Journal of Affective Disorders 205 (2016) 159–164

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Tracking medication changes to assess outcomes in comparative effectiveness research: A bipolar CHOICE study

Noreen A. Reilly-Harrington [a,b,*], Louisa G. Sylvia [a,b], Dustin J. Rabideau [c], Alexandra K. Gold [a], Thilo Deckersbach [a,b], Charles L. Bowden [d], William V. Bobo [e], Vivek Singh [d], Joseph R. Calabrese [f], Richard C. Shelton [g], Edward S. Friedman [h], Michael E. Thase [i], Masoud Kamali [j], Mauricio Tohen [k], Melvin G. McInnis [j], Susan L. McElroy [l,m], Terence A. Ketter [n], James H. Kocsis [o], Gustavo Kinrys [a,b], Andrew A. Nierenberg [a,b]

[a] Department of Psychiatry, Massachusetts General Hospital, Boston, MA, United States
[b] Harvard Medical School, Boston, MA, United States
[c] Biostatistics Center, Massachusetts General Hospital, Boston, MA, United States
[d] Department of Psychiatry, University of Texas Health Science Center, San Antonio, TX, United States
[e] Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, United States
[f] Bipolar Disorders Research Center, University Hospital's Case Medical Center, Case Western Reserve University, Cleveland, OH, United States
[g] Department of Psychiatry, University of Alabama at Birmingham, Birmingham, AL, United States
[h] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States
[i] Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, United States
[j] Department of Psychiatry, University of Michigan, Ann Arbor, MI, United States
[k] Department of Psychiatry, University of New Mexico, Health Sciences Center, Albuquerque, NM, United States
[l] Lindner Center of HOPE, Mason, OH, United States
[m] Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH, United States
[n] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States
[o] Department of Psychiatry, Weill Cornell Medical College of Cornell University, New York, NY, United States

ARTICLE INFO

Article history:
Received 19 March 2016
Received in revised form
23 May 2016
Accepted 2 July 2016
Available online 5 July 2016

Keywords:
Bipolar disorder
Medication
Comparative effectiveness
Big data
Electronic medical record

ABSTRACT

Background: Comparative effectiveness research uses multiple tools, but lacks outcome measures to assess large electronic medical records and claims data. Aggregate changes in medications in response to clinical need may serve as a surrogate outcome measure. We developed the Medication Recommendation Tracking Form (MRTF) to record the frequency, types, and reasons for medication adjustments in order to calculate Necessary Clinical Adjustments (NCAs), medication adjustments to reduce symptoms, maximize treatment response, or address problematic side effects.

Methods: The MRTF was completed at every visit for 482 adult patients in Bipolar CHOICE, a 6-month randomized comparative effectiveness trial.

Results: Responders had significantly fewer NCAs compared to non-responders. NCAs predicted subsequent response status such that every additional NCA during the previous visit decreased a patient's odds of response by approximately 30%. Patients with more severe symptoms had a greater number of NCAs at the subsequent visit. Patients with a comorbid anxiety disorder demonstrated a significantly higher rate of NCAs per month than those without a comorbid anxiety disorder. Patients with greater frequency, intensity, and interference of side effects had higher rates of NCAs. Participants with fewer NCAs reported a higher quality of life and decreased functional impairment.

Limitations: The MRTF has not been examined in community clinic settings and did not predict response more efficiently than the Clinical Global Impression-Bipolar Version (CGI-BP).

Conclusions: The MRTF is a feasible proxy of clinical outcome, with implications for clinical training and decision-making. Analyses of big data could use changes in medications as a surrogate outcome measure.

* Correspondence to: Massachusetts General Hospital, Bipolar Clinic & Research Program, 50 Staniford Street, Suite 580, 02114 Boston, MA, United States.
E-mail address: nharrington11@mgh.harvard.edu (N.A. Reilly-Harrington).

http://dx.doi.org/10.1016/j.jad.2016.07.007
0165-0327/

1. Introduction

Comparative effectiveness research involves multiple research designs, including prospective randomization of monotherapies, hybrid designs that randomize one aspect of treatment, allowing clinical researchers to vary other treatments to help patients, and analysis of large databases (i.e., big data) including electronic health records and claims data. Particularly with hybrid designs and outcomes research, treatment complexity can make it challenging to determine outcomes.

Comparative effectiveness research of bipolar disorder (BD) is particularly challenging since patients with BD commonly have complex medication regimens involving medications with varying mechanisms of action (Suppes et al., 2005). BD patients take an average of four different psychiatric medications, and such complex regimens often necessitate both dosing and psychotropic changes in order to maximize efficacy and safety/tolerability (Post et al., 2003). The complexity of BD patients' treatment regimens has created limitations for comparative effectiveness research trials, or trials that mirror real world clinical care, as medication and dosing changes can confound results in research studies. However, on the other hand, medication changes made to a treatment regimen may indicate efficacy or lack of efficacy of the treatment regimens that patients are taking. Thus, it is necessary to account for medication changes that are an integral part of a BD patient's course of treatment to effectively study treatment outcomes (Reilly-Harrington et al., 2013).

To systematically account for these medication changes, the Bipolar Trials Network (BTN), a collaboration of clinical research centers specializing in the treatment of bipolar disorder, created the Medication Recommendation Tracking Form (MRTF) to capture physician prescribing behavior and clinical decision-making (Reilly-Harrington et al., 2013). The MRTF is the first psychiatric instrument to assess the frequency, types, and reasons for medication adjustments. Changes in treatment are operationalized by the metric Necessary Clinical Adjustments (NCA), which are defined as medication adjustments to reduce symptoms, optimize treatment response and functioning, or to address intolerable side effects. Changes due to planned dose titrations are not counted as NCAs. The MRTF represents an innovative methodological advance for comparative effectiveness research, as it standardizes the reporting and rationale for medication adjustments, providing a novel outcome metric for clinical effectiveness.

The aim of the present study was to assess how Necessary Clinical Adjustments could serve as a proxy for outcomes in a randomized comparative effectiveness trial of adults with bipolar disorder. Given the high rates of anxiety comorbidity in bipolar disorder and the association of poorer treatment response, it was predicted that patients with comorbid anxiety disorders at baseline would have higher rates of NCAs than patients without comorbid anxiety disorders.

2. Methods

2.1. Procedure

The Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE) was a six-month, multi-site randomized comparative effectiveness trial comparing a classic mood stabilizer (lithium) to an antipsychotic commonly used to treat bipolar disorder (quetiapine). All subjects also received adjunctive personalized treatment (APT), consisting of guideline-based additional medications to manage symptoms or side effects. The Bipolar CHOICE rationale, design, and methods are reported elsewhere (Nierenberg et al., 2014) and will only be discussed briefly here. Subjects (n=482) were between 18 and 68 years of age. All met DSM-IV-TR diagnostic criteria for bipolar I or II disorder and were required to be at least mildly symptomatic at study entry [Clinical Global Impressions for Bipolar Disorder Overall Severity (CGI-BP-S) $\geq$ 3]. The study employed broad inclusion and limited exclusion criteria in order to maximize the representativeness of the study sample. The study protocol was approved by the Institutional Review Boards of the 11 sites. All subjects gave their informed consent to participate after the study procedure was fully explained.

2.2. Measures

Trained raters confirmed psychiatric and substance use diagnoses using the electronic version of the extended Mini-International Neuropsychiatric Interview prior to randomization (Sheehan et al., 1998). Basic clinical and demographic data were also collected at baseline using standardized forms (please refer to Table 1, which has been modified from Nierenberg et al., 2016). Study visits occurred at week 0 (screening), and weeks 2, 4, 6, 8, 12, 16, 20, and 24 (follow-up) visits. The CGI-BP was used to assess bipolar disorder severity on three distinct subscales for mania, depression, and overall severity of bipolar illness on a scale from 1 (normal) to 7 (severely ill; Spearing et al., 1997). Psychiatric symptom severity was assessed through the Bipolar Inventory of Symptoms Scale (BISS; Bowden et al., 2007; Thompson et al., 2010), which is a structured clinical interview that also provides the basis for scoring the Montgomery Asberg Depression Scale (MADRS; Montgomery and Asberg, 1979) and Young Mania Rating Scale (YMRS; Young et al., 1978). In addition to providing a total score, the BISS also provides depression, mania, and anxiety subscale scores. The three-question Frequency and Intensity of Side Effects Ratings (FISER; Wisniewski et al., 2006) was used to assess the frequency, intensity, and day-to-day burden of side effects experienced in the prior week on a scale ranging from 0 to 6 (no side effects to present all the time). Quality of life and life functioning were assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott et al., 1993) and the LIFE-Range of Impaired Functioning Tool (LIFE-RIFT; Leon et al., 2000).

Physicians completed the MRTF (Reilly-Harrington et al., 2013) at baseline and at every office visit, at unscheduled office visits, or when medication changes were made over the phone or electronically. Comprehensive training on the MRTF was provided at the initial investigators' meeting by the BTN's Director of Training and Assessment (Author NRH) and study physicians were carefully monitored throughout the entire study to ensure that the appropriate coding schemes were being used. The MRTF can be completed in an average of 5 min, even when multiple medication changes are made at a visit.

2.3. Assessment

The MRTF consists of nine sections (see Fig. 1). Because the MRTF aims to reflect the medication recommendations made to optimize treatment, all medications and recommended doses were included on the form regardless of patients' compliance or actual consumption of the medication. The "Timepoint" column refers to the study visit of the medication recommendation. Recommendations could also be made into the future (e.g., after the time-point or study visit date) if part of a planned titration schedule. The second column of the MRTF (Medication Name) indicates the name of the recommended medication while the third column (Dose/Units) indicates the physician's recommended dose. In the event that alternating daily doses of a medication were recommended, the recorded dose was the average of the two alternating daily doses. Medications that were discontinued were noted as 0 mg. The fourth

Please cite this article as: Reilly-Harrington, N.A., et al., Tracking medication changes to assess outcomes in comparative effectiveness research: A bipolar CHOICE study. Journal of Affective Disorders (2016), http://dx.doi.org/10.1016/j.jad.2016.07.007