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The Medication Recommendation Tracking Form: A novel tool for tracking changes in prescribed medication, clinical decision making, and use in comparative effectiveness research

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ABSTRACT

This paper describes the development and use of the Medication Recommendation Tracking Form (MRTF), a novel method for capturing physician prescribing behavior and clinical decision making. The Bipolar Trials Network developed and implemented the MRTF in a comparative effectiveness study for bipolar disorder (LiTMUS). The MRTF was used to assess the frequency, types, and reasons for medication adjustments. Changes in treatment were operationalized by the metric Necessary Clinical Adjustments (NCA), defined as medication adjustments to reduce symptoms, optimize treatment response and functioning, or to address intolerable side effects. Randomized treatment groups did not differ in rates of NCAs, however, responders had significantly fewer NCAs than non-responders. Patients who had more NCAs during their previous visit had significantly lower odds of responding at the current visit. For each one-unit increase in previous CGI-BP depression score and CGI-BP overall severity score, patients had an increased NCA rate of 13% and 15%, respectively at the present visit. Ten-unit increases in previous Montgomery Asberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) scores resulted in an 18% and 14% increase in rates of NCAs, respectively. Patients with fewer NCAs had increased quality of life and decreased functional impairment. The MRTF standardizes the reporting and rationale for medication adjustments and provides an innovative metric for clinical effectiveness. As the first tool in psychiatry to track the types and reasons for medication changes, it has important implications for training new clinicians and examining clinical decision making. (ClinicalTrials.gov number NCT00667745).

1. Introduction

Bipolar disorder (BD) is a mental disorder characterized by episodes of mania and depression (American Psychiatric Association, 2000). Bipolar I disorder (BDI) is characterized by episodes of mania and often depressive episodes, which causes a chaotic and chronic course of illness. Bipolar II disorder (BDII), is defined by hypomanic (or less severe/impairing and shorter episodes of elevated mood)

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and depressive episodes. It is estimated that 1% of the general adult population of the United States will have BDI, but that the full spectrum of the disorder increases its lifetime prevalence to 4.5% (BDI − 1.0%, BDII 1.1%, and sub-threshold BD 2.4%) (Merikangas et al., 2007).

BD episodes may be exacerbated and/or trigged by life stressors, but the etiology of episodes is grounded in structural and functional abnormalities of the brain making pharmacotherapy the foundation of treatment (Post et al., 2003; Suppes et al., 2005). These abnormalities are still not clearly understood, making the treatment of BD difficult. To further complicate treatment, BD has the highest number of co-occurring psychiatric illnesses compared to any other mental disorder. The National Comorbidity Survey Replication study has reported that 97.7% of patients with BD I and 95.8% of those with BD II have another lifetime co-occurring Axis I disorder (Merikangas et al., 2007). It is estimated that 86% individuals with BD have at least three co-occurring Axis I disorders (Merikangas et al., 2007). For these reasons, complex regimens of multiple medications are typically employed to manage the course of BD. Thus, despite the development of treatment algorithms for BD (Suppes et al., 2005), the use of psychiatric medications to manage patients with BD tends to be "personalized" due to the complex nature of BD. Rarely are BD patients maintained on fixed medication and dosing regimens, and individuals with BD take an average of four different psychiatric medications which often each require several changes to optimize efficacy (Post et al., 2003).

This need for medication changes in treating BD poses limitations both in clinical research trials and in community treatment settings. In research, allowing for flexible dosing and medication changes may confound results. For example, if one treatment arm has more changes, or opportunities to optimize treatment than the comparison arm, this could improve treatment outcomes for that group. This is particularly relevant for comparative effectiveness research trials which are designed to test real-world treatments, requiring the use of treatment arms that mimic care in community settings. Thus, the Bipolar Trials Network (BTN), a group of clinical research centers that specialize in treating BD, developed the Medication Recommendation Tracking Form (MRTF) to monitor medication recommendations by study physicians. This form allows the BTN to determine whether the number of medication changes to optimize treatment outcomes (e.g., reduce side effects, minimize symptoms) differs between the groups and possibly, confounds the treatment outcomes.

The MRTF is also relevant for community providers, helping them to monitor new clinicians' prescribing behavior to determine if they are appropriately following the current, empirically-based treatment algorithm for BD (Suppes et al., 2005). The MRTF could also be used to track experienced clinicians' prescribing behavior in the community to assess when and how these clinicians diverge from the current treatment algorithms. These data could inform how the algorithms or guidelines are falling short in describing treatment for BD and possibly be used to design future research trials. Using the MRTF to improve upon the current treatment algorithms is vital since they can aid in clinical decision making, limit the amount of variation in clinical practice, and enhance the overall quality of treatment (Crismon et al., 1999; Gilbert et al., 1998). They also provide more specific information regarding clinical care through being more explicit and prescriptive, allowing for individually tailored medication adjustments (Trivedi and Kleiber, 2001). It has been shown that clinical care guided by empirically-based treatment algorithms is more effective than treatment as usual (TAU) as it yielded shorter time to remission (Adli et al., 2006; Bauer et al., 2009).

To our knowledge, the MRTF is the first tool in psychiatry to track medication changes and the physician's reason for making the recommendation. We believe that such a tool will increase the conscientiousness of prescriptive behavior, and more specifically, the likelihood of physicians using empirically-based algorithms if they are required to justify their treatment decisions. Similarly, this will increase physicians' awareness when they are diverging from established algorithms which could then be tracked systematically to further refine the current treatment guidelines for BD. The MRTF was also developed to improve the methodology of comparative effectiveness research by standardizing the reporting of medication adjustments. Thus, the aim of this paper is to describe the development of the MRTF, report data on the use of the MRTF in a clinical trial, and generate a discussion on how this tool could benefit both researchers and clinicians.

2. Methods

2.1. Procedure

The MRTF was developed by the BTN National Coordinating Center (NCC) at MGH (a group of psychologists, psychiatrists, and statisticians experienced in BD clinical trials), with input from the Principal Investigators at each of the six original BTN sites, as part of the Lithium Treatment Moderate Dose Use Study (LiTMUS), funded by the National Institute of Mental Health. LiTMUS was a multi-site, prospective, randomized, comparative effectiveness clinical trial of outpatients with BD. The nature, scope, and overall design of the research project have previously been described in greater detail (Nierenberg et al., 2009, 2013).

Participants were screened to verify that they met primary inclusion criteria: age 18 years or older, diagnosis of bipolar I or II disorder, and currently symptomatic, as defined as CGI-BP-S score ≥ 3. Primary exclusion criteria were any contraindication to lithium (e.g., prior hypersensitivity to lithium, severe cardiovascular or renal disease, or pregnancy), current crisis such that inpatient hospitalization or other crisis management should take priority, current lithium use, and unwillingness to comply with study requirements. A total of 283 participants were randomized to one of two treatment groups: lithium plus optimized personalized treatment (OPT), a guideline-informed, evidence-based, and personalized treatment, or to OPT alone. Table 1 describes the demographic and clinical characteristics of the sample.

The primary hypothesis was that patients randomized to lithium + OPT (optimized treatment; guideline-informed, evidence-based, personalized pharmacotherapy), compared to those who just received OPT would fare better in terms of improvement in clinical state (as measured by the Clinical Global Impression Scale-Bipolar Version (CGI-BP; (Spearing et al., 1997))), and would also require fewer changes in their treatment over the course of the six month study. Changes or adjustments in treatment were comprehensively monitored by tracking physicians' recommendations using the MRTF (see Fig. 1) which served as a measure for whether medication changes confounded treatment outcomes as well as whether physicians were following the treatment guidelines for BD.

Physicians were trained on the MRTF at the study initiation meeting and through a series of conference calls with the BTN's Director of Rater Training and Assessments (Author NRH). Use of the MRTF was monitored throughout the duration of the study. In terms of physician compliance, regular reports were generated to ensure that the proper coding schemes were being followed. Prescribing physicians completed the MRTF at the Baseline visit and at every office visit (i.e. Weeks 2, 4, 6, 8, 12, 16, 20, 24) and every time a clinically significant medication change was made outside of the office (e.g. phone, email). Once trained, physicians completed the MRTF in an average of 5 min.