Joint modeling of dropout and outcome in three pivotal clinical trials of schizophrenia

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ABSTRACT

Background: Dropout is a serious challenge to clinical trials in psychiatry, yet standard outcome analyses with mixed models do not account for dropout, while joint modeling uses dropout from a survival model to adjust the outcome from a mixed model, but is untested in clinical trials of schizophrenia.
Aims: To compare mixed and joint modeling in three acute phase pivotal placebo controlled trials of schizophrenia.
Method: Data were reanalyzed on 611 in-patients with acute schizophrenia who participated in three pivotal randomized controlled trials that compared placebo with olanzapine or risperidone (dropout rates placebo: 62.6% and medication: 37.4%). The outcome measures were BPRS or PANSS total change scores. Mixed-effects models for repeated measures and joint models were computed and compared to examine the time-treatment interaction. Effect size comparisons were made.
Results: Antipsychotic treatment was superior to placebo across analyses. Time treatment interactions were significant ($p < .05$) for the mixed (beta = 2.33) and joint models (beta = 2.62). Compared with mixed modeling, joint modeling reduced the estimated change score for treatment (21.24 vs 19.74) and placebo (1.64 vs −1.11). The effect size differences between placebo and treatment groups were greater for joint (ES = .89) than mixed modeling (ES = 0.83). Sensitivity analysis replicated this trend of results in each of the three trials.
Conclusion: Compared to mixed modeling, joint modeling results in a greater separation between treatment and placebo groups. This offers preliminary evidence that joint modeling may be useful in the analysis of antipsychotic placebo controlled RCTs.

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1. Introduction

Premature dropout challenges the success of clinical trials in general (Wahlbeck et al., 2001; Kemmler et al., 2005; Rabinowitz et al., 2009). In antipsychotic clinical trials in particular, dropout rates often exceed 50% (Wahlbeck et al., 2001; Martin et al., 2006), and, interestingly, are higher in the placebo- than active-controlled trials (48.1% vs 28.3%, respectively) (Kemmler et al., 2005). Moreover, in many clinical trials dropout constitutes the primary trial outcome (Lieberman et al., 2005; Kahn et al., 2008), since it may reflect drug inefficacy, intolerability and lack of compliance (Rabinowitz and Davidov, 2008). Despite being an important outcome, dropout is primarily a methodological artefact, since it leads to missing information (e.g., regarding symptom change) affecting modeling, and analysis. Hence, dropout endangers the validity of evidence-based conclusions. This has made dropout a topic of debate

(Mallinckrodt et al., 2003; Molenberghs et al., 2004; Leon et al., 2006). There are three dropout mechanisms: missing completely at random, missing at random and missing not at random (Little and Rubin, 2002). First, missing completely at random occurs when dropout and outcome are unrelated, and dropout occurs randomly. Statistical analyses of such data that are missing completely at random do not introduce bias; but statistical power is reduced due to dropout. During a clinical trial, missing completely at random data may occur if a patient moves too far away from the study site to participate (Mallinckrodt et al., 2003). In this case, dropout is unrelated to the trial outcome (e.g., PANSS scores). Second, missing at random occurs when dropout is systematically related to a study variable (e.g., symptom severity). For example, missing at random data may occur if a patient drops out due to symptom exacerbation (Mallinckrodt et al., 2003) that is observed in the data as increasingly worse PANSS scores. Third, missing not at random occurs when an unmeasured factor increases dropout. Missing not at random may occur if a patient drops out due to exacerbation that occurred after their last midway assessment. In that case, the exacerbation would not be recorded in the data (Mallinckrodt et al.,

2003). The last two dropout mechanisms are informative since missing data contain information about the outcome (e.g. response); thus, ignoring them may introduce bias.

Statistics should account for dropout, maximize data availability at all visits, minimize bias and maximize statistical power in clinical trials. Mixed modeling is a widely applied (Lieberman et al., 2005) statistical approach in clinical trials. It uses repeated clinical assessments of the outcome over time (e.g. from a longitudinal study), taking into account that the measurements from one patient may be more correlated than measurements from different patients. Thus, in mixed modeling, a fixed-effect component describes the average outcome evolution over time for all the patients, whereas a random-effect component describes the outcome evolution over time for each patient. Mixed modeling, however, ignores the effect of dropouts on the outcome assuming that these two are unrelated. Research has shown that this is not the case in clinical trials of schizophrenia (Rabinowitz and Davidov, 2008); thus, the use of mixed modeling has the potential to introduce bias.

To address the dropout problem, there are statistical approaches that simultaneously model the outcome accounting for dropouts within a unified model-based framework (Little, 1995; Hogan and Laird, 1997; Rizopoulos, 2010). Joint modeling is a framework that appropriately integrates the dropout and outcome processes. The framework acknowledges that there are two different, but not independent, simultaneous processes: (i) the *survival event process* that refers to the time to dropout; and (ii) the *longitudinal process* that refers to the outcome (e.g., the follow-up of PANSS change scores over time). First, the survival event process estimates dropout from a survival analysis. Then, adjusting for the resultant survival event process, the longitudinal outcome process is computed similar to a mixed model with all available assessments. Joint modeling acknowledges that the dropout mechanism is informative, specifically that the outcome analysis (e.g., PANSS change) is dependent on the dropout mechanism. The joint modeling approach has already been used to analyze clinical trial data on cancer (Li et al., 2013; Ediebah et al., 2014) and aids (Baghfalaki et al., 2014) but not schizophrenia. The current manuscript aims to compare the results of joint and mixed modeling in three clinical trials of risperidone and olanzapine versus placebo in the treatment of schizophrenia.

2. Method

2.1. Included RCTs

A comprehensive systematic review of 15 major antipsychotic drugs and identified 97 placebo-controlled trials (Leucht et al., 2013a). Of these, we had access to individual participant data from three randomized clinical trials (RCTs) (Chouinard et al., 1993; Marder and Meibach, 1994; Beasley et al., 1996a, 1996b) without influence on the study design, conduct or reporting of the primary data analyses. The studies were pivotal RCTs comparing olanzapine or risperidone against placebo in the acute phase treatment of schizophrenia. The two olanzapine RCTs constitute all the placebo-controlled trials for the FDA registration of the compound (Beasley et al., 1996a, 1996b). The RCT comparing risperidone with placebo is its pivotal registration study (the US and Canadian parts of the study have been published separately; Chouinard et al., 1993; Marder and Meibach, 1994). All data were anonymized prior to access.

Of all the treatment arms in the RCTs, we only included the arms that used dosages indicated as efficacious in the US FDA labels or the British National Formulary (i.e., 10 to 30 mg/d for olanzapine, and 4 to 16 mg/d for risperidone; see Table 1).

We excluded fixed-dose arms with olanzapine below 10 mg/day (one 1 mg/day arm (Beasley et al., 1996a) and one 5 ± 2.5 mg/day arm (Beasley et al., 1996b)) and one 2 mg/day risperidone arm (Chouinard et al., 1993; Marder and Meibach, 1994), because in such arms all patients are "forced" to take very low doses which are not efficacious for many of them (Leucht et al., 2013a), although such very low doses may be effective for some patients (Leucht et al., 2014). All the included arms were fixed-dose arms; in all but one trial, the fixed dose was administered immediately after randomization; in one study (Chouinard et al., 1993; Marder and Meibach, 1994), the dosage was titrated up to the maintenance dose within 3–7 days.

2.2. Analyses

One olanzapine trial (Beasley et al., 1996b) used the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), while the remaining two trials used the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) to measure global symptom severity. To have the same outcome measure across all trials and to perform the analysis on the same scale, we converted the BPRS scores into PANSS using an established algorithm: the correlation coefficient between BPRS Total and PANSS Total has been reported to range between 0.93 and 0.96 (Leucht et al., 2013b). All items on PANSS were recalibrated, where necessary, to be rated between 1 and 7, so that the possible score range was 30–210.

First, descriptive statistics were presented for the trials. Second, to examine whether dropout was informative, the dropout rates and last-visit outcome values were presented for dropouts and completers delineated by antipsychotic and placebo groups. Whether dropout was missing completely at random was tested with Little's χ^2 MCAR test; where statistically significant values represent a departure from missing completely at random (Little, 1988).

Third, multivariate statistics consisting of Cox regression, mixed and joint modeling were computed in R (Ihaka and Gentleman, 1996). All the multivariate models were adjusted for confounding effects of baseline, age and sex. Cox regressing modeling was computed to examine whether time to dropout was related to treatment, thereby ascertaining if dropout was informative. Cox modeling was computed using the

Table 1
Trial descriptions.

Trial	Primary publication	Outcome	Randomization	Excluded	Weekly visits	Selection criteria All: inpatients	Sex	Dropouts
1	Beasley et al. (1996b)	BPRS	Placebo (N = 68) Olanzapine 15 ± 2.5 mg (N = 69) & 10 ± 2.5 mg (N = 64)	Haloperidol 15 ± 2.5 mg (N = 69) & Olanzapine 5 ± 2.5 mg (N = 65)	0.5, 1, 2, 3, 4, 5, 6	Acute exacerbations of schizophrenia (DSM-III-R), BPRS total score ≥ 24 (items 0–6) before and after placebo run-in	172 M 29 F	PBO: 46 Ola10 m: 38 Ola15 mg: 35
2	Beasley et al. (1996a)	PANSS	Placebo (N = 50) Olanzapine 10 mg (N = 50)	Olanzapine 1 mg (N = 52)	1, 2, 3, 4, 5, 6	Schizophrenia (residual type excluded) (DSM-III-R), CGI-S ≥ 4, BPRS total score ≥ 24 (items 0–6) before and after placebo run-in	70 M 30 F	Ola: 31 PBO: 40
3	Chouinard et al. (1993), Marder and Meibach (1994)	PANSS	Placebo (N = 88) Risperidone 6 mg (N = 86), 10 mg (N = 87), & 16 mg (N = 88)	Risperidone 2 mg (N = 87) & Haloperidol 20 mg (N = 87)	1, 2, 4, 6, 8	Schizophrenia (DSM-III-R), PANSS total score ≥ 60 before placebo run-in	284 M 57 F	PBO: 61 Ris6: 34 Ris10: 39 Ris16: 34