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

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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 4243 patients with schizophrenia. Insight was assessed with item G12 of the Positive and Negative Syndrome Scale (PANSS) 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 is associated with SGA induced improvements in other symptoms, though the causal relationship may not be established.

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1. Introduction

Poor insight is highly prevalent in patients with schizophrenia (Bayard et al., 2009). 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. Lack of insight has been associated with poorer prognosis e.g. with respect to hospitalisations and remission (Lincoln et al. 2007, Cannavò et al., 2016), poorer functioning, including work performance and social functioning (Lincoln et al. 2007), and poorer treatment adherence (Buckley et al., 2007). The role of insight in depressive symptoms and suicidality in patients with schizophrenia has also been repeatedly studied. (López-Moríñigo et al., 2012; Belvederi Murri et al., 2015) Despite the role and importance of insight in schizophrenia, the effect of antipsychotic medication on insight has not been extensively studied. In a small switching study (N=22) Aguglia et al. (2002) 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 (Bianchini et al., 2014). In a recent large randomized open label trial (N=455), Pijnenborg et al. (2015) found that the antipsychotics amisulpride, haloperidol, olanzapine, quetiapine and ziprasidone 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 (Kinon et al., 2011). 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= 4243) of randomized, double-blind, placebo-controlled trials.

2. Experimental procedures

2.1. 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 (CHMP 2010) (EMA/CHMP/40072/2010 Rev. 1). Subsequently, the companies were asked to provide the raw data.

2.2. Assessments

Insight was assessed with item G12 of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). 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.

2.3. 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, PANSS G12 score, PANSS total score and the subscale scores) and a chi-square test (for gender) were applied.

A linear mixed model regression analysis with change in PANSS 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 PANSS total score, the analysis was repeated while controlling for the change in the PANSS total score (minus the score on item G12). In addition, each of the PANSS 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. As a secondary analysis, a two-step, random effects meta-analysis using Comprehensive Meta-Analysis version 2 was performed. As the results were compatible with the primary analysis, these results are not presented in this paper.

3. Results

3.1. Trials

Of the total 29 trials that were requested, 22 (76%) were submitted, including data from 5233 patients. However, from these 22 trials, only 14 also included the PANSS scale (N= 4243) and data of these trials were included in the present analysis. These trials examined the efficacy of five different SGAs: olanzapine, paliperidone, quetiapine, risperidone and sertindole.

3.2. 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.