Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Accounting for group differences in study retention in a randomized trial of specialized treatment for first episode psychosis

Kyaw Sint [a], Robert Rosenheck [a], Delbert G. Robinson [b,c,d], Nina R. Schooler [b,c,d], Patricia Marcy [b,c], John M. Kane [b,c,d], Kim T. Mueser [e], Haiqun Lin [a,*], other RAISE ETP Investigators

[a] Yale School of Public Health, New Haven, CT, USA
[b] The Zucker Hillside Hospital, Psychiatry Research, North Shore - Long Island Jewish Glen Oaks, NY, USA
[c] The Feinstein Institute for Medical Research, Manhasset, NY, USA
[d] Hofstra Northwell School of Medicine, Departments of Psychiatry and Molecular Medicine, Hempstead, NY, USA
[e] Center for Psychiatric Rehabilitation, Departments of Occupational Therapy, Psychiatry, and Psychology, Boston University, Boston, MA, USA

ARTICLE INFO

Article history:
Received 23 March 2017
Received in revised form 17 August 2017
Accepted 18 August 2017
Available online xxxx

ABSTRACT

Background: Schizophrenia is a chronic disabling disorder for which current treatments are only partially effective. While the evaluation of novel interventions is a high priority, loss to follow-up is a major threat to validity.
Methods: Pattern mixture modeling is a statistical technique that incorporates information on patterns of retention that may bias comparisons between randomized treatment groups. This study used pattern mixture mixed model (PMMM) in the analysis of outcomes of a two-year cluster-randomized trial, the Recovery after an Initial Schizophrenia Episode-Early Treatment Program, which compared a coordinated specialty care intervention called NAVIGATE to usual community care (CC). PMM-adjusted outcome differences between NAVIGATE and CC were estimated by the weighted-average of effects across the retention patterns.
Results: Compared to the original analysis, PMMM improved model fit and the estimated effectiveness of NAVIGATE as compared to CC. On the Quality of Life Scale NAVIGATE effectiveness increased by 1.50 points (25.4%); on the Positive and Negative Syndrome Scale, by 1.72 points (39.8%), and on the Calgary Depression Scale by 0.49 points (62.1%). PMMM did not improve model fit for employment days, substance use days, or hospital days.
Conclusion: Use of PMMM improved model fit and increased the estimated differences between NAVIGATE and CC for major outcomes. Patients with differential retention patterns may have different outcome trajectories. PMMM is a useful tool for addressing potential biases arising from these differences.

1. Introduction

Randomized clinical trials are essential tools for evaluating the effectiveness of new treatments. A major impediment to the validity of randomized clinical trials is the differential retention or loss to follow-up between treatment groups. Such differences can bias estimates of the differential effectiveness of treatments in randomized trials because they undermine the assumption that treatment groups are equivalent since patients with better or worse prognosis may be more likely to drop out of one group as compared to the other. In addition, patients with different patterns of retention may have different outcome trajectories within or across treatment groups, regardless of differences in overall rates of retention.

The problem of differential retention or dropout may be especially important in studies of severe mental illness, and especially in cases of first episode psychosis, because patients with these disorders are often less likely to participate for the full duration of a study due to poor psychosocial functioning and impaired insight into their illness (Mohamed et al. 2009).

There has been particular interest in recent years in early intervention in psychosis and in first episode schizophrenia in particular. It has been hypothesized that early intervention can substantially improve both short and long-term outcomes because it prevents the deterioration in functioning that is believed to come with prolonged untreated or under-treated psychosis (Addington 2007; Álvarez-Jiménez et al. 2011; Bird et al. 2010). Several recent trials of intensive early intervention in psychosis have shown promising results lending support for this hypothesis (Craig et al. 2004; Gafoor et al. 2010; Garety et al., 2006; Kane et al. 2015; Petersen et al. 2005; Srihari et al. 2015).

The NIMH-funded Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP) study (Kane et al. 2016) is currently the largest real-world study of specialized coordinated care for first episode psychosis yet conducted in the United States. This

* Corresponding author.
E-mail address: haiqun.lin@yale.edu (H. Lin).

http://dx.doi.org/10.1016/j.schres.2017.08.029
0920-9964/

multisite, two-year study showed significant benefits for a coordinated specialty care intervention called NAVIGATE in quality of life and symptoms as compared to usual community care (CC). There were, however, substantial differences in retention patterns between the two conditions, presumably because NAVIGATE patients were more engaged in treatment and less likely to drop out as they received more intensive and comprehensive services. While 129 of 223 NAVIGATE patients (57.8%) completed the 24-month assessment, only 76 of 181 (41.9%) of CC patients did so. Whether this differential follow up biased the results of this study, and whether modeling differences in retention would alter the results, has not been examined.

A major methodological advance in this area in recent decades has been the use of mixed models which allow the use of all available data even when some data are missing from some subjects (Gueorguieva and Krystal 2004; Lavori et al. 1990). However, mixed models are based on the assumption that data are missing at random (MAR) given observed measurements (Little and Rubin 2002) and may be of uncertain validity when there is extensive loss to follow-up. MAR is an untestable assumption which may well be violated (Fitzmaurice et al. 2008) since loss to follow-up may be dependent on the missing outcome. While improving retention through aggressive follow-up and outcome assessment is the best way to minimize dropout bias, statistical remedies may also be used.

For a brief review of the analytic approaches including pattern mixture model (PMM) for dealing with data that are Missing Not at Random (MNAR) in clinical trials (Little and Rubin 2002), please see Dziura et al. (2013). Molenberghs et al. (2002) used imputation method in their PMM. Mixed-effects analysis has also been an appealing approach in PMM where discrete variables for dropout patterns are used in regular mixed-effects model (Little 1993; Hedeker and Gibbons 1997; Demirtas and Schafer 2003). This paper uses the pattern mixture mixed model (PMMM) approach. In this approach, participants in a clinical trial are stratified post-hoc according to the discrete groups representing their observed pattern of retention, or missing data, and each retention pattern has its pattern-specific parameterization in its own mixed-effect model. The weighted average of estimated outcomes across retention patterns in such models can then be calculated. We used several pattern-specific mixed-effect models while the mixed-effect PMM used a common mixed-effect model with terms of dropout patterns included as predictor but the two PMMs are otherwise similar.

Using different parameters for different retention patterns in PMM is thus a type of missing not at random (MNAR) model in which missing responses depend on the missingness pattern and vice versa. The PMM therefore may correct some bias when the MAR assumption is violated, however, it may still suffer bias if the missing response depends on additional unobserved variables besides the missingness pattern.

In this study, we used **PMMMs** to characterize the differential retention patterns among the subjects in RAISE-ETP, and to explore whether such models improve the goodness of fit of the outcome analyses and modify the estimated magnitude of group differences.

2. Methods

2.1. Sample

A total of 404 individuals aged 15 to 40 who presented for treatment for a first episode psychosis (FEP) and who had been prescribed antipsychotic medication for less than six months in lifetime, were enrolled between 2010–2012: 223 in NAVIGATE and 181 in CC. A CONSORT diagram of recruitment has been previously published (Kane et al. 2016). Thirty-four community mental health treatment centers were randomized to NAVIGATE or CC with equal probability following a national invitation and selection process. None of the centers withdrew after randomization.

2.2. Outcomes

Trained clinician interviewers who were masked to study participants' treatment assignment assessed the primary outcome measure, the Quality of Life Scale (QLS) (Heinrichs et al. 1984), using two-way, live video conferencing at baseline and at 6, 12, 18, and 24 months. The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al. 1990) were also completed by the interviewers. Days of employment or school attendance, days in the hospital and days of alcohol or drug use were documented at monthly interviews using structured self-report questions.

2.3. Statistical Analysis

2.3.1. Identifying variables associated with dropout

Among patients who had a baseline visit, we first used a time-to-dropout model with frailty terms (Clayton 1978) for each individual variable, to identify patient characteristics associated with dropping out of the study for each of the baseline and time-varying covariates listed in Table 1. Because the trial was a clustered randomized trial in which the two treatment conditions were randomized at the site-level rather than the patient-level, we used frailty terms to account for clustering of individual patients within sites. Particularly, in the time-to-dropout models with frailty terms, patients within a site share the same frailty value to account for correlation of data among patients within the same site. Frailty terms serve a similar role as random effects in linear mixed model regression analyses.

2.3.2. Analysis with pattern mixture mixed model

We groups individual study participants using three different approaches to the classification of retention patterns. The first approach was based on the number of follow-up visits out of a possible total of four (range = 0 to 4). The second approach was based on the time of the last follow-up visit (0, 6, 12, 18, or 24 months). The third approach added an additional indicator variable to the second approach to represent the situation in which patients missed an assessment and then completed at least one subsequent assessment (i.e., who had intermittent missing data) and otherwise were set to zero. The three different approaches to characterizing retention patterns serve as sensitivity analyses to compare how treatment effects change under different missingness classifications.

For each outcome using PMMM, with the addition of a class variable distinguishing different retention patterns in each of the three classification approaches described above, a pattern-specific mixed model within each retention pattern was fitted. For all the patterns with at least one followup visit, the pattern-specific mixed models were similar to those mixed model in the original trial report (Kane et al. 2016). The mixed models included term of time, the interaction between treatment group and time, and baseline measures that had been determined to be significantly different between treatment groups and significant for predicting the outcome. Specifically, the baseline covariates included were male gender, student status, and PANSS baseline score (Kane et al. 2016). The term for time was the square root of months since randomization which resulted approximately linear relationship between time and outcome (Kane et al. 2016). The model also included individual-specific and site-specific random intercept and slope of time. For patients in Stratum 0 who had only baseline measurements without followup visit, no model term involving time was included in their pattern-specific mixed models. For the outcome measures assessed monthly (days of work, substance use and hospitalization), mixed negative binomial regressions were conducted with terms analogous to the linear mixed models except with only random intercepts for individuals and sites. As there was no statistically significant difference between the two treatment groups for baseline measures of the outcomes except for the PANSS, baseline values were used as outcomes.

Please cite this article as: Sint, K., et al., Accounting for group differences in study retention in a randomized trial of specialized treatment for first episode psychosis, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.08.029