Medication burden in bipolar disorder: A chart review of patients at psychiatric hospital admission

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ABSTRACT

Individuals with bipolar disorder (BD) often receive complex polypharmacy regimens as part of treatment, yet few studies have sought to evaluate patient characteristics associated with this high medication burden. This retrospective chart review study examined rates of complex polypharmacy (i.e., ≥ 4 psychotropic medications), patterns of psychotropic medication use, and their demographic and clinical correlates in a naturalistic sample of adults with bipolar I disorder (BDI; $N=230$) presenting for psychiatric hospital admission. Using a computer algorithm, a hospital administrator extracted relevant demographic, clinical, and community treatment information for analysis. Patients reported taking an average of 3.31 (S.D.=1.46) psychotropic medications, and 5.94 (S.D.=3.78) total medications at intake. Overall, 82 (36%) met criteria for complex polypharmacy. Those receiving complex polypharmacy were significantly more likely to be female, to be depressed, to have a comorbid anxiety disorder, and to have a history of suicide attempt. Women were significantly more likely than men to be prescribed antidepressants, benzodiazepines, and stimulants, even after controlling for mood episode polarity. Study data highlight the high medication burden experienced by patients with BD, especially those who are acutely symptomatic. Data also highlight the particularly high medication burden experienced by women with BD; a burden not fully accounted for by depression.

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1. Introduction

Bipolar disorder (BD) is a serious, disabling, and highly recurrent illness that poses numerous treatment challenges (Ketter, 2010). Despite a growing armamentarium of psychotropic medications for the treatment of BD (American Psychiatric Association, 2002; Blanco et al., 2002; Yatham et al., 2009), morbidity and mortality remain high. Over 90% of individuals with the disorder report multiple affective episodes across their lifetimes (Solomon et al., 1995), and prospective, naturalistic data reveal that patients with BD remain symptomatically ill for roughly 50% of their lives (Judd et al., 2002, 2003a; Post et al., 2003). Owing in large part to its depression-predominant course (Judd et al., 2003a,b), BD is also characterized by marked psychosocial and functional impairment (Judd et al., 2008) and particularly high risk of mortality due to suicide (Weinstock et al., 2009, 2010).

Given this clinical reality, it is not surprising that the use of complex polypharmacy for BD has increased dramatically over the years (Lin et al., 2006). For example, among inpatients treated at the NIMH Biological Psychiatry Branch between 1974 and 1996, the percentage of those discharged with treatment regimens containing three or more psychotropic medications increased 13-fold over this 22 year period (Frye et al., 2000). More recent data from the 1996–2006 National Ambulatory Medical Care Survey have revealed a continued similar trend, with the mean number of prescriptions increasing 40% over this 10 year period, and a greater than two-fold increase (from 14% to 33%) in the number of people prescribed three or more psychotropic medications (Mojtabai and Olfson, 2010). Although there are many instances of "rational polypharmacy" (Kingsbury et al., 2001; Post, 2007), and anecdotal evidence that some patients may benefit from certain complex regimens, this increased reliance on polypharmacy does not appear to be contributing to decreased rates of illness chronicity or functional impairment in BD, which have only continued to climb in recent decades (Huxley and Baldessarini, 2007). It should also be noted that this increased rate of complex polypharmacy has occurred in the absence of any

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clinical trial demonstrating the efficacy of combined BD treatment consisting of three or more medications (Sachs et al., in press). Lack of a formal evidence base supporting complex polypharmacy may, in large part, account for the substantial variability in community prescribing (Blanco et al., 2002; Dennehy et al., 2005) and poor adherence to published guidelines (Unutzer et al., 2000; Lim et al., 2001) for BD treatment that have been reported in the literature.

Whether "rational" or "irrational", the medication burden associated with increased use of complex polypharmacy nevertheless raises several concerns, including risk of adverse side effects (Kingsbury et al., 2001), drug interactions (Gören and Tewksbury, 2013), medication error (Stawicki and Gerlach, 2009), patient non-adherence (Velligan et al., 2009; Bates et al., 2010), and certain medical comorbidities (Krishnan, 2005; Misawa et al., 2011), the latter of which have increasingly become a concern among patients with BD (van Winkel et al., 2008). Indeed, individuals with BD have been found to be at especially high risk for metabolic syndrome and cardiovascular-related difficulties, such as obesity, diabetes, hypertension, and hyperlipidemia (Kemp et al., 2010). Not only has it been argued that such medical comorbidities may result from the use of certain psychotropic medications (Misawa et al., 2011), but the high incidence of such comorbidities also contributes to overall medication burden experienced by individuals with BD, who are often prescribed numerous psychotropic *and* non-psychotropic medications (Kupfer, 2005).

Although relatively small, there is a growing literature that has attempted to examine patterns of psychotropic drug use in community samples of patients with BD, and to evaluate demographic and clinical factors that may predict use of complex multi-drug regimens. Among 8073 subscribers with a bipolar I diagnosis in the Medco claims database, Sachs et al. (in press) recently reported that 33% of patients were exposed to at least four concurrent psychotropic medications. Analysis of a large pharmacy database containing over 7000 cases revealed that, among individuals undergoing initial monotherapy for BD, more than 50% were receiving two or more medications within one year (Baldessarini et al., 2007). In a subset of data from a large, voluntary registry of outpatients with BD, Levine et al. (2000) reported that nearly 50% were receiving three or more psychotropic medications, and 25% received four or more. These data yielded no evidence of demographic or clinical correlates of specific medication use or polypharmacy, which contrasts with more recent data reported from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (Goldberg et al., 2009). Among 4035 outpatients enrolled in STEP-BD, 40% used three or more medications for BD, and 18% used four or more. Complex polypharmacy, defined by Goldberg et al. (2009) as ≥ 4 medications, was most often associated with atypical antipsychotic and antidepressant use, and least often associated with use of Lithium, divalproex, and carbamazepine. These data further revealed that complex polypharmacy was significantly more common in patients with greater depressive illness burden, attempted suicide, and higher income, perhaps reflecting greater access to resources to support treatment with multiple medications.

In the STEP-BD analysis, however, certain classes of medication (i.e., benzodiazepines, hypnotics, and stimulants) were not accounted for in the operationalization of complex polypharmacy (Goldberg et al., 2009). Given relatively high rates of pharmacotherapy augmentation with such agents in BD patients (Levine et al., 2000; Baldessarini et al., 2007), including benzodiazepine use in as many as 40% (Levine et al., 2000), study data may have therefore underestimated medication burden, which may have, in turn, influenced findings concerning demographic and clinical correlates of complex polypharmacy. Further, given the increasing

awareness of high medical comorbidity in BD (Kupfer, 2005), it would be helpful to understand how non-psychotropic medication use contributes to overall medication burden for those with the illness. Existing studies (Levine et al., 2000; Goldberg et al., 2009) have also relied upon generally stable, primarily depressed outpatient samples, therefore limiting power to evaluate polypharmacy patterns in patients with active mania, mixed episodes, or psychosis, and excluding those patients who are most acute and potentially most likely to experience aggressive and complex pharmacotherapy from community prescribers.

The purpose of the current study was to further advance an understanding of medication burden in BD by evaluating patterns of community prescribing in a sample of patients with bipolar I disorder (BDI) presenting for psychiatric hospitalization. Using a retrospective chart review methodology, our aims were threefold: (1) to examine rates of psychotropic and non-psychotropic medication use immediately prior to hospitalization, (2) to examine rates of complex polypharmacy for BD, using Goldberg et al.'s (2009) definition of ≥ 4 psychotropic medications, and (3) to examine clinical and demographic factors associated with both complex polypharmacy and the use of specific medication classes. By evaluating medication use in an acutely symptomatic sample of patients with BD, the current study builds off of prior research in that it allows for the evaluation of polypharmacy patterns across bipolar mood states. Other strengths of this study include an operationalization of complex polypharmacy that includes all classes of psychotropic medication, and the evaluation of both psychotropic and non-psychotropic medication use, thus providing estimates of both psychiatric and overall medication burden in a sample of patients with BD within the context of routine clinical care.

2. Methods

2.1. Sample

A retrospective chart review was conducted for patients with bipolar I disorder (BDI) admitted to the inpatient or partial hospitalization programs at Butler Hospital in Providence, RI during the 2010 calendar year. To be considered eligible for inclusion, patients must have been 18 years or older and given a primary diagnosis of BDI at both hospital admission *and* discharge. There were no other study inclusion or exclusion criteria. For those patients with more than one hospitalization during this time period, we selected the first hospitalization within the calendar year as the index hospitalization. The resulting sample included 230 unique cases for analysis. Prior to initiating the study, a Protected Health Information (PHI) waiver and approval to conduct the chart review were obtained from the Butler Hospital Institutional Review Board.

2.2. Procedure

Relevant demographic, clinical, and community treatment information was extracted from electronic medical records by a hospital administrator and provided to the study first author (LMW) in a single Microsoft Excel file. Using standard form fields in the hospital admission report, the hospital administrator used a computer algorithm to extract the following data: patient age, sex, race, ethnicity, civil status, insurance status, history of suicide attempt, history of prior psychiatric hospitalization, and type of index hospitalization (i.e., inpatient vs. partial). Psychiatric diagnoses at hospital admission were made by the admitting psychiatrist, following routine clinical care. Using standard form fields from the admission record, the hospital administrator extracted corresponding DSM-IV-TR diagnostic codes in order to establish presence of a BDI diagnosis, the presence of psychosis at hospital admission, and global assessment of functioning (GAF) at hospital admission. All remaining diagnostic data, including presence of BDI diagnosis at hospital discharge, were extracted from the discharge report. Using standard form fields in this report, the hospital administrator extracted corresponding DSM-IV-TR and ICD diagnostic codes, which were quantified into the following variables: polarity of BD mood episode, presence of any comorbid anxiety disorder, alcohol or substance use disorder (SUD), or other axis I disorder, and presence of any cardiometabolic comorbidity. All categorical variables were dummy coded (0=no, 1=yes).

From the patient's medication reconciliation form, also in the electronic medical record, the hospital administrator extracted string data listing all