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Predictors of risk for relapse in patients with schizophrenia or schizoaffective disorder during olanzapine drug therapy

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Abstract

Purpose: To evaluate the relationship of dose decrease, symptom worsening, and baseline covariates on subsequent relapse during olanzapine treatment in patients with schizophrenia or schizoaffective disorder.
Methods: In two 28-week, randomized, double-blind clinical trials, a Cox proportional hazards model was used to determine potential correlates of relapse (defined as $\geqslant 20\%$ worsening on PANSS total and CGI-Severity $\geqslant 3$) among patients ($N = 271$) who responded to 8 weeks of olanzapine treatment (10–20 mg/day). Variables examined included: demographics, illness characteristics, baseline symptoms, symptom change, dose, adverse events, and functioning.
Results: Patients with a lower last dose relative to the preceding visit interval were 4 times more likely to relapse during that visit interval than other patients ($p < .001$). A similar finding was observed for a decrease in interval modal dose, although this variable was more predictive of relapse in the visit interval immediately following dose decrease ($p = .027$). In a subgroup analysis by gender, there was a significantly greater incidence of relapse in men with a dose decrease, whereas a dose decrease in women did not correlate with relapse. Relapse was also correlated with the emergence or worsening of a psychiatric adverse event during the same ($p < .001$) and preceding ($p = .007$) visit intervals, and with increased rating scale measures of psychopathology. The occurrence of a non-psychiatric adverse event was not associated with relapse.
Conclusion: Dose decrease is a significant predictor of relapse in male but not female patients. Psychiatric adverse events also predicted relapse. Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

Keywords: Schizophrenia; Olanzapine; Relapse; Predictors; Dose

1. Introduction

Relapse can have a dramatic impact on the long-term outcome of patients with schizophrenia and related psychotic disorders (Lieberman, 1993). Early reports demonstrated that treatment with conventional antipsychotics decrease a patient's risk for relapse (Ayuso-Gutierrez and Rio Vega, 1997), and more recent evidence has suggested that there may be differences in relapse rates following treatment with different antipsychotic drugs. In this regard,

Abbreviations: AE, adverse event; CGI, Clinical Global Impressions Scale; CI, confidence interval; MADRS, Montgomery–Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; OLZ, olanzapine.

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a lower risk of relapse has been reported in patients treated with second-generation antipsychotics compared with those treated with first generation antipsychotics (Leucht et al., 2003); risk for relapse may also differ among atypical agents (Tran et al., 1997). Indeed, the recently published CATIE trial sponsored by the National Institute of Mental Health has reported a significant difference in time to discontinuation of treatment for any cause between olanzapine and other atypical antipsychotic drugs (Lieberman et al., 2005).

Although poor medication compliance has been implicated in relapse (Csernansky and Schuchart, 2002), relapse is common even in patients who regularly take their antipsychotic medications. Controlled clinical trials may offer an advantage in identifying risk factors in patients who, for the most part, are taking their medication and who may have fewer confounding variables such as drug abuse. Furthermore, it is possible to select patients in clinical trials who meet explicit criteria for acute response, allowing one to determine those variables that play an important role in relapse in patients who initially respond to treatment.

In the present analysis, we were interested in evaluating 2 main hypotheses: (1) impact of dose decrease on subsequent relapse, and (2) worsening of specific psychiatric symptoms as a possible early sign of psychiatric relapse. The evaluation of such hypotheses may be hindered by possible confounding factors. Therefore, we also considered various baseline covariates to see whether their inclusion would impact the main findings.

2. Subjects and methods

2.1. Subjects

The data were drawn from patients in 2 randomized, multicenter, double-blind clinical trials of olanzapine (OLZ) treatment. Study 1 compared the efficacy of OLZ to risperidone in patients with schizophrenia or schizoaffective disorder (Tran et al., 1997). Study 2 evaluated the efficacy of OLZ versus ziprasidone in patients with schizophrenia (Breier et al., 2005). The primary outcome results of these studies can be found in the previously mentioned publications. In each study, patients had acute psychotic symptoms at study entry (Brief Psychiatric Rating Scale [BPRS] score of at least 42), and the duration of study treatment was 28 weeks. Visits were weekly for the first 8 weeks, and then the visit intervals ranged from 2 to 4 weeks. All patients gave written informed consent prior to entering the studies. Appropriate institutional review boards reviewed each study protocol.

The analyses were performed using data from week 8 to week 28 of treatment (i.e., endpoint) in patients who met responder status at week 8. Responders were defined as those patients with $\geqslant$20% improvement on the Positive and Negative Syndrome Scale (PANSS) total score. All patients who had at least 1 evaluation after week 8 were included in this analysis.

2.2. Dosing

In Study 1, after 1 week of a fixed-dose regimen (OLZ, 15 mg/day), the dosing of OLZ was flexible and could range from 10 to 20 mg/day. Dose adjustments ($\pm$5 mg/day) could occur every 7 days. In Study 2, the dose of OLZ was initiated at 10 mg and could increase by 5 mg/day every 5 days up to a maximum of 20 mg/day. Dose decreases were allowed, but the dose could not fall below a minimum of 10 mg/day. Patients who were noncompliant with study medication were discontinued from study participation.

2.3. Variables assessed

This analysis was a retrospective *post hoc* evaluation of data collected from 2 previous clinical trials in which relapse was not the primary objective of the original studies. Therefore, we identified stable patients who had responded to OLZ treatment at week 8. First occurrence of psychotic relapse was defined as evaluation visit after week 8 in which patients had at least a 20% worsening on PANSS total score from evaluation at week 8, and Clinical Global Impressions-Severity (CGI-S) score $\geqslant$3.

Variables examined as correlates or predictors of relapse after week 8 included: (a) occurrence of a decrease in dose; (b) changes in symptom severity between evaluation visits as measured by PANSS total score (Kay et al., 1986) and PANSS 5 factor subscores (Marder et al., 1997); and (c) occurrence or worsening of adverse events (AE) (yes/no). Dose per visit interval was summarized as (i) "modal dose" per visit interval, and (ii) "last dose" received at a given visit interval. "Modal dose" is the most frequent dose received during a given visit interval that captures the prescribed dosing regimen, whereas "last dose" is the last dose taken prior to a patient's evaluation visit and is a more volatile measurement that could capture possible noncompliance. AEs were classified into 3 groups: all, psychiatric, and non-psychiatric. Psychiatric AEs included the MedDRA Psychiatric Disorders category and were further categorized as being related to (i) anxiety, aggression, agitation, hostility, irritability; (ii) mood disturbances; (iii) psychosis; and (iv) other psychiatric AEs. Non-psychiatric AEs included all AEs not in the MedDRA Psychiatric Disorders category (e.g., EPS, somnolence, weight gain).

The relationships were evaluated between variables a, b, and c and risk of occurrence of relapse during (i) the *current* visit interval, and (ii) the *subsequent* visit interval. While analyses (i) are useful in assessing *concurrence* of relapse with specific psychiatric symptoms and medication dose, (ii) are more appropriate in assessing a, b, c as *predictors/early signs* of relapse.

Covariates considered for adjustment of these major analyses included patient demographics (age, gender, race), disease history (duration of illness prior to study enrollment, number of previous psychiatric episodes), physical