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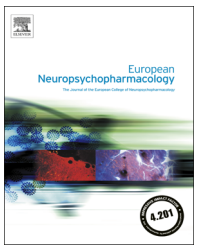

Geographic variation in efficacy of atypical antipsychotics for the acute treatment of schizophrenia – An individual patient data meta-analysis

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Abstract
Generalizability of efficacy results from medication trials across geographic regions is disputed. Geographic differences in factors such as patient characteristics, treatment practices and disease definitions might lead to differences in effect sizes across regions. This study examined geographic variation in efficacy results of schizophrenia trials with atypical antipsychotics using individual-patient data meta-analysis. Twenty-two studies including in total 5233 patients from three regions (North America, Europe, and the rest of the world) were included in the random effects meta-analysis. The effect size in North American patients was smaller in terms of mean change from baseline and in terms of responders (Hedge's G=0.37, 95% CI 0.28–0.46; OR 1.71, 95% CI 1.35–2.17) as compared to patients in Europe (Hedge's G=0.56, 95% CI 0.34–0.79; OR 2.25, 95% CI 1.62–3.12) and the rest of the world (Hedge's G=0.53, 95% CI 0.12–0.75; OR 2.61, 95% CI 1.66–4.17). The differences were not statistically significant. The observed differences remained when the confounding effect of unequal distribution of compounds was controlled for by analyzing separately the compounds that were studied across all three regions. Based on these results it cannot be excluded that there are differences in efficacy results of atypical antipsychotics trials across geographic regions. The observed trend towards differential efficacy across geographic regions warrants further examination of the determinants of these differences.

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1. Introduction

Placebo controlled randomized clinical trials are the gold standard for testing efficacy of new pharmaceutical compounds (ICH, 1998, 2001). However, the external validity of such trials has been regularly disputed. Issues that may affect external validity include differences in study design and routine practice, highly selective trial inclusion/exclusion criteria and the setting of the trial. (Rothwell, 2005, 2006). An important factor related to setting of the trial is the geographic area where the trial was performed. Regional differences in factors such as health care availability, medicinal practice, disease definition and patient characteristics (e.g. race and treatment compliance) may lead to different results with respect to efficacy and/or safety in the different regions (Rothwell, 2005, 2006; ICH, 1995). Therefore generalizability of the results across geographic regions has been questioned. Extrapolation of results across regions is currently addressed by regulatory authorities on a case-by-case assessment (CHMP, 2008, US Department of Health and Human Services, 2013a, 2013b). The United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) prefer studies to be conducted in their own geographical region. Moreover in recent years there is a shift in location of conducting clinical trials from traditional sites in North America and Western Europe to emerging regions, such as Eastern Europe and Asia. Globalization of clinical trials is beneficial in terms of spreading medical knowledge and effective medicinal practice, and it enables patients' access to medical care. Conducting clinical trials in these new regions is also advantageous to industry as costs can be reduced while still recruiting large numbers of patients (Thiers et al., 2008). Therefore there is a growing interest in the generalizability of efficacy and safety results of clinical trials across regions.

In the current study, we examine the generalizability of the results of placebo controlled trials of atypical antipsychotics in the acute treatment of schizophrenia across geographic regions. Schizophrenia is a disorder characterized by positive symptoms (e.g. hallucinations and delusions), negative symptoms (e.g. flat affect and avolition) and impairments in cognition (e.g. attention, memory, and flexibility). Patient's social and occupational functioning is commonly severely affected. Schizophrenia affects about 7 per 1000 in the adult population (McGrath et al., 2008). Pharmacotherapy of schizophrenia is commonly grouped into two classes, typical and atypical antipsychotics. It is known that there are differences in the prevalence of schizophrenia between latitudes (Davies et al., 2003) and rural versus urban areas (Pedersen and Mortensen, 2001; Krabbendam and van Os, 2005; March et al., 2008). However, only limited evidence is available on the potentially modifying effect of geographic factors on the efficacy of pharmacological compounds in schizophrenia. For example, studies investigating the influence of race-ethnicity on the effect of antipsychotics in the treatment of patients with schizophrenia suggest that such differences may exist due to differences in metabolism (Bersani et al., 2011; Bigos et al., 2011), differences in side effects (Stauffer et al., 2010), differences in compliance/drop-out, or other race-ethnicity related factors, ultimately resulting in differences in overall treatment response (Teo et al., 2013). However, other studies found no effect of race-ethnicity on treatment response to antipsychotics in patients with schizophrenia (Ciliberto et al., 2005; Stauffer et al., 2010).

A recent study conducted by the FDA, which mainly focused on changes over time in efficacy of medications for the treatment of schizophrenia, also explored differences in results between trials conducted in North America and elsewhere (Khin et al., 2012). No significant differences in effect size were observed between North American and multiregional trials, although the effect size was numerically smaller in North America. However, the classification of geographic regions may not be considered optimal in this trial-level meta-analytic study (32 studies, $N=11,567$) as trials were divided into North American, North-America predominant and foreign-predominant studies. As a consequence, foreign-predominant studies could include up to 50% patients from North America. In addition, the study failed to stratify the results by compound, which may have confounded the conclusions since trials with different compounds cannot be assumed to be equally distributed across geographic regions. These two issues illustrate why a traditional meta-analysis based on information described in articles and reviews is not optimal for examining geographic variation with regards to efficacy, namely that variables possibly affecting this variability are available only on study level and not on individual patient level.

A recent individual patient data meta-analysis by Chen et al. (2010) (33 studies, $N=12,585$) also investigated regional heterogeneity of treatment effect of medications used for the treatment of schizophrenia. In this study the following geographic regions were ascertained for each patient: Asia, Eastern Europe, Western Europe, North America, South Africa, and Latin America. Among the three largest regions, treatment effect was observed to be larger in Asia and Eastern Europe as compared to North America. However, this study also failed to control for the potential effect of compound and therefore the findings may be confounded by differences in the distribution of compounds across geographic regions.

The objective of the current study is to investigate geographic variation in efficacy in short-term efficacy studies of different atypical antipsychotics in the acute treatment of schizophrenia using individual patient data meta-analysis, taking into account the potential confounding effect of compound.

2. Experimental procedures

2.1. Selection of studies

Double-blind, randomized, placebo controlled short-term efficacy trials with atypical antipsychotics for the treatment of psychotic episodes in patients with DSM-III-R or DSM-IV schizophrenia were identified from documentation submitted to the Dutch regulatory authority for the purpose of marketing authorization application. Of note, the same data were also used for the registration of these products in other European countries. A study period of six weeks was chosen for the analysis cut-off point, 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

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