). Accordingly, the CGI score (global improvement item) revealed that three patients (21%) were "very much improved", eight patients (57%) "much improved", two patients (14%) "minimally improved", and only one patient (7%) was "not improved". No patients experienced deterioration, and no severe side effects were reported.

*Conclusions:* It is concluded that a combination of clozapine and amisulpride might be useful for patients not improving sufficiently under clozapine monotherapy (German J Psychiatry 2003; 6(3): 64-68)

*Keywords:* clozapine, amisulpride, combination treatment, schizophrenia

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## Introduction

Clozapine was the first antipsychotic drug lacking the typical extrapyramidal motor side effects of classical neuroleptics. Despite the risk of lethal agranulocytosis (Amsler et al. 1977) which forced a restricted prescription, clozapine remains the "gold standard" in the treatment of schizophrenia with atypical antipsychotics.

Clozapine shows a unique receptor profile with high affinities for D<sub>4</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, mACh (M<sub>1</sub> und M<sub>4</sub>),  $\alpha_1$ , H<sub>1</sub> receptors and low affinities for D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>5</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>3</sub>,  $\alpha_2$ , mACh (M<sub>2</sub>) receptors.

The efficacy of clozapine and its superiority over typical antipsychotics in the treatment of schizophrenia, especially

for "treatment resistant" patients and patients suffering from negative symptoms has been demonstrated in many double-blind, controlled studies over the years (Kane et al. 1988, Wagstaff et al. 1995, Buchanan 1995, Wahlbeck et al. 1999, Rosenheck et al 1999).

Side effects like hypotension, constipation, increase in liver enzymes, and fever usually occur within the first weeks of treatment, but other side effects such as fatigue, EEG alterations, hypersalivation, and tachycardia, may impede a successful treatment.

In order to reduce side effects, we often reduce the dosage of clozapine, which may hamper further improvement or at worst cause deterioration. These patients, who either do not improve or suffer from severe side effects during clozapine therapy, could benefit from an add-on medication, using another atypical antipsychotic with a different side-effect

Table 1. An Overview of the Patients Included

No.	ICD 10	Age	Sex	Comb. therapy Weeks	Daily Dose		CGI, Severity		CGI, Global Improvement
					Clozapine	Amisulpride	Before Combination Therapy	After Combination Therapy	
1	F25.0	32	f	56	200 mg	400mg	severely	mildly	very much
2	F20.0	34	m	4	400mg	100mg	severely	moderately	very much
3	F25.2	42	m	10	450mg	800mg	markedly	borderline	very much
4	F20.0	47	m	60	600 mg	800mg	severely	moderately	much
5	F25.0	38	m	56	150 mg	200 mg	severely	moderately	much
6	F25.0	46	m	24	150 mg	400mg	severely	moderately	much
7	F20.0	34	f	24	200 mg	600mg	severely	moderately	much
8	F20.0	21	m	6	325mg	600mg	severely	markedly	much
9	F25.0	22	m	9	600mg	600mg	markedly	mildly	much
10	F20.0	36	m	6	150mg	400mg	markedly	mildly	much
11	F20.5	40	f	6	400mg	400mg	markedly	moderately	much
12	F20.0	31	m	4	350mg	800mg	severely	markedly	minimally
13	F20.0	20	f	2	150mg	300mg	markedly	moderately	minimally
14	F20.0	38	m	8	600 mg	800mg	severely ill	severely ill	no change

profile. Although clinicians should avoid a polypragmatic approach, it may be justified in selected cases.

The latest review of the current literature about combining antipsychotics, atypical with atypical or conventional antipsychotics, states that empirical evidence for the efficacy of combining antipsychotics is too limited to draw firm conclusions. But the practice of augmenting clozapine with more 'tightly bound' D<sub>2</sub> receptor antagonists such as amisulpride has some empirical and theoretical support (Freudenreich et al. 2002).

Amisulpride, a benzamide, binds selectively to dopamine D<sub>2</sub> and D<sub>3</sub> receptors, preferentially in the limbic system. Low doses of amisulpride block presynaptic D<sub>2</sub> and D<sub>3</sub> autoreceptors, thereby enhancing dopaminergic transmission, whereas higher doses block postsynaptic receptors, thus inhibiting dopaminergic hyperactivity (Perrault et al. 1997). In comparison with clozapine, amisulpride shows no affinity to the other dopaminergic receptors and also not to central 5-HT, mACh, H and  $\alpha$  receptors (Schoemaker et al. 1997). Amisulpride is clinically effective on the negative symptoms of acute schizophrenia at low dosages (50-300 mg/day) (Boyer et al. 1995), and also on the positive symptoms of the disease at high dosages (400-800 mg/day). The efficacy of amisulpride in the treatment of acute exacerbations of schizophrenia has been shown in several open and double-blind studies (Rüther et al. 1989, Möller et al. 1997, Lemperiere 1999). The efficacy of amisulpride for patients with predominantly negative symptoms could also be demonstrated in several studies (Loo et al 1997, Speller et al. 1997).

To shed light on the question whether there is a synergistic add-on effect, we analyzed the clinical records of patients who had received a combination treatment of clozapine and amisulpride.

## Methods

The clinical records of all patients from two hospitals between 1999 and 2002 were screened for combination therapy

of clozapine and amisulpride. Fourteen patients had received this particular combined treatment during this period of time. The clinical records of these patients (10 male, 4 female) were used for this open retrospective trial. Eight were inpatients (6 male, 2 female), 6 were outpatients (4 male, 2 female). The mean age was 34.4 (SD 8.6), ranging from 20 to 47 years. Following the ICD-10 classification, 8 patients were suffering from schizophrenia (F20.0), 6 from a schizoaffective disorder (F20.5). Before amisulpride was added, all patients had already received a mean clozapine dosage of 337.5 mg (SD 176.7 mg), ranging from 150 to 600 mg for at least 4 weeks without significant improvement of the schizophrenic symptoms.

While amisulpride was added no other neuroleptic was given during the treatment phase.

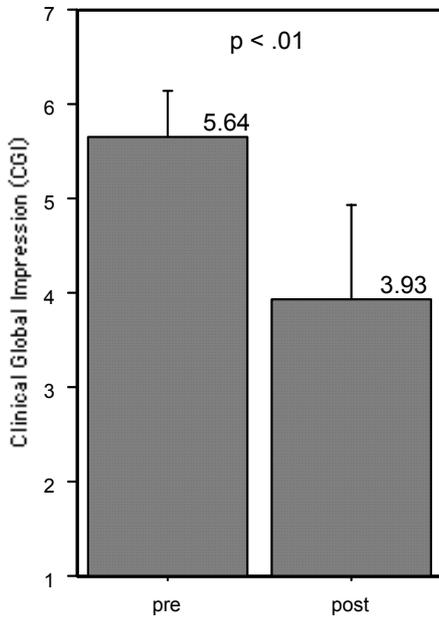
The mean combined treatment duration was 19.6 weeks (SD 21.5), ranging from 2 to 60 weeks. During the combined treatment period the patients received the same clozapine dosage as before. The mean dosage for amisulpride was 514.3 mg (SD 234.9 mg), ranging from 100 to 800 mg per day.

The Clinical Global Impression scale was used to assess the treatment response in this trial. The severity of illness was rated before and after the treatment, along with the global improvement.

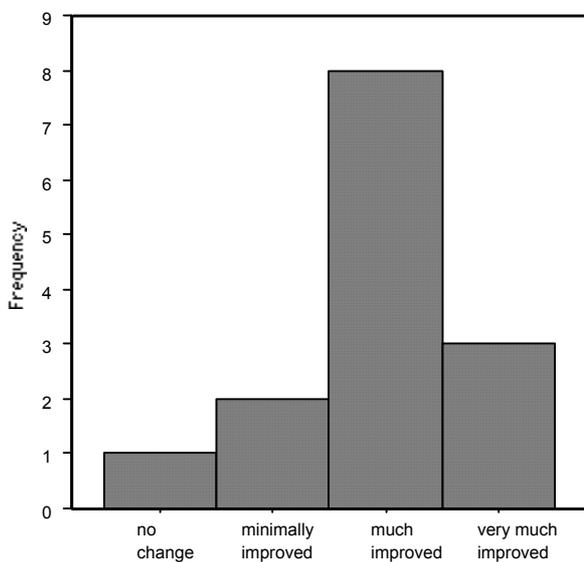
## Statistical Analysis

Because of the small sample size and the use of ordinal scales, non-parametric statistical procedures (Spearman's Rho, Wilcoxon signed rank test, Mann-Whitney U-test) were used for testing of the hypotheses.

**Figure 1. Mean CGI Score (Severity of Illness Item) Before and After Combined Treatment. Error Bars Represent Standard Deviations**



**Figure 2. Frequency Distribution of CGI Score (Global Improvement Item)**



## Results

The mean CGI score (severity of illness item) decreased from 5.6 (SD 0.5) to 3.9 (SD 0.99) (Wilcoxon test,  $p = .0015$ ), indicating a highly significant improvement (see Figure 1).

Accordingly, the CGI score (global improvement item) revealed that three patients (21%) were “very much improved”, eight patients (57%) “much improved”, two patients (14%) “minimally improved”, and only one patient (7%) was “not improved”. No patients showed a deterioration (see Figure 2).

The correlations between CGI outcome and clozapine dosage or amisulpride dosage were not significant ( $Rho = .14$  and  $= .11$ , respectively).

CGI improvement seems to be independent of treatment setting, since inpatients and outpatients showed similar CGI changes (Wilcoxon tests; inpatients:  $p < .05$ , outpatients:  $p < .05$ ); moreover, both groups showed no CGI differences at pre or post measurement (Mann-Whitney U-test; pre:  $p < .05$ ; post:  $p < .05$ ).

With regard to side effects, no serious side effects were observed; patients tolerated the combination treatment well.

## Discussion

The results of this investigation lead to the conclusion that the majority of patients were either very much or much improved as a result of the combined treatment. Tolerability was good; no severe side effects like the extrapyramidal-motor symptoms, insomnia, hyperkinesias, anxiety and galactorrhoea observed by Coulouvrat et al. (1999) were reported here.

Similar results are reported by other groups, investigating effectiveness of selective  $D_2$ -antagonists in combination with clozapine. A report on sulpiride augmentation is the only double-blind, controlled study to date (Shiloh et al., 1997). In this study significantly greater improvement was attained on the Brief Psychiatric Rating Scale (BPRS) in the clozapine-sulpiride group. No significant adverse effects were observed in patients with sulpiride co-administration beside an increase in serum prolactin levels. Similar results were reported when pimozide was added to clozapine (Friedman et al. 1997).

Croissant et al. (2001) reported on a patient who showed improvement in psychotic symptoms under a clozapine treatment, but developed marked side effects, leading to substantial compliance problems. The psychotic symptoms deteriorated when the clozapine dose was reduced. After amisulpride addition, the dose of clozapine was reduced without the recurrence of psychotic symptoms. Similar effects could be seen in a clinical study on 9 inpatients by Ziegenbein et al. (2002). Other investigators have reported on clozapine combined with other atypical antipsychotics. For example, Raskin et al. (2000) described a significant reduction in PANSS positive symptom scores and clinical improvement by adding risperidone to clozapine treatment and vice versa. Henderson and Goff (1996) described significantly decreased total BPRS scores after adding risperidone. An improvement in patients' clinical status under a clozapine and risperidone combination therapy was seen by Morera et al. (1999). Successful augmentation of clozapine

with olanzapine has also been reported in two cases (Gupta et al. 1998). Taylor et al. (1999) described a significant improvement in negative, but not positive symptoms after risperidone addition. In contrast, De Groot et al. (2001) and Chong et al. (1996) reported a lack of efficacy for a combination therapy with risperidone.

Compared with studies about combination treatment with risperidone, where some reports suggest that risperidone increases plasma concentrations of clozapine (Tyson et al., 1995), our patients did not show any increase in the plasma serum levels of clozapine or its active metabolites. Because of the different pharmacokinetics between clozapine and amisulpride, an increase is not to be expected. The protein bound part of clozapine represents 95% and it is mainly metabolized in the liver by cytochrome P450-isoenzyme CYP 1A2 and CYP 3A4 (Jann et al. 1993), whereas amisulpride shows a low protein binding (17%). Only a small part is metabolized to inactive metabolites in the liver through de-ethylation and oxidation. Renal elimination accounts for 75% of elimination, and it is predominantly eliminated in the urine as the parent compound (Rosenzweig et al. 2002). As McCarthy (1995) reports on the risperidone effect, possible pharmacokinetic interactions are not the basis for symptom reduction. The additive pharmacodynamic effect on the D<sub>2</sub> and D<sub>3</sub> receptor might be the most relevant synergistic effect in the clozapine and amisulpride combination treatment. Results of neuroimaging studies with PET and SPECT also point in this direction. A clozapine dosage of 125-600mg/d resulted in a D<sub>2</sub> receptor blockage of 20-67% (Nordstrom et al. 1995), whereas amisulpride treatment leads to a dose-dependent blockage of D<sub>2</sub>-receptors, at 70-85% (Martinot et al. 1996). In patients receiving a clozapine monotherapy the mean occupancy in the basal ganglia was 46%, increasing to a mean of 73% after the addition of amisulpride, and all patients showed some degree of clinical improvement on the drug combination (Matthiasson et al. 2000). Similarly, the addition of haloperidol to ongoing clozapine treatment has been reported, leading to a significantly increased D<sub>2</sub> receptor occupancy, from a mean of 55% to 79% (Kapur et al. 2001).

Keeping our results and the above-mentioned in mind, we conclude that a combination therapy of clozapine and amisulpride might be useful for patients who suffer either from a treatment resistant form of schizophrenia or have an exacerbation once again under a permanent clozapine treatment.

Double-blind studies will have to be conducted in the future to substantiate the results of our investigation.

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