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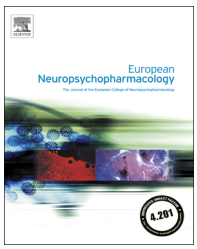

Effectiveness of different dosing regimens of risperidone and olanzapine in schizophrenia

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Abstract
The objective of this study was to evaluate the effectiveness and impact of once- versus twice-daily dosing of risperidone and olanzapine on clinical outcomes in patients with schizophrenia. Data from phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study were used. Patients with schizophrenia were randomly allocated to treatment with risperidone and olanzapine, and were also randomly assigned to once-daily ($N=173$ and 169, respectively) or twice-daily ($N=168$ and 167, respectively) dosing and followed for up to 18 months. Discontinuation rate and time to discontinuation were used as primary outcome measures to compare the two groups. The following outcome measures were also analyzed: efficacy, safety, medication adherence, adverse events, and concomitant psychotropic medications. No significant differences in discontinuation rates and time to discontinuation were observed between the once- and twice-daily dosing groups ($P>0.05$) in patients receiving risperidone or olanzapine. The once-daily dosing group demonstrated significantly lower mean daily doses of risperidone and olanzapine across phase 1, and lower rates of hospitalization for exacerbation of schizophrenia, sleepiness, and orthostatic faintness in patients receiving olanzapine ($P<0.05$) compared to the twice-daily dosing group. No significant differences were found in any other outcome measures between the two dosing groups. In conclusion, effectiveness and efficacy outcomes between once- and twice-daily dosing for risperidone and olanzapine were not significantly different. However, in view of the

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lower mean dose and better side effect profile, it is advisable to adhere to a once-daily dosing regimen, especially in the case of olanzapine.

1. Introduction

Risperidone and olanzapine are among the most widely prescribed antipsychotic drugs in clinical practice (Correll et al., 2011; Jauhar et al., 2012); these medications are commonly administered in a once-daily dosing regimen because of their relatively long plasma half-lives (Patteet et al., 2012). This said, these drugs are occasionally prescribed in a divided dosage regimen in clinical practice as well as in controlled trials, especially in the case of risperidone (Agarwal and Chadda, 2001; Nair, 1998) whose package insert notes that this drug can be administered either once- or twice-daily (Janssen Pharmaceuticals, Risperdal, 2012).

The question of which dosing regimen is more beneficial has not been systematically addressed for these medications; there are two published randomized controlled trials specifically examining the impact of dosing schedules for risperidone in the treatment of schizophrenia (Agarwal and Chadda, 2001; Nair, 1998), but none for olanzapine. Both of the two studies compared once- versus twice-daily dosing of risperidone and failed to demonstrate any significant differences in efficacy and safety measures between the two dosing regimens. However, study durations of these studies were relatively short (i.e., up to 2 months), which limits any interpretation of results in terms of relapse prevention in long-term maintenance treatment. In addition, these trials focused primarily on efficacy and safety outcomes, and did not assess other outcomes associated with schizophrenia such as medication adherence or functional outcome; moreover, no study has examined effectiveness, an outcome variable of important clinical value (Correll, 2011), of different dosing regimens for these drugs.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Lieberman et al., 2005) have proven an ideal dataset to address a number of clinically related questions given its unprecedented sample size, comprehensive assessments, and long duration of follow-up (i.e. up to 18 months) (Stroup et al., 2003). As part of this trial, a subgroup of patients were randomly allocated to treatment with risperidone, olanzapine, or perphenazine; within this arm, they were also randomly assigned to once daily or twice daily dosing (Stroup et al., 2003). We have previously reported the results on perphenazine (Takeuchi et al., 2014). The objective of this analysis was to evaluate the effectiveness and impact of once- versus twice-daily dosing of risperidone and olanzapine on various clinical outcomes in patients with schizophrenia.

2. Experimental procedures

2.1. Study design

The CATIE study is a double-blind randomized controlled trial comparing the effectiveness of olanzapine, risperidone, ziprasidone, quetiapine, and perphenazine in patients with schizophrenia (N=1493); the primary results have been detailed elsewhere (Lieberman et al., 2005).

Patients allocated to risperidone, olanzapine, and perphenazine were also randomly assigned to either a once- or twice-daily dosing regimen at baseline (Stroup et al., 2003). The present analysis specifically focused on risperidone and olanzapine, and the impact of these two dosing schedules on clinical outcomes, using the phase 1 data where patients received treatment for up to 18 months or until treatment was discontinued for any reason (phase 1). We analyzed the data on each group of patients receiving risperidone (1.5–6.0 mg/day) or olanzapine (7.5–30 mg/day).

2.2. Outcome measures

2.2.1. Discontinuation rate and time to discontinuation

Discontinuation rate and time to discontinuation were used as primary outcome measures, which is consistent with the original aim of the CATIE study (Lieberman et al., 2005).

2.2.2. Efficacy and safety measures

The efficacy measures were as follows: Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) to assess psychopathology; Clinical Global Impressions-Severity scale (CGI-S) (Guy, 1976) to assess overall impression of clinical severity; Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990) to assess depressive symptoms; Drug Attitude Inventory (DAI-10) (Hogan et al., 1983) to assess attitude toward medication; and Quality of Life Scale (QLS) (Heinrichs et al., 1984) to assess functioning. The safety measures were as follows: Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) to assess dyskinesia; Barnes Akathisia Rating Scale (BARS) (Barnes, 1989) to assess akathisia; Simpson–Angus Scale (SAS) (Simpson and Angus, 1970) to assess extrapyramidal symptoms; body weight; and waist circumference. All efficacy and safety measures other than the DAI-10 and QLS were assessed at baseline and 1, 3, 6, 9, 12, 15, and 18 months, while the DAI-10 and QLS were rated at baseline and 6, 12, and 18 months.

2.2.3. Medication adherence

The Clinical Global Judgment of Medication Adherence and proportion of capsules taken across phase 1 were used to evaluate medication adherence (Stroup et al., 2003). The Clinical Global Judgment of Medication Adherence is a 4-point clinician-rated scale that ranges from 1, “always/almost always (76–100% of the time)”, to 4, “never/almost never (0–25% of the time)”. Proportion of capsules taken was calculated based on pill count in the returned bottle since the previous visit. Both were assessed at every visit (i.e., every month) through phase 1.