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A latent variable approach in simultaneous modeling of longitudinal and dropout data in schizophrenia trials

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Abstract

Dropouts impact clinical trial outcome analyses. Ignoring missing data is not an acceptable option when planning, conducting or interpreting the analysis of a clinical trial. Treatment related efficacy and safety data observed in the trial may not always be sufficient in explaining the dropouts' mechanism. Nevertheless, these dropout data may carry important treatment-related information and present as an outcome by itself. Traditional analyses involve the use of the time-to-event approach assuming that the dropouts' hazard is solely related to the efficacy or safety profiles observed in a study. A latent variable approach was developed to generalize this approach and to implement a more flexible dropout hazard function in a schizophrenia trial. This unobserved latent variable was used to jointly model the longitudinal efficacy data and dropout profiles across treatments. The analysis provides a framework to model informative dropouts simultaneously with primary efficacy outcomes and make intelligent decisions in drug development.

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1. Introduction

Dropout is an important outcome in randomized clinical trials (RCTs) because it may reflect drug tolerability, adverse effects, and lack of compliance. For this reason it is often used as an outcome measure in clinical trials of antipsychotic medications. For instance, in the recent clinical antipsychotic trials of intervention effectiveness

(CATIE), study discontinuation was a primary outcome measure. Seventy four percent of CATIE trial participants discontinued their assigned study medication before study completion at 18 months (Lieberman et al., 2005). A recent meta-analysis of RCTs of antipsychotic medication was conducted to compare dropout rates for first- and second-generation antipsychotic drugs and to examine how a broad range of design features affect dropout. Ninety-three RCTs that met specific inclusion criteria were included. The analysis showed that dropout rates are lower for second- than first-generation antipsychotic drugs and appear to be partly explained by trial design features thus providing direction for future trial design (Rabinowitz et al., 2009).

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A major issue in the analysis of RCTs is presented by missing data caused by patients dropping out from the study before study completion. This problem can result in biased treatment comparisons and also impact the overall statistical power of the study (Myers, 2000). In addition, the exclusion of missing data from the analysis violates the intent to treat (ITT) principle which requires analyses conducted on all measurements of all subjects randomized in the trial regardless of protocol adherence. This principle is of critical importance as confirmatory clinical trials should estimate the effect of the experimental intervention in the population of patients with greatest external validity and not the effect in the unrealistic scenario where all patients receive treatment with full compliance to the treatment schedule and with a complete follow-up as per protocol (EMA Committee for Medicinal Products for Human Use (CHMP), 2010).

There are many possible reasons for dropouts (e.g. patient refusal to continue in the study, patient withdrawals due to treatment failure, treatment success or adverse events, patient emigration), some of which are related to study treatment. There has been an increasing amount of work discussing various methods to tackle missing information due to patient dropping out from a trial. Dropout data needs appropriate assessment to provide a valid analysis of the primary efficacy data and cannot be simply ignored. Nevertheless, it is equally challenging to adequately characterize such missing data. The assumption that the dropout process can only be attributed to a random event or to an event related to the observed or to the model-predicted level of efficacy seems too restrictive. In fact, many other treatment-related and treatment-unrelated causes can be reasonably considered as valuable predictors of dropout (i.e. level of tolerability, adverse events, etc). Thus often one may be able to only partially explain the dropout or missing data based on the observed efficacy and/or safety data.

To account for treatment-related causes not pertaining to efficacy we introduce the concept of latent variable. For the purpose of our analysis, we define a latent variable as an unknown predictor of the dropout event that is treatment dependent but that has not been measured in the clinical trial or that is not directly measurable. Using this paradigm, we developed a model based approach to efficiently describe the hazard of trial dropout due to treatment specific unobserved or unknown factors.

Data from a clinical trial conducted to evaluate an anti-schizophrenic treatment have been used to illustrate the implementation of the proposed methodology. Patient dropout is a well-known event characterizing schizophrenia trials with typical dropout rates as high as 50% (Wahlbeck et al., 2001; Martin et al., 2006; Rabinowitz and Davidov, 2008a). Specifically, it has been shown that patients who drop out prematurely tend to display progressive deterioration, indicated by a change in their Positive and Negative Syndrome Scale (PANSS)—a clinical score used to evaluate the disease status, while trial completers demonstrate progressive amelioration throughout the trial. Dropouts have been described as permanent interruption of a planned/regular treatment. The decision to discontinue can be made by the patient or the administrative/clinical team (Fassino et al., 2009). More often, dropouts denote such a decision being made by the patient. There may be different reasons for such dropouts as

discussed above. Nevertheless, dropouts result in treatment discontinuation in clinical trials resulting in incomplete data with respect to primary endpoint(s) and cause uncertainty in interpreting outcome of such studies (Rabinowitz and Davidov, 2008b). Analyzing such trial outcomes by plainly ignoring the dropout information can lead to highly biased conclusions.

The dropout event could be completely at random for reasons completely unrelated to the treatment. (e.g. emigration of the subject from the study site, missingness due to analytical limitation) (Little and Rubin, 1987). Alternatively, the dropout could be related to the observed responses in the trial. One such scenario would be the subject on an anti-psychotic drug dropping out due to lack of efficacy measured/observed in that individual. Similarly, the presence of an adverse effect, observed or un-recorded) may also explain the trial discontinuation by the patient. A step further to this scenario may be a case wherein dropout can be related to the level of expectation of a patient for the future treatment outcome (subject's efficacy scores/disease progression) through some parameter not observed or measured in the trial (Hu and Sale, 2003). Missing data presents a major challenge while performing model based analyses to describe pharmacokinetic-pharmacodynamic relationships, disease progression models or primary efficacy endpoint analysis with longitudinal data (Gastonguay et al., 2010). Different approaches have been proposed to analyze the efficacy endpoints in presence of missing data. Some of them include: Last observation carried forward (LOCF), baseline observation carried forward (BOCF) or the likelihood based analyses methods such as mixed effects model for repeated measures (MMRM). There are advantages and shortcomings with each of the methods based on the dropout mechanism but no method is universally applicable to adjust for this missingness.

The clinical trial outcomes in presence of missing information warrant analyzing not only the primary efficacy endpoint(s) appropriately, but adequately characterizing the dropouts and extracting any information that may be contained in the dropout patterns or profiles. The latter is based on the assumption that dropout is a surrogate for patient preference, acceptability with therapy, and therefore it can be considered as a study outcome by itself for the assessment of the treatment effect. The present research was focused on this aspect with the objective to understand and efficiently characterize the high dropout rates observed in an in-house schizophrenia treatment trial when the probability for dropping out is not a random event and when this probability cannot be predicted by any data (e.g. efficacy and safety) collected in the trial. The analyses presented here plays an important role in developing a novel metric that combines the primary efficacy outcome with dropout information to compare different treatments in an efficient manner (Goyal and Gomeni, 2012).

2. Experimental procedures

2.1. Study population

This was a placebo-controlled, parallel-group, study to evaluate the safety and efficacy of new antipsychotic treatment (TD-20 mg and

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