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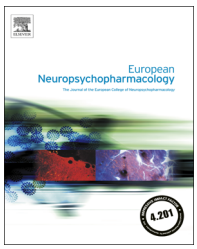

Antipsychotic response in first-episode schizophrenia: efficacy of high doses and switching

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Abstract
Clinicians treating schizophrenia routinely employ high doses and/or antipsychotic switching to achieve response. However, little is actually known regarding the value of these interventions in early schizophrenia. Data were gathered from a treatment algorithm implemented in patients with first-episode schizophrenia that employs two antipsychotic trials at increasing doses before clozapine. Patients were initially treated with either olanzapine or risperidone across three dose ranges, (low, full, high), and in the case of suboptimal response were switched to the alternate antipsychotic. We were interested in the value of (a) high dose treatment and (b) antipsychotic switching. A total of 244 patients were evaluated, with 74.5% (184/244) responsive to Trial 1, and only 16.7% (10/60) responsive to Trial 2. Percentage of response for subjects switched from olanzapine to risperidone was 4.0% (1/25) vs. 25.7% (9/35) for those switched from risperidone to olanzapine. High doses yielded a 15.5% response (14.6% for risperidone vs. 16.7% for olanzapine).The present findings concur with other research indicating that response rate to the initial antipsychotic trial in first-episode schizophrenia is robust; thereafter it declines notably. In general, the proportion of responders to antipsychotic switching and high dose interventions was low. For both strategies olanzapine proved superior to risperidone, particularly in the case of antipsychotic switching (i.e. risperidone to olanzapine vs. vice versa). It remains to be established whether further antipsychotic trials are associated with even greater decrements in rate of response. Findings underscore the importance of moving to clozapine when treatment resistance has been established.

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1. Introduction

Antipsychotic response in schizophrenia varies according to stage of illness. Notwithstanding the different trial designs and thresholds that define clinical response, studies in patients with first-episode schizophrenia report initial response rates in the range of 40–90% (Agid et al., 2011; Boter et al., 2009; Crespo-Facorro et al., 2006; Derks et al., 2010; Emsley et al., 2006a, 2006b; Lieberman et al., 1989; Merlo et al., 2002; Perkins et al., 2004; Schennach-Wolff et al., 2010; Stauffer et al., 2011). Thereafter the figure drops off substantially, however, with chance of response declining over time (Lieberman et al., 1996). In the face of this, treatment algorithms routinely advocate antipsychotic dose increases or switching to optimize outcome (NICE Guidelines, 2009; American Psychiatric Association, 2004; Canadian Psychiatric Association, 2005; Leucht et al., 2011; Moore et al., 2007).

In the context of dose optimization, it is not uncommon for clinicians to employ doses exceeding recommended therapeutic guidelines (Barbui et al., 2007; Botts et al., 2004; Hanssens et al., 2006; Sernyak and Rosenheck, 2007), although the value of high doses has been challenged (Kinon et al., 1993, 2008; Leucht et al., 2011; McEvoy et al., 1991). Similarly, antipsychotic switching is commonly undertaken as the illness unfolds (Buckley and Correll, 2008) despite recent evidence calling into question the benefit of switching between two non-clozapine antipsychotics (Essock et al., 2006; McEvoy et al., 2006; Rosenheck et al., 2008, 2009).

Much of this work has focused on more chronic populations and, surprisingly, the success of these different strategies in the earliest stages of schizophrenia has received little attention. Our First-Episode Psychosis program has developed a treatment algorithm that systematically moves individuals through trials of two second generation antipsychotics (SGAs) at increasing doses before a trial of clozapine is offered (Agid et al., 2007, 2011). We have been interested in better understanding the value of (a) high dose treatment and (b) antipsychotic switching in the early stages of schizophrenia. Using a naturalistic design, the present study set out to investigate these strategies over the initial two antipsychotic trials in first-episode schizophrenia.

2. Experimental procedures

2.1. Participants

A description of the treatment algorithm has been detailed previously (Agid et al., 2007, 2011). Patients were advised that their treatment would be applied according to this algorithm, but flexibly administered based on the individual's specific clinical condition and preferences. Summarizing, a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnosis was made at baseline through clinical interview by a staff psychiatrist (O.A.) who oversaw the care and assessment of this cohort of patients with first-episode schizophrenia. Clinical ratings included the Clinical Global Inventory (CGI) (Guy, 1976) and 18-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), administered weekly during the first month, and monthly thereafter. Response to treatment was defined as (a) CGI-improvement (much or very much improved) and/or (b) BPRS thought disorder subscale (conceptual disorganization; hallucinatory behavior; suspiciousness; unusual thought content) ≤ 6.

2.2. Treatment algorithm

Two antipsychotic trials are carried out before a trial of clozapine is offered (Agid et al., 2007, 2011). In this particular sample, patients were started on either olanzapine or risperidone and switched to the other if a second trial was required. Each antipsychotic trial was divided into three stages based on increasing dose, and each stage could last a maximum of four weeks. If the patient failed to meet criteria for response at this point, they were advanced to the next stage, and the treating psychiatrist could also increase the dose before the 4-week assessment if clinically indicated. The three dosing stages for each trial were as follows (dose adjustment within range as clinically indicated/tolerated): low dose (olanzapine 5–10 mg, risperidone 2–3 mg); full dose (olanzapine 12.5–20 mg, risperidone 4–6 mg); and, high dose (olanzapine 22.5–30 mg, risperidone 6.5–10 mg). If, after two trials, response criteria were not met, a trial of clozapine was offered, initiated at 12.5 mg/day and titrated upward daily in 25 mg increments, as tolerated. Medication adherence was assessed through a combination of approaches including patient and caregiver feedback, as well as random pill counts.

2.3. Data analysis

We were interested in the first two antipsychotic trials before individuals were designated as treatment resistant and offered a trial of clozapine. The goal was to determine the extent of benefit associated with use of high doses or antipsychotic switching.

For a switch or increase in dose to be worthwhile, a certain degree of success must be achieved as a result of this change. In the absence of any consistently agreed upon gold standard definition of success (i.e. what is the minimum response rate we must observe for a change in treatment to be warranted?), we explored a series of potential thresholds and compared each of these to our observed success rates. This paper identifies the minimum thresholds (% response) significantly greater than our observed response rates, rates at which our data would imply that an increase in dose/medication switch is not beneficial.

From the standpoint of data analysis, the observed proportion of responders for each provided an estimate of the "population proportion", which was then used for comparison purposes. More specifically, proportion of observed responders with each strategy was compared to a series of different population proportions ranging from 0–50%, in increments of 5%, using one-tailed exact tests of proportions. Employing such an approach allowed the identification of a threshold beyond which the observed proportion of responders was significantly smaller than the population proportion. Any level below that threshold was seen as warranting that particular intervention. In addition, we could also identify a threshold below which the identified proportion of responders was significantly greater than the population proportion. Below this threshold, clinicians could feel even more confident in choosing a particular intervention.

For each of the treatments (high dose; antipsychotic switching), data were examined collectively as well as according to specific treatment (i.e. high dose risperidone; high dose olanzapine; switching risperidone [Trial 1] to olanzapine [Trial 2]; switching olanzapine [Trial 1] to risperidone [Trial 2]).

3. Results

3.1. Subjects

Demographic data for the sample ($n=244$) have been published previously (Agid et al., 2011), and can be summarized as follows: mean age 22.2 years (range 16-