Methodological issues in studies of major depression and schizophrenia. Implications for the "Committee for proprietary medicinal products" guidelines
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6. Amisulpride: Is there a treatment for negative symptoms in schizophrenic patients?

Abstract

In this article we report a meta-analysis of the published studies of amisulpride which were conducted in order to demonstrate efficacy on primary negative symptoms in schizophrenia. Four placebo controlled studies were conducted in patients with predominantly negative symptoms. In all studies a significant improvement was observed on the SANS in the amisulpride groups (50-300 mg daily) as compared to placebo. The improvement on the SANS was not accompanied by a simultaneous improvement on the SAPS or a decrease in EPS in three of the four studies, indicating a genuine effect on primary negative symptoms. The overall analysis shows that the improvement on the SANS was accompanied by a small simultaneous improvement in the SAPS. Moreover in the studies where depressive symptoms were measured, also a significant improvement was shown in favor of amisulpride. However, as the SAPS and MADRS baseline scores were rather low the improvement on both scales in favor of amisulpride are probably not responsible for the improvement on the SANS. A positive correlation was found between the severity on the mean SANS score at baseline and mean improvement at endpoint and a surprisingly high success rate was observed in the placebo-groups, indicating either that primary negative symptoms are not as persistent as had previously been thought, or that the concept of primary negative symptoms should be reconsidered according to the theory of Grederen and Tandon; primary, enduring negative symptoms that are intrinsic to the disease process and primary nonenduring negative symptoms that are intrinsic to the disorder but wax and wane like positive symptoms. Probably amisulpride is efficacious on these nonenduring primary negative symptoms.
Introduction

Kraepelin (1913) regarded schizophrenia primarily as a defect state with a deteriorative course. Although there was a continued interest in (the treatment of) negative symptoms (Strauss et al. 1974; Carpenter et al. 1985) gradually more emphasis has been put on positive symptoms as pathognomonic of the disorder and even prerequisites for its diagnosis (Kay and Opler 1987). The significance attached to positive symptoms is evidenced, for example, in the diagnostic criteria for schizophrenia as put forth by Schneider (1959), Feighner et al. (1972), the RDC (1987) and DSM-III (R) (APA 1980; APA 1987). The emphasis on positive symptoms has led to the view that in the treatment of schizophrenia two stages can be distinguished: the first stage being the treatment of acute exacerbation, and the second stage being the maintenance phase, which strives to prevent relapse/recurrence. Dopamine receptor blocking compounds, the classic antipsychotics, have been shown to be efficacious in both stages.

In the last decade interest in negative symptoms has re-emerged and since DSM IV (APA 1994) three negative symptoms: affective flattening, alogia and avolition, are now included in the definition of Schizophrenia. Carpenter et al. (1988) made a distinction between primary and secondary negative symptoms. Primary negative symptoms correspond to a deficit state, while secondary negative symptoms may be due to many reasons such as psychotic turmoil, extrapyramidal symptoms (EPS), depression or environmental understimulation. This renewed interest in negative symptoms has led to a greater awareness of the treatment of such symptoms. Although primary negative symptoms were always considered as enduring traits (Carpenter et al. 1988) and not responsive to classic antipsychotic treatment (Crow 1985), amisulpride, a substituted benzamide with high affinity for dopamine (D₂/D₃) receptors (Perrault et al. 1997) is alleged to be effective on primary negative symptoms. At low doses it shows selective blockade of presynaptic dopamine autoreceptors and increased release of dopamine (Schoemaker et al. 1997; Perrault et al. 1997). In animal models low dose amisulpride did not result in catalepsy and shows prohedonic, behavior in rats that could be predictive for efficacy on negative symptoms (Scatton et al. 1997). At high doses, amisulpride shows merely post-synaptic binding at limbic dopamine receptors and animals behavior that could be predictive for efficacy on positive symptoms (Perrault et al. 1997). However the clinical relevance of these findings is unclear.

This paper reviews the clinical studies which have been conducted with amisulpride in the treatment of negative symptoms, and discusses the methodology and the results of these studies.

Method

study identification
We searched the Medline data base (from 1966 through July 1999) for literature with the key words “amisulpride” and “controlled study”. The search was restricted to studies in patients with predominantly negative symptoms.

data analysis
Confidence intervals (95%) were computed for differences between amisulpride and placebo, with respect to mean changes of total scores for the primary efficacy outcome measurements from baseline, based on the data presented in the papers. Standard errors of changes in mean scores were estimated from corresponding SD values, either as published (Danion et al. 1999) or as derived from relevant information about variability in the paper (Loo et al. 1997; Paillère et al. 1995). However, such information was not available in Boyer et al. (1995). Therefore we decided to use the average SD as an approximate estimate of the SD value for that study. This seemed justified, since two of the authors were also involved in the paper by Paillère et al. (1995), which implies similar circumstances. The resulting SD values turned out to be fairly homogeneous with regard to the SANS, the average being 45.0. With regard to SAPS we used a similar approach, although the SD values were more heterogeneous than for the SANS scores. The overall estimate and confidence intervals were based on a fixed model, weighed for variance differences between the studies.

Results

Four controlled studies were identified (Paillère-Martinot et al. 1995; Boyer et al. 1995; Loo et al. 1997; Danion et al. 1999). In all studies schizophrenic patients with predominantly negative symptoms were included. In the study of Paillère-Martinot et al. (1995) six patients who met the criteria for schizotypal personality disorder were also included.

With regard to exclusion criteria, in the study of Paillère-Martinot et al. (1995) patients with organic brain disorder, somatic disease or alcohol or drug abuse and patients with prominent positive symptoms or depression were excluded. Patients fulfilling criteria for positive schizophrenia were excluded in the study of Boyer et al. (1995) and in the study of Loo et al. (1997) patients presenting other major DSM-III-R diagnosis, risk of suicide, alcohol or drug abuse, Parkinson or any other severe somatic disease were excluded. In the study of Danion et al. (1999) patients with other DSM-III-R criteria were not excluded.

All studies were placebo-controlled and used different types of the Scale for the Assessment of Negative Symptoms (Andreasen 1984b) and the Scale for the Assessment of Positive Symptoms (Andreasen 1984a) as primary outcome measurement. In table 1 an overview is presented of these four placebo-controlled studies. The duration of the double-blind period varied from 6 weeks to 26 weeks. The dose of amisulpride ranged from 50 mg to 300 mg.

The severity scores at baseline on the SANS and SAPS indicated marked negative symptoms and rather low positive symptoms. Drop-out percentages ranged from 12% to 68%, the highest appearing in the study of 26 weeks. There was a tendency for more drop-outs in the placebo groups than in the amisulpride groups. The main reason for drop-out was the occurrence of exacerbation and/or lack of efficacy.

Figure 1 shows the differences between active treatment and placebo in mean change from baseline on the SANS and the SAPS. In the study of Danion et al. (1999) the improvement in the amisulpride group on the SANS was accompanied by an improvement on the SAPS. In the other three studies the beneficial effect of amisulpride on the SANS was not accompanied by simultaneous improvement on
the SAPS. The overall analysis shows that the improvement on the SANS was accompanied by a small simultaneous improvement on the SAPS.

In the studies reviewed a positive correlation between the mean SANS baseline scores and the mean improvement on the SANS at endpoint was found. (Pearson correlation coefficient: 0.735; p=0.015, n=10 treatment arms.)

Table 2 shows the SANS subscale effects. On all subscales of the SANS amisulpride was superior to placebo and in most cases the difference was statistically significant.

The studies differed considerably in the assessment of extrapyramidal symptoms. In the study of Boyer et al. (1995) the score on the Extrapyramidal Symptom Scale was low in all treatment groups at baseline. At the end of the study there was a small decrease in all treatment groups without statistically significant differences between groups.

In the study of Paillère-Martinet et al. (1995) EPS data were rated according to the items from the somatic subscale of the AMDP system. Sixty five percent of the patients had some extrapyramidal abnormalities before treatment. At the end of this study more patients in the amisulpride group had EPS than patients on placebo.

In the study of Loo et al. (1997) EPS scores on the Webster scale were rated as mild at the start of the study. Seven out of 72 patients in the placebo group and eight patients out of 69 in the amisulpride group used anti-Parkinsonian drugs from the start of the study. During the study anti-Parkinson medication was initiated in one patient in the placebo group and in four patients in the amisulpride group. At the end of the study EPS was still rated as mild in both groups with no statistically significant difference between treatments.

In the study of Danion et al. (1999) EPS was measured on the Simpson-Angus Rating Scale and the Abnormal Involuntary Movement Scale. EPS was rated as mild in all three treatment groups which was still the case at endpoint. Two patients received anti-Parkinsonian drugs in the placebo-group and two in the amisulpride 50 mg group.

In the study of Paillère et al. (1995) and Danion et al. (1999) severity of depression was measured. At endpoint a significant difference in mean improvement on the MADRS in favor of the active treatments compared to placebo was observed.

Discussion

Efficacy on negative symptoms has been associated with classic antipsychotic treatment (Goldberg 1985; Meltzer et al. 1986) and claimed for clozapine (Kane et al. 1988) but this has never been shown in placebo-controlled studies conducted in patients with predominantly negative symptoms. In most of the pivotal short-term randomized placebo-controlled trials of recently developed anti-schizophrenic agents (Borison et al. 1992; Chouinard et al. 1993; Marder and Meibach 1994; Peuskens 1995; Beasley et al. 1996; Beasley et al. 1996; Tollefson et al. 1997; Zimbroff et al. 1997; Arvantis et al. 1997; Small et al. 1997; Borison et al. 1996; King et al. 1998; Keck et al. 1998) efficacy on negative symptoms has been claimed. However, since patients with predominantly positive symptoms were included in these studies, these findings might be explained by the primary beneficial effect on positive symptoms, causing secondarily an improvement on the negative symptom score (Möller 1993;
Möller et al. 1994). An improvement on the negative symptom score might also be explained by the lower EPS properties of these new compounds compared to the classic antipsychotics. In conclusion in these studies, it is impossible to disentangle which part of the improvement on negative symptom score is due to the improvement on positive symptoms and which part to less EPS, or to an improvement on depressive symptoms, or to an actual effect on primary negative symptoms. For this reason specific study designs have been developed with the primary objective to show efficacy on primary negative symptoms (Möller et al. 1994; CPMP 1998). In these studies patients with predominantly negative symptoms ought to be included. Moreover, the patients ought to have low levels of positive symptoms, depressive symptoms and EPS at baseline and these symptoms should stay relatively stable during the study. A wash-out period with sufficiently long duration before the start of the study should ensure that the patients included are free of (depot) medication effects including EPS. Oral antipsychotic medications have antidopaminergic effects for at least 2 weeks, while depot medications may have these actions for months (Farde et al. 1992). Thus a short period of discontinuation of prior medication (e.g., less than 7 days) is not a "true" medication-free assessment (Harvey and Keefe 2001).

EPS at baseline can lead to an improvement on the SANS during the study which is a pseudo improvement of negative symptoms since it might only be due to wash-out of previously taken classic antipsychotics with the associated EPS. The amisulpride studies which were conducted to demonstrate efficacy in negative symptoms included patients with predominantly negative symptoms, with low SAPS scores and low scores on EPS scales at baseline. However, depression scores were not rated in two studies (figure 1) and in two studies no-wash out period was observed (table 1). In the study of Loo et al. (1997), the lack of wash-out period was not a major shortcoming, as this study had a long duration. The influence of EPS at baseline in both placebo and amisulpride groups has probably been washed out during the study, making fairly implausible that efficacy results at the end are influenced by the EPS at baseline.

In all studies a significant difference on the SANS was shown in favor of low doses of amisulpride (50-300 mg) compared to placebo. These results are not suggestive for a dose-effect relationship in the dose range between 50 and 300 mg. The improvement on the SANS was not accompanied by a simultaneous improvement on the SAPS or a decrease in EPS in three of the four studies, suggesting efficacy on primary negative symptoms. However, the overall analysis showed a significant improvement on the SAPS in favor of the amisulpride treated group. Moreover, in the studies where depressive symptoms were measured, a significant improvement was shown in favor of amisulpride also. This might be interpreted as that the effect shown on negative symptoms was due to the improvement on positive symptoms and/or on depressive symptoms. However, the SAPS and MADRS baseline scores were rather low. Therefore the improvement on both scales in favor of amisulpride only has modest clinical impact and is probably not responsible for the improvement on the SANS. Another option for the depression score improvement might be that it is due to the improvement on the SANS.

With regard to the SANS it should be noted that this instrument is reliable and valid for rating negative symptoms. However, it is not developed for making a distinction between primary and secondary negative symptoms. Therefore, although the
patients included in the studies had high SANS scores at baseline, this was not completely a guarantee that they were the representative population. Maybe not only the use of the SANS but also the use of the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al. 1989; Kirkpatrick et al. 2000) could be an option in future studies, as this instrument is able to make a distinction in patients with and those without primary negative symptoms by longitudinal assessment of relevant parameters. This instrument was already used in several studies to distinguish primary from secondary negative symptoms (Conley et al. 1994; Buchanan et al. 1998; Rosenheck et al. 1999; Kopelowicz et al. 2000).

An impressive finding in the studies reviewed was the success rate in the placebo-groups. It has always been assumed that primary negative symptoms were persistent and stable (Carpenter et al. 1988) and improvement was expected to be slower than in positive symptoms. All studies showed, however, a substantial success rate in the placebo-group which was between 8% and 25% after 6 weeks, 18% after 12 weeks and 20% after 26 weeks. The positive correlation between mean SANS baseline scores and endpoint scores as well as the success rate in the placebo-groups might be explained as an example of regression to the mean.

Another interpretation for these phenomena might be that the concept of primary negative symptoms should be reconsidered and changed according to the theory of Greden and Tandon (1991) that was recently summarized by Kopelowicz et al. (2000). In this theory two types of primary negative symptoms are distinguished; deficit or primary, enduring negative symptoms that are intrinsic to the disease process and primary nonenduring negative symptoms that are intrinsic to the disorder but wax and wane like positive symptoms. The results of the amisulpride studies indicate that low doses of amisulpride is efficacious on the non-enduring primary negative symptoms and probably not on the enduring primary negative symptoms.

As the pharmacodynamic profile of low doses of amisulpride is not indicative to prevent an acute exacerbation, treatment under low doses of amisulpride might increase the risk of relapse/recurrence. What is to be done when a patient who is treated with low doses of amisulpride experiences an exacerbation?

Five active controlled studies in schizophrenic patients with predominately positive symptoms were conducted (Delcker et al. 1990; Möller et al. 1997; Puech et al. 1998; Wetzel et al. 1998; Peuskens et al. 1999). Amisulpride was given in doses five to ten times higher than in studies in patients with predominantly negative symptoms. However in studies in schizophrenia there is always the problem of assay sensitivity; assay sensitivity is the ability of a study to distinguish between active and inactive treatments (Temple and Ellenberg 2000). Since no placebo control was used in these amisulpride studies efficacy for the traditional treatment of schizophrenia was not demonstrated unequivocally (Storosum et al. 1998). Hence in case of an acute exacerbation under low dose amisulpride, it is questionable whether increasing the dose is the right strategy. Moreover it is not clear what will happen with the improvement on negative symptoms due to amisulpride when patients are treated for an acute exacerbation (with positive symptoms).
References

Andreasen, N. Scale for the Assessment of Negative Symptoms. Iowa City, IA: University of Iowa, 1984a.

Andreasen, N. Scale for the Assessment of Positive Symptoms. Iowa City, IA: University of Iowa, 1984b.


Schoemaker, H.; Claustre, Y.; Fage, D.; Rouquir, L.; Chergui, K.; Curet, O.; Oblin, A.; Gonon, F.; Carter, C.; Benavides, J.; and Scatton B. Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both


**Table 1. Characteristics of the 4 placebo-controlled studies conducted to demonstrate efficacy on negative symptoms**

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients included</th>
<th>Other Inclusion criteria</th>
<th>Wash-out</th>
<th>Study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pailhère et al.</td>
<td>DSM III-R diagnosis of schizophrenia; disorganised and undifferentiated or schizotypal personality disorder</td>
<td>young age, SANS: mean items rating of 3 in at least two subscales, short disease course, neuroleptic naïve condition or treatment &lt; 1 month</td>
<td>no (drug free patients) or lifetime drug treatment &lt; 1 month</td>
<td>6 weeks</td>
</tr>
<tr>
<td>(1995)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyer et al.</td>
<td>DSM III diagnosis of schizophrenia: disorganised, catatonic, undifferentiated or residual type</td>
<td>Andreasen criteria for negative schizophrenia* SANS ≥ 75 points SAPS ≤ 60 points</td>
<td>6 weeks, 12 weeks if they had received depot medication</td>
<td>6 weeks</td>
</tr>
<tr>
<td>(1995)</td>
<td></td>
<td></td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Loo et al.</td>
<td>DSM III-R diagnosis of schizophrenia: disorganised or residual type Subchronic or chronic</td>
<td>Andreasen criteria for negative schizophrenia* SANS ≥ 60 points SANS ≤ 60 points</td>
<td>66 weeks</td>
<td>26 weeks</td>
</tr>
<tr>
<td>(1997)</td>
<td>or &lt; 20 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danion et al.</td>
<td>DSM III-R diagnosis of schizophrenia: residual type or &lt; 20 years</td>
<td></td>
<td>4 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>(1999)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* the presence of at least two of the following symptoms with severe/marked intensity: alogia, affective blunting, anhedonia, asociality, avolition/apathy, attentional impairment.
### Table 2: Patients randomized, analyzed and early terminated

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatments</th>
<th>N randomized/analyzed</th>
<th>Exacerbation</th>
<th>Early terminated worsening</th>
<th>LOE</th>
<th>ADEs</th>
<th>other reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paillère et al. (1995)</td>
<td>amisulpride 50 mg placebo:</td>
<td>14</td>
<td>10</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Boyer et al. (1995)</td>
<td>amisulpride 100 mg</td>
<td>34</td>
<td>30</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>amisulpride 300 mg placebo</td>
<td>36</td>
<td>30</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>34</td>
<td>24</td>
<td>4</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Loo et al. (1997)</td>
<td>amisulpride 100 mg placebo</td>
<td>69</td>
<td>69</td>
<td>4</td>
<td>19</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Danion et al. (1999)</td>
<td>amisulpride 50 mg placebo</td>
<td>84</td>
<td>84</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>amisulpride 100 mg placebo</td>
<td>75</td>
<td>74</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>

LOE: loss of efficacy  
ADE's: adverse events
<table>
<thead>
<tr>
<th>Source</th>
<th>Treatments</th>
<th>Affective flattening</th>
<th>Alogia</th>
<th>Avulsion, apathy</th>
<th>Anhedonia, asociality</th>
<th>Attention impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>baseline</td>
<td>endpoint</td>
<td>baseline</td>
<td>endpoint</td>
<td>baseline</td>
</tr>
<tr>
<td>Pailièr et al. (1995)</td>
<td>Amisulpride 50 mg</td>
<td>17.2 (7.6)</td>
<td>13.0 (6.3)</td>
<td>9.3 (4.8)</td>
<td>6.6 (3.3)</td>
<td>9.9 (1.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>17.7 (4.4)</td>
<td>17.9 (5.1)</td>
<td>8.9 (3.3)</td>
<td>8.4 (3.4)</td>
<td>9.1 (2.8)</td>
</tr>
<tr>
<td>Boyer et al. (1995)</td>
<td>Amisulpride 100 mg</td>
<td>24.5 (6.4)</td>
<td>13.0 (6.3)</td>
<td>13.8 (3.3)</td>
<td>8.0 (3.4)</td>
<td>13.2 (2.8)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>23.0 (2.0)</td>
<td>18.1 (1.7)</td>
<td>13.9 (3.1)</td>
<td>10.7 (3.1)</td>
<td>13.7 (3.1)</td>
</tr>
<tr>
<td>Loo et al. (1997)</td>
<td>Amisulpride 100 mg</td>
<td>20.8 (5.6)</td>
<td>16.0 (8.1)</td>
<td>10.9 (3.1)</td>
<td>8.8 (4.2)</td>
<td>10.6 (2.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>20.8 (5.6)</td>
<td>16.0 (8.1)</td>
<td>10.9 (3.1)</td>
<td>8.8 (4.2)</td>
<td>10.6 (2.4)</td>
</tr>
<tr>
<td>Danion et al. (1999)</td>
<td>Amisulpride 50 mg</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

1 amisulpride statistically significant superior to placebo (Mann-Whitney U test; one-tailed)
2 amisulpride statistically significant superior to placebo (MANOVA)
3 amisulpride statistically significant superior to placebo (One way analysis of variance)

In the publication of Boyer et al (1995) standard deviation data were not provided
In the publication of Danion et al. (1999) SANS subscales results were not provided
The graphs represent the mean differences and 95% confidence intervals between amisulpride and placebo on the SANS and SAPS respectively. The overall estimate and confidence intervals were based on a fixed model, weighed for variance differences between the studies. There was no indication for heterogeneity between the studies: $\chi^2_{\text{SANS}} = 4.07 \text{ Df}=5, p=0.54$, Test for heterogeneity $\chi^2_{\text{SAPS}} = 6.33 \text{ Df}=5, p=0.28$. 

**Table:**

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatments</th>
<th>Baseline/change at endpoint</th>
<th>SANS</th>
<th>SAPS</th>
<th>MADRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paillère et al.</td>
<td>Ami. 50 mg</td>
<td>74.9/-24.0</td>
<td>15.3/-3.8</td>
<td>13.2/-5.6</td>
<td></td>
</tr>
<tr>
<td>(1995)</td>
<td>Placebo</td>
<td>73.5/-5.9</td>
<td>14.3/-3.3</td>
<td>11.5/-0.6</td>
<td></td>
</tr>
<tr>
<td>Boyer et al.</td>
<td>Ami. 100 mg</td>
<td>96.9/-41.9</td>
<td>23.1/-8.3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(1995)</td>
<td>Ami. 300 mg</td>
<td>97.0/-47.3</td>
<td>22.4/-8.4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>95.8/-23.8</td>
<td>23.5/-4.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Loo et al.</td>
<td>Ami. 100 mg</td>
<td>81.0/-33.5</td>
<td>22.4/-1.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(1997)</td>
<td>Placebo</td>
<td>81.5/-16.7</td>
<td>19.4/-0.1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Danion et al.</td>
<td>Ami. 50 mg</td>
<td>76.3/-24.8</td>
<td>20.0/0.6</td>
<td>13.5/-4.1</td>
<td></td>
</tr>
<tr>
<td>(1999)</td>
<td>Ami. 100 mg</td>
<td>77.6/-25.4</td>
<td>20.0/-2.5</td>
<td>13.3/-3.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>74.9/-13.4</td>
<td>18.3/5.8</td>
<td>13.5/0.4</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1:** Mean baseline score, mean improvement on the primary outcome measure and 95% CI of the difference between amisulpride and placebo.