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REVIEW

How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis

Yikang Zhu[a,b], Chunbo Li[b], Maximilian Huhn[a], Philipp Rothe[c], Marc Krause[a], Irene Bighelli[a], Johannes Schneider-Thoma[a], Stefan Leucht[a,*]

[a]*Department of Psychiatry and Psychotherapy, Technische Universität München, Klinikum rechts der Isar, Ismaningerstraße 22, 81675 Munich, Germany*
[b]*Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, South Wan Ping Road 600, 200030 Shanghai, China*
[c]*Kbo-Isar-Amper-Klinikum Taufkirchen (Vils), Bräuhausstraße 5, 84416 Munich, Germany*

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Abstract
It is often stated that first-episode patients tend to respond better to antipsychotics than chronic patients, but the exact numbers and moderators of response in this population are unclear. We, therefore, present the first systematic review on response rates of first episode patients with schizophrenia in randomized trials. We searched multiple databases for randomized-controlled trials of antipsychotics in acutely ill patients with a first episode of schizophrenia (last search: November 17, 2016). The outcomes were response rate based on two criteria, at least 50% PANSS or BPRS total score reduction from baseline and at least 20% reduction. Data were pooled in a single-group summary meta-analysis using Comprehensive Meta-Analysis software. Moreover, several potential moderators of response to antipsychotics were examined by meta-regression. We included 17 studies with a total of 3156 participants. On the average, 81.3%/51.9% of the first-episode patients reached an at least 20%/50% PANSS or BPRS reduction from baseline, respectively. Meta-regressions revealed a better treatment response in female patients, in more severely ill patients at baseline, in antipsychotic naïve patients, in patients with a shorter illness duration and in open studies. Study duration and dosage were no significant moderators of

*Corresponding author. Fax: +49 89 4140 4888.
E-mail address: stefan.leucht@tum.de (S. Leucht).

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response. Our finding suggest that more than 80% of first-episode patients achieved 20% PANSS/BPRS reduction from baseline and around 50% achieved a 50% PANSS/BPRS reduction. Several patient characteristics moderated response rates.

1. Introduction

Schizophrenia is a severe disorder, and a leading cause of disability according to the World Health Report (DALYs and Collaborators, 2016). Schizophrenia typically onsets in early adulthood, between the ages of 15 and 25 (Buchanan and Carpenter, 2005). Men tend to have earlier age of onset than women, and women have a second peak after menopause (Sham et al., 1994). The course is variable but often chronic (Jaaskelainen et al., 2013). The effectiveness of antipsychotic drugs has been proven by many randomized clinical trials, but most studies have been conducted in chronic patients (Leucht et al., 2017). The first episode of schizophrenia is widely viewed as a critical phase of treatment in schizophrenia, because gaining optimum improvement at this stage may determine the long-term outcome. First episode patients have been shown to be different from chronic patients in various aspects such as age, symptom patterns (Sanger et al., 1999), cognitive impairment (McCleery et al., 2014), brain volume loss (Torres et al., 2016) and functional changes (Li et al., 2017). It also seems to be generally accepted that people with a first episode of schizophrenia tend to respond better to antipsychotics than chronic patients (Gaebel et al., 2002; Lieberman et al., 1996; Ohlsen et al., 2004). For example, studies have shown that the time needed to reach a remission is considerably longer already after a second episode of schizophrenia compared to a first psychotic break (Emsley et al., 2013; Lieberman, 1996). Or in a meta-analysis of chronic patients only 53% reached at least 20% Positive and Negative Syndrome Scale (PANSS) total score or Brief Psychiatric Rating Scale (BPRS) total score reduction from baseline (Leucht et al., 2017), and only 23% of chronic patients reached at least 50% PANSS or BPRS total score reduction from baseline (Leucht et al., 2017). The hypothesis is that the improvement of first episode patients is much better, but a systematic assessment is not available. To fill this gap, we present the first systematic review of response rates in patients with a first episode of schizophrenia who participated in randomized controlled trials. The purpose of the meta-analysis was twofold: i) how well do patients with a first episode of schizophrenia respond to antipsychotics; ii) what are determinants of antipsychotic response in this population.

2. Experimental procedures

2.1. Search strategy and study inclusion criteria

We searched MEDLINE, EMBASE, PsycINFO, Cochrane Library, PubMed, Biosis, and ClinicalTrials.gov for reports published up to Nov 17, 2016 for randomized controlled trials that compared antipsychotic drugs with each other or with placebo in people with schizophrenia, and we inspected the reference lists of previous reviews (Crossley et al., 2010; Leucht et al., 2013; Zhang et al., 2013). Quasi-randomized studies (e.g. allocation by day of the week) were excluded. Due to the limited number of RCTs in first-episode schizophrenia, we also included open-label RCTs. In cross-over trials only data up to the point of the first cross-over were used to avoid carryover effects (Elbourne et al., 2002). Cluster-randomized trials were generally excluded. We excluded studies from mainland China to avoid a systematic bias because serious quality concerns have been raised (Woodhead, 2016). The exception was a Chinese study conducted by international renowned international researchers so that we were confident that international standards had been applied (Lieberman et al., 2003a). For reasons of consistency, this study was excluded in a sensitivity analysis, however.

We included people (no age limit, no restriction in setting, gender, ethnicity) with a first-episode of schizophrenia or related disorders (such as schizophreniform, or schizoaffective disorders). We allowed all definitions of “first episode” by the original authors. We excluded studies in treatment resistant patients, in patients with predominant negative symptoms, in patients with concomitant medical or psychiatric illness (e.g. studies in which all patients also had concomitant cannabis abuse), and studies in stable patients (mainly relapse prevention studies), because the response rates of such patients may be very different, while we focused on “typical” patients with acute exacerbations so that meta-analytic pooling with the rest of the studies would have been problematic. (Except one study in patients with co-occurring cannabis use and several relapse prevention studies, no RCTs had to be excluded on this basis, in particular there were neither RCTs in patients with predominant negative symptoms nor RCTs in treatment resistant patients). Following the rules of the Cochrane Schizophrenia Group we included trials irrespective of the diagnostic criteria used (Adams et al., 2011). We included studies of any orally administered antipsychotics (SGAs and FGAs) that are licensed in at least one country. In fixed-dose studies we followed the International Consensus Study on Antipsychotic dose (Gardner et al., 2010) which recommends 25–30% lower doses for first-episode patients than for chronic patients. We included all flexible-dose studies, because these allow the investigators to titrate to the adequate dose for the individual patient.

2.2. Screening and data extraction

Two reviewers out of YZ, MH, MK independently inspected all abstracts identified in the searches based on the inclusion criteria. Disagreement was resolved by discussion, and where doubt still remained, we acquired the full article for further inspection. Once the full articles were obtained, two reviewers out of YZ, MH, MK independently decided whether the studies met the review criteria. If disagreement could not be resolved, we discussed with the team leader SL and also contacted the authors per e-mail for seeking further information. Again, two reviewers YZ and PR independently reviewed the main reports and supplementary materials, extracted the relevant data from the included trials on electronic forms, and assessed risk of bias in terms of sequence generation, allocation concealment,

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