Bridging from drug registration trials to meaningful clinical evidence: The case of schizophrenia

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Citation for published version (APA):
Chapter 5

The impact of second generation antipsychotics on insight in schizophrenia: Results from 14 randomized, placebo controlled trials

Manuscript in preparation

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Abstract

Despite the negative impact of lack of insight on the prognosis, general functioning and treatment adherence, the effect of antipsychotic medication on insight has been investigated only in small samples and uncontrolled studies. In this study we examine whether previously reported effects of antipsychotics on insight from uncontrolled studies can be confirmed in a database including 14 randomized, double-blind, placebo-controlled trials.

The database contained placebo-controlled RCTs of five second-generation antipsychotics (SGAs: olanzapine, paliperidone, quetiapine, risperidone and sertindole) and included a total of 4,243 patients with schizophrenia. Insight was assessed with item G12 of the Positive and Negative Syndrome Scale (PANNS) at baseline and at six weeks.

Overall, SGA treatment resulted in a significantly larger improvement in insight than placebo (0.43 points versus 0.15 points; Hedge’s g 0.23; p<0.001). However this difference in improvement in insight was largely explained by improvement in other symptoms. In the initial analysis, one of the compounds was significantly less effective in improving insight than the other SGAs, but this difference no longer persisted when improvement in other symptoms was taken into account. The effect of SGAs on improvement in insight was not moderated by geographic region, illness duration or drop-out.

The present study showed that SGA treatment of patients with schizophrenia is associated with improved insight, but that this improvement largely is explained by SGA induced improvements in other symptoms though the causal relationship may not be established.
Introduction

Poor insight is highly prevalent in patients with schizophrenia (1). Insight does not only refer to the awareness of mental illness, but also to the recognition of the need for treatment and the relabeling of symptoms such as delusions and hallucinations. Despite the known negative impact of lack of insight on prognosis, functioning and treatment adherence, the effect of antipsychotic medication on insight has not been extensively studied. In a small switching study (N=22) Aguglia et al. (2) reported that the second generation antipsychotics (SGAs) clozapine, risperidone and olanzapine had a better effect on insight than the first generation antipsychotic (FGA) haloperidol. More recently, another switching study in 55 patients with a psychotic exacerbation confirmed the superiority of SGAs over haloperidol, and no differences were observed between the included SGAs olanzapine, aripiprazole and ziprasidone (3). In a recent large randomized open label trial (N=455), Pijnenborg et al. (4) found that the antipsychotics amisulpride, haloperidol, olanzapine, quetiapine and ziprazidone all improved insight over and above improvements in other symptoms, with the largest effects in the first three months of treatment and with quetiapine being significantly less effective than the other antipsychotics.

An important limitation of all these studies is the lack of placebo control, as there is a high overall placebo response to antipsychotics (5). Therefore the present study was initiated to examine whether the previously reported effects of antipsychotics on insight can be confirmed using a large dataset (N=4,243) of randomized, double-blind, placebo-controlled trials.

Experimental procedures

Trials

Double-blind, randomized, placebo controlled efficacy trials with SGAs for the treatment of acute psychotic episodes in patients with schizophrenia were identified from documentation submitted to the Dutch regulatory authority for the purpose of marketing authorisation application. A study period of six weeks was chosen for the endpoint, because this is the duration of short-term schizophrenia trials recommended in the EMA Committee for Medicinal Products for Human Use (CHMP) guideline on clinical investigation of medicinal products in the treatment of schizophrenia (6) (EMA/CHMP/40072/2010 Rev. 1). Subsequently, the companies were asked to provide the raw data.

Assessments

Insight was assessed with item G12 of the Positive and Negative Syndrome Scale
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(PANSS) (7). Item G12, i.e. lack of judgement and insight, is assessed on a 7-point scale: absent (1), minimal (2), mild (3), moderate (4), moderate severe (5), severe (6) and extreme (7), thus a score of 1 means that the patient has a good insight in his/her illness. For studies shorter than six weeks or for patients who dropped out before the end of a six-week study, the last observation was carried forward to week 6.

Statistical analysis
An ITT analysis of all randomized patients with at least one post-baseline assessment was performed.
Active comparator arms other than the studied SGAs (e.g. haloperidol) were excluded from the analysis, as well as treatment arms with dosages lower than the lowest effective dose, as indicated in the current Summary of Product Characteristics (SPC) of each compound. All SGAs and doses were collapsed under the same active arm.
To examine whether there were any differences between the SGA and placebo group in baseline characteristics, independent samples t-test (for age, illness duration, PANNS G12 score, PANNS total score and the subscale scores) and a chi-square test (for gender) were applied.
A linear mixed model regression analysis with change in PANNS G12 score as dependent variable and treatment condition (SGA vs. placebo) as independent variable was performed to analyse the effect of treatment on insight. To examine whether the difference in change in insight was independent of the PANNS total score, the analysis was repeated while controlling for the change in the PANNS total score (minus the score on item G12). In addition, each of the PANNS subscales scores (minus the score on insight in the subscale general psychopathology) was examined for independence.
We also examined whether the effect of SGAs on insight was modified by geographical region (Western Europe, Eastern Europe, North America and Asia), by illness duration or by study drop-out at 6-week treatment, using the interaction term of treatment condition by the potentially modifying variables (region, illness duration and study drop-out). Possible differences between medications were tested using the same method.
In all regression analyses, study was used as a level 2 variable and a random intercept was used to account for dependencies within trials. For these analyses IBM SPSS Statistics version 20 was used as the statistical package.

Results

Trials
Of the total 29 trials that were requested, 22 (76%) were submitted, including data from 5,233 patients. However, from these 22 trials, only 14 also included the PANNS scale (N=4,243) and data of these trials were included in the present analysis. These
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trials examined the efficacy of five different SGAs: olanzapine, paliperidone, quetiapine, risperidone and sertindole.

Patients
Table 1 presents the baseline demographic and clinical characteristics of all included patients. There were no statistically significant differences between the active and placebo groups with respect to any baseline characteristics. None of the patients had a missing G12 score at baseline or at 6 weeks, and the mean baseline score on PANNS item G12 was 3.7 indicating moderate lack of insight.

Table 1.
Baseline demographic and clinical characteristics of the included patients (N=4,243).

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=1173)</th>
<th>Active (N=3070)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>39.3 (11.8)</td>
<td>38.9 (11.3)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>28.9%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Illness duration (mean, SD)</td>
<td>14.8 (10.2)</td>
<td>14.5 (10.7)</td>
</tr>
<tr>
<td>PANNS item G12, lack of insight (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 absent</td>
<td>3.8%</td>
<td>5.4%</td>
</tr>
<tr>
<td>2 minimal</td>
<td>11.3%</td>
<td>10.9%</td>
</tr>
<tr>
<td>3 mild</td>
<td>25.0%</td>
<td>25.4%</td>
</tr>
<tr>
<td>4 moderate</td>
<td>35.0%</td>
<td>34.3%</td>
</tr>
<tr>
<td>5 moderate severe</td>
<td>15.6%</td>
<td>15.0%</td>
</tr>
<tr>
<td>6 severe</td>
<td>8.5%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.8%</td>
<td>0.9%</td>
</tr>
<tr>
<td>PANNS total (mean, SD)</td>
<td>93.2 (15.4)</td>
<td>93.4 (16.0)</td>
</tr>
<tr>
<td>PANNS positive (mean, SD)</td>
<td>23.4 (5.1)</td>
<td>23.5 (5.2)</td>
</tr>
<tr>
<td>PANNS negative (mean, SD)</td>
<td>24.0 (6.0)</td>
<td>24.3 (6.1)</td>
</tr>
<tr>
<td>PANNS general (mean, SD)</td>
<td>45.8 (8.5)</td>
<td>45.6 (8.7)</td>
</tr>
</tbody>
</table>

a illness duration information was available for 2654 patients

The mean improvement in insight score from baseline to 6 weeks (with the standard error and p-values obtained from the linear mixed model regression analysis) is presented in Figure 1. The mean improvement in insight score from baseline to 6 weeks was 0.43 (p<0.001) in the active treatment group compared to 0.15 (p=0.113) in the placebo group. The difference between active and placebo group was statistically significant (β -0.27, p<0.001), with an effect size of Hedge’s g 0.23. The mean improvement in PANNS
total score from baseline to 6 weeks was 15.7 (p<0.001) in the active treatment group and 6.1 (p=0.005) in the placebo group. The difference between active and placebo group was statistically significant (β -9.4, p<0.001), with an effect size of Hedge’s g 0.44. After correcting for the change in PANNS total score (minus item G12 score), the difference in improvement in insight disappeared (β 0.06, p=0.072), indicating that the observed improvement in the insight score is (statistically) explained by the improvement of other symptoms. Similar results were obtained after correction for the PANNS subscales, although the impact of improvements in the negative subscale (β -0.07, p=0.058) was smaller than improvements in the positive (β 0.03, p=0.391) and general (β 0.02, p= 0.606) subscales.

When examining the differences between different medications on insight, it was observed that while as a group SGAs had a statistically significant effect on insight, one of the compounds was significantly less effective in improving insight than the other SGAs(p=0.008). However, after correcting for the change in PANNS total score, there were no statistically significant differences between the SGAs anymore (p= 0.358). Correction for each of the PANNS subscales yielded the same result.

There were no significant differences in the effect of SGAs on insight compared to placebo for different geographic regions (interaction p=0.099), illness duration (interaction p=0.742) or between patients who dropped out and patients who completed the study (interaction p=0.527). Correction for the change in PANNS total score or subscales resulted in similar findings.

![Figure 1](image-url)

**Figure 1.**
Mean improvement in insight score from baseline to 6 weeks per treatment arm, uncorrected and corrected values (for PANNS total, positive, negative and general), standard errors and p-values.
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Discussion

The aim of this study was to examine the effects of SGAs on insight in a large sample of patients with schizophrenia, using data from randomized, placebo-controlled trials. Our study shows that poor insight is a common phenomenon in patients with schizophrenia: 59% of the patients reported at least moderate lack of insight. This is similar to most other studies on this subject (1,4). Furthermore, our results show a small improvement in insight after 6 weeks SGA treatment: Hedge’s g is 0.23. This is in contrast to the study by Pijnenborg et al. (4) where the improvement in the insight score was considerably higher at 1 month (approximately 1 full-point improvement in the active arm compared to 0.43 point in the active arm of our study). However the patients in the study by Pijnenborg and colleagues had a higher mean baseline score (4.2 vs. 3.7 in our study) and the mean score at one month was almost identical to what we observed in our study in the SGA group at 6 weeks (3.26 vs. 3.27). The higher baseline score in the study by Pijnenborg et al. is probably explained by the fact that only patients with at least minimal lack of insight (score higher than 1) were included, while we included all patients irrespective of the baseline insight score. The larger improvement in insight in the study by Pijnenborg et al. may also be related to the fact that only patients with first episode were included, whereas in our study also patients with a longer duration of illness were included.

We also found that the improvement in insight was associated with improvement in other symptom domains, in particular with symptoms belonging to the positive and general psychopathology subscales of the PANNS. Previous studies have shown conflicting results on the relationship of symptoms and insight (3,8-9), and in the largest study performed so far by Pijnenborg and colleagues (4), it was concluded that the effects of antipsychotics on insight were independent from the improvement in PANNS scores. Our results, however, suggests that this mediation effect does exist, although the direction of the effect could not be examined due to the lack of intermediate assessments.

While as a group the five different SGAs had a significant effect on insight, one of the compounds seemed to improve insight the least of the SGAs. However after correcting for the PANNS total or subscale scores, there were no significant differences between the different SGAs anymore. This is in contrast with the study by Pijnenborg et al. (4) where treatment with quetiapine was significantly less effective in improving insight than the other included antipsychotics during the first three months of the study. The inferiority of quetiapine in the study by Pijnenborg et al. may be related to lower acceptability of quetiapine or insufficient power to reliably detect differences between treatments. However in our sample, drop-out rate was the lowest in the quetiapine group, which does not support overall lower adherence to quetiapine.

We also found that the effects of SGAs compared to placebo on insight did not differ
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between geographic regions, illness duration or treatment completion. The fact that duration of illness did not moderate the improvement in insight is surprising, because it has been suggested that insight improvement with medication is more pronounced in the early phase schizophrenia as compared to chronic patients (10). However there were very few patients in our sample who could be considered patients in early phase schizophrenia, as only 6% of patients had illness duration of a year or less. We therefore can not exclude that the effect of antipsychotics on insight is larger in the early phase of the disorder.

The current study has both strengths and limitations. The main strength of our study is the large sample size and the randomized, double-blind, placebo-controlled design of the included trials. Previous studies on the effects of antipsychotics on insight have used uncontrolled designs, therefore not accounting for the natural course of the disease and the possible effects of being under close supervision of professional medical care. Our results show that placebo treatment was associated with a small improvement of the insight score of 0.15 points in the first weeks of treatment, indicating that previous uncontrolled studies may have overestimated the effect. It is nonetheless interesting that placebo may improve insight in schizophrenia.

The main limitation of this study is the fact that we did not have a separate scale for the assessment of insight; instead item G12 of the PANNS scale was used. However, it has been shown that this item and specific scales for the assessment of insight are highly correlated (11). Another limitation is that although we could conclude that improvement in insight is associated with improvement in other symptom domains, we could not determine the direction of causality, i.e. which improves first.

In conclusion, treatment with SGAs is associated with a small improvement in insight in the first 6 weeks and that this improvement is largely explained by improvements in other symptoms, in particular those of the positive and general psychopathology subscales of the PANNS.
References