Amisulpride – a selective dopamine antagonist and atypical antipsychotic: results of a meta-analysis of randomized controlled trials

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Abstract
The pharmacological profiles of the atypical antipsychotics, clozapine, olanzapine, quetiapine and risperidone, all show a combined serotonin (5-HT$_2$) and dopamine type-2 (D$_2$) receptor antagonism. Amisulpride, a highly selective dopamine D$_2$/D$_3$ receptor antagonist that binds preferentially to receptors in the mesolimbic system, is also an ‘atypical’ antipsychotic despite having a different receptor-affinity profile. A meta-analysis of 18 clinical trials was undertaken to compare the efficacy and safety of amisulpride with conventional antipsychotics. The improvement in mental state was assessed using the Brief Psychiatric Rating Scale (BPRS) or the Scale for the Assessment of Negative Symptoms (SANS). In a pooled analysis of 10 studies of acutely ill patients, amisulpride was significantly more effective than conventional neuroleptics with regard to improvement of global symptoms. Amisulpride is, to date, the only atypical antipsychotic for which several studies on patients suffering predominantly from negative symptoms have been published. In four such studies, amisulpride was significantly superior to placebo. Three small studies with conventional neuroleptics as a comparator showed only a trend in favour of amisulpride in this regard. Amisulpride was associated with fewer extrapyramidal side-effects and fewer drop-outs due to adverse events than conventional neuroleptics. These results clearly show that amisulpride is an ‘atypical’ antipsychotic, and they cast some doubt on the notion that combined 5-HT$_2$–D$_2$ antagonism is the only reason for the high efficacy against negative symptoms and fewer extrapyramidal side-effects.

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Introduction
The pharmacological profiles of the atypical antipsychotics, clozapine, olanzapine, risperidone and quetiapine, all show a combined serotonin (5-HT$_2$) and dopamine type-2 (D$_2$) receptor antagonism, with a greater affinity for the 5-HT$_2$ receptors. This was the main theory underlying ‘atypicality’ for at least 10 yr and drug research was focused on this concept. More recently, amisulpride, a highly selective dopamine D$_2$/D$_4$ antagonist, was shown to preferentially bind to receptors in the mesolimbic system. Despite having no action on 5-HT-2A receptors, like the others, amisulpride should also be considered an atypical antipsychotic by transiently occupying D$_2$ receptors (Seeman, 2002).

Here I summarize the data from our previous meta-analysis of clinical studies comparing amisulpride with the other atypical antipsychotics (Leucht et al., 2002) and I expand further on the issue of side-effects.

The mechanism of action of amisulpride
Four dopaminergic pathways exist in the brain: the nigrostriatal dopamine pathway, the mesolimbic dopamine pathway, the mesocortical dopamine pathway and the tuberoinfundibular dopamine pathway. A model has been proposed according to which amisulpride blocks D$_2$/D$_4$ receptors in the mesolimbic pathway, preventing dopamine transmission resulting in the relief of positive symptoms. Meanwhile, the blockage of pre-synaptic D$_2$/D$_3$ receptors by amisulpride in the mesocortical pathway may enhance the release of
dopamine in the frontal area and improve negative symptoms (Scatton et al., 1997), which are believed to arise from a hypodopaminergic function in that area. This model is thought to explain the effectiveness of amisulpride for both positive and negative symptoms of schizophrenia. Amisulpride does not seem to block dopamine receptors in the nigrostriatal pathway to an important extent. The blockade of these receptors is responsible for the EPS associated with antipsychotic medications. Finally, the tuberoinfundibular pathway is associated with prolactin increase that can be caused by some antipsychotics.

Overview of the meta-analysis

Randomized controlled trials that compared amisulpride with conventional neuroleptics or placebo in patients with schizophrenia were combined in a meta-analysis. The results were compared with those of meta-analyses of the other atypical antipsychotics. Eleven double-blind amisulpride studies on acutely ill patients and seven double-blind studies of patients with predominantly negative symptoms were found, which involved approx. 2000 patients. The treatment duration ranged between 3 wk and 1 yr. Details of these trials are listed elsewhere (Leucht et al., 2002).

To assess the improvement of mental state, the mean changes from baseline to end-point in the total score on the Brief Psychiatric Rating Scale (BPRS) and in the score on the Scale for the Assessment of Negative Symptoms (SANS) were analysed. When the latter scales were not available, the Positive and Negative Symptoms Scale (PANSS) was used. Other outcome measures discussed in this paper include the use of antiparkinson medication to assess extrapyramidal side effects, and drop-out rates due to adverse events.

Reduction in BPRS score

Amisulpride was significantly more effective than conventional neuroleptics in improving mental state, according to 10 studies with acutely ill patients. The effect size, a measure of the magnitude of difference between two interventions, and 95% confidence intervals (CIs) for each of the studies are shown in Figure 1. When the effect size is on the right-hand side of the y-axis, the study favours amisulpride, and when the 95% CIs do not cross the y-axis, the result is statistically significant. Hence, with the exception of one small study, Figure 1 shows that there was at least a trend in favour of amisulpride.

When the studies were pooled, the superiority of amisulpride in reducing the BPRS score from baseline to end-point was shown to be statistically significant ($r = 0.11$, $p < 0.0001$, $N = 10$, $n = 1654$). Olanzapine and risperidone also showed superiority over conventional

Figure 1. Differences in mean change in BPRS score in comparisons of amisulpride with conventional neuroleptics. [From Leucht et al. (2002). Copyright © 2002 American Psychiatric Association (http://Ajp.psychiatryonline.org). Reprinted with permission.]
neuroleptics in reducing the BPRS score from baseline to end-point. As many clinicians and researchers had previously believed that the atypicals were not as effective as conventional neuroleptics, such as haloperidol, these findings were important, although there are also potential sources of bias such as the inclusion of relatively chronic patients.

**Negative symptoms**

According to the available studies, all atypical antipsychotics have been shown to be superior to placebo in the treatment of negative symptoms. However, with the exception of studies on amisulpride, all trials were performed on subjects with mainly positive symptoms. This raises the question of whether the observed superiority was an improvement of the primary negative symptoms or merely of the negative symptoms that are secondary to the positive symptoms of schizophrenia. To determine whether a drug has an impact on primary negative symptoms, studies should be conducted in such patients – as has been done with amisulpride. Amisulpride has been shown to be significantly superior to placebo in four studies of patients suffering predominantly from persistent negative symptoms (Boyer et al., 1995; Danion et al., 1999; Loo et al., 1997; Paillere-Martinot et al., 1995).

In direct comparisons of new and conventional antipsychotics, amisulpride, olanzapine and risperidone were significantly superior to conventional drugs for negative symptoms (Figure 2), but these results were only derived from studies of acutely ill patients. There were only three small studies directly comparing amisulpride with conventional neuroleptics in patients with predominantly negative symptoms (Pichot and Boyer, 1989; Saletu et al., 1994; Speller et al., 1997). There was no statistically significant differences although there was a trend in favour of amisulpride. Further studies including all of the new generation antipsychotics are necessary to clarify this issue.

**Use of antiparkinson medication**

The use of antiparkinson medication provides a surrogate outcome measure for extrapyramidal symptoms (EPS), as single EPS are not monitored consistently in trials. In the meta-analysis, patients receiving amisulpride did not use significantly more antiparkinson medication than patients receiving placebo. In contrast, haloperidol treatment was associated with significantly more use of antiparkinson medication compared to placebo. However, amisulpride doses have only been examined up to 300 mg/d; placebo-controlled trials with higher amisulpride doses have not been carried out.

When compared directly with conventional antipsychotics, amisulpride clearly induced fewer extrapyramidal side-effects; this trend was reflected in the use of antiparkinson medication (Figure 3). There are, however, two methodological problems regarding the direct comparisons between atypical antipsychotics and conventional neuroleptics. First, haloperidol, a...
A high-potency antipsychotic known to be associated with EPS, was the comparator in most studies, and secondly, it was often used at relatively high doses (20 mg/d) that were typical when these studies were designed. Nowadays, much lower doses are used but even so, haloperidol seems to cause significantly more EPS than atypical antipsychotics, even at doses as low as 4 mg/d (Zimbroff et al., 1997).

**Drop-out rates**

In studies of acutely ill patients, significantly fewer patients treated with amisulpride left the studies early because of adverse effects than those patients treated with conventional neuroleptics ($r = 0.15$, 95% CI = 0.07–0.25, $N = 9$, $n = 1546$, $p = 0.003$).

**Side-effects**

Two potential adverse events associated with these compounds are elevated prolactin levels and weight gain. Although it has been shown that amisulpride and risperidone each increase prolactin levels, the exact impact on the endocrine system is unclear. A direct comparison of these two atypical antipsychotics revealed that more risperidone recipients than amisulpride recipients experienced endocrine problems, but the difference was not statistically significant (Sechter et al., 2002).

A meta-analysis investigating the effects of antipsychotics on body weight (Allison et al., 1999) revealed that clozapine and olanzapine had the greatest potential to cause weight gain; after 10 wk of treatment, mean increases in weight were 4.45 kg with clozapine and 4.15 kg with olanzapine. Risperidone also induced weight gain (a mean increase of 2.1 kg after 10 wk of use) while ziprasidone was found to cause the least...
gain (Figure 4; there are current concerns regarding cardiac side-effects – an increase of the QTc-interval – with ziprasidone, however, the clinical relevance of these side-effects is under debate). Amisulpride has since been found to induce minor weight gain, which was approx. 0.8 kg after 10 wk of treatment (Figure 4).

**Methodological issues**

While the results of this meta-analysis indicated the superiority of atypical antipsychotics over conventional agents, several methodological problems must also be mentioned. First, the differences in the mean effect sizes regarding efficacy clearly showed that all the antipsychotics (conventional and atypicals) were more effective than placebo, but the mean effect sizes were smaller than expected; the mean effect size of all antipsychotics vs. placebo was $r = 0.25$ ($n = 2000$), which means that the difference was only 25%. One reason for this small difference is the design of drug trials. Of necessity, patients need to fill out rather long consent forms, which acutely ill schizophrenic patients cannot sign. Therefore, the study designs often allow clinicians to stabilize patients for some time in the hospital prior to their inclusion in the study, leading to a reduced treatment effect.

Secondly, a recent review of randomized controlled trials ($n \sim 18000$ patients) on atypical antipsychotics and conventional neuroleptics, which are summarized in the Cochrane library database, showed a constant increase in drop-out rates since the 1950s (Wahlbeck et al., 2001). In recent studies, drop-out rates as high as 30–60% have been found. Drop-out rates tend to be particularly high in placebo-controlled studies. Analyses, therefore, have to be based on various assumptions using such models as ‘last observation carried forward’. Whether this provides a true reflection of the data is uncertain.

**Conclusion**

This meta-analysis reveals that amisulpride has been studied rather extensively, particularly concerning the negative symptoms of schizophrenia. It is an effective and well-tolerated atypical antipsychotic for both positive and negative symptoms of schizophrenia. The optimum dosage of amisulpride is higher for patients with positive symptoms (400–800 mg/d) than for patients experiencing pure negative symptoms (50–300 mg/d). The favourable profile of amisulpride in treating schizophrenia further supports the notion that the combined blockade of 5-HT$_2$ and D$_2$ receptors is not the only mechanism of action that makes an antipsychotic atypical.

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**Statement of Interest**

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**References**


