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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 ($SD=1.46$) psychotropic medications, and 5.94 ($SD=3.78$) 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.

Keywords

polypharmacy; bipolar depression; mood stabilizers; antidepressants; benzodiazepines; demography; psychopharmacology

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

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Declaration of interest

None of the authors declare any conflicting interests.

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(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; Post et al., 2003; Judd et al., 2003a). Owing in large part to its depression-predominant course (Judd et al., 2003a; Judd et al., 2003b), 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 3 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 2-fold increase (from 14% to 33%) in the number of people prescribed 3 or more psychotropic medications (Mojtabai & 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 & Baldessarini, 2007). It should also be noted that this increased rate of complex polypharmacy has occurred in the absence of any clinical trial demonstrating the efficacy of combined BD treatment consisting of 3 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 & Tewksbury, 2013), medication error (Stawicki & 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 4 concurrent psychotropic medications. Analysis of a large pharmacy database containing over 7,000 cases revealed that, among individuals undergoing initial monotherapy for BD, more than 50% were receiving 2 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 3 or more psychotropic medications, and 25% received 4 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 4,035 outpatients enrolled in STEP-BD, 40% used 3 or more medications for BD, and 18% used 4 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 prescribed medications immediately prior to hospital admission. This form was typically completed by the admitting physician in collaboration with the patient, but at times involved additional input from the hospital pharmacist and/or other collateral reports (e.g., a patient's family member, community pharmacist). Medication data were coded by a trained research assistant, using a code book developed by study investigators, and quantified into the following variables: any psychotropic medication, any non-psychotropic medication, total number of psychotropic medications, total number of all medications, lithium, any anticonvulsant, any antipsychotic, any atypical antipsychotic, any typical antipsychotic, any antidepressant, any selective serotonin reuptake inhibitor (SSRI), any serotonin norepinephrine reuptake inhibitor (SNRI), any other antidepressant (i.e., tricyclic, MAOI, mirtazapine, bupropion, buspirone), any benzodiazepine, any stimulant, or any hypnotic. All categorical variables were dummy coded (0 = no, 1 = yes). Complex polypharmacy at the time of hospital admission was dummy coded (0 = no, 1 = yes) and defined using the operational criteria described by Goldberg et al. (2009) (i.e., taking 4 psychotropic medications). Following coding of medication, data were checked for errors by the study first author (LMW), and all data were imported into SPSS v.20 for analysis.

2.3. Data Analysis

In addition to presenting descriptive data on medication usage patterns in this sample, we used independent t-test and chi-square analyses to evaluate demographic and clinical differences between patients receiving vs. not receiving complex polypharmacy for BD. For any significant differences identified, multivariate logistic regression analyses were used to examine which variables accounted for unique variance in complex polypharmacy when controlling for the effects of any potential covariates (e.g., mood episode polarity)¹. Logistic regression analyses were also used to evaluate associations between specific medication classes and odds of receiving complex polypharmacy.

Examination of demographic and clinical characteristics associated with the use of specific medication classes relied upon chi-square analyses to evaluate differences between those receiving vs. not receiving specific medication types (e.g., Lithium). As in the complex polypharmacy analyses, for any significant differences identified, analyses were repeated using multivariate logistic regression models to control for the effects of any potential covariates (e.g., mood episode polarity). As this was an exploratory analysis, *p*-values were set at 0.05.

3. Results

Demographic and clinical characteristics of the study sample are presented in Table 1. Of the 230 patients, 186 (81%) reported psychotropic medication use prior to hospitalization and 122 (53%) reported taking medication for non-psychiatric purposes. Among those in pharmacotherapy for BD, patients reported taking an average of 3.31 (*SD* = 1.46) psychotropic medications at the time of hospitalization. Average total medication usage (including both psychotropic and non-psychotropic medication) was 5.94 (*SD* = 3.78). One hundred and twenty-six (55%) of the study sample reported taking 3 or more psychotropic medications at the time of hospitalization, and 82 (36%) of the study sample met the operational criteria for complex polypharmacy (i.e., taking 4 psychotropic medications). This figure represents 44% of those receiving any pharmacotherapy for BD at the time of hospital admission.

3.1. Characteristics associated with complex polypharmacy

Characteristics associated with complex polypharmacy for BDI are presented in Table 2. Overall, 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. Conversely, those receiving complex polypharmacy were significantly less likely to be manic and to present with active psychosis at the time of hospital admission. Controlling for mood episode polarity, female sex ($B(SE) = 0.58(.29)$, $\chi^2(1) = 3.88$, $p = 0.049$, $OR = 1.78$), anxiety disorder comorbidity ($B(SE) = 0.72(0.32)$, $\chi^2(1) = 5.18$, $p = 0.023$, $OR = 2.05$), and history of suicide attempt ($B(SE) = 0.79(.34)$, $\chi^2(1) = 5.60$, $p = 0.018$, $OR = 2.21$) remained significant predictors of complex polypharmacy for BDI, whereas psychosis did not ($B(SE) = -0.50(0.32)$, $\chi^2(1) = 2.40$, $p = 0.121$, $OR = 0.61$). Each psychotropic medication class was significantly associated with increased likelihood of complex polypharmacy (see Table 3).

3.2. Patterns of medication use by mood episode polarity

Analyses of specific psychotropic classes revealed no differences in patterns of medication use between depressed and mixed polarity patients (all *ps* = 0.11 – 0.94). As such, these groups were combined for purposes of comparison against patients presenting with pure mania. Use of antidepressants was significantly higher in the depressed/mixed polarity patients in comparison to patients presenting with pure mania (45% vs. 20%; $\chi^2(1) = 15.49$, $p < 0.001$). This pattern of effects held for the use of SSRIs (26% vs. 12%; $\chi^2(1) = 7.64$, $p = 0.006$), SNRIs (10% vs. 2%; $\chi^2(1) = 5.65$, $p = 0.017$), and all other antidepressants (19% vs. 7%; $\chi^2(1) = 5.93$, $p = 0.015$). Use of benzodiazepines was also significantly higher in the depressed/mixed polarity patients vs. those presenting with mania (47% vs. 33%; $\chi^2(1) = 4.42$, $p = 0.036$). Use of all remaining medications (i.e., Lithium, anticonvulsants,

¹Given that medication decisions may be especially driven by mood episode polarity (e.g., antidepressants prescribed for a depressive vs. manic episode), we decided, on an *a priori* basis, to treat mood episode polarity as a covariate in any subsequent multivariate analysis of significant univariate effects. This strategy allowed for the evaluation of demographic and clinical factors associated with complex polypharmacy and patterns of specific medication use, over and above any shared variance with mood episode.

antipsychotics, stimulants, hypnotics) did not differ as a function of episode polarity (all $ps = 0.08 - 0.90$).

3.3. Patterns of medication use by axis I psychiatric comorbidity

There were no differences in patterns of specific medication use between those with and without a comorbid anxiety disorder (all $ps = 0.09 - 0.99$), with the exception of greater use of any antidepressant (45% vs. 29%; $\chi^2(1) = 5.93, p = 0.015$) or benzodiazepine (51% vs. 36%; $\chi^2(1) = 4.69, p = 0.030$). After controlling for mood episode polarity upon admission, these effects were no longer significant (B(SE) = 0.29(0.32), $\chi^2(1) = 0.84, p = 0.359$, OR = 1.34 and B(SE) = -0.26(0.32), $\chi^2(1) = 0.65, p = 0.419$, OR = 0.77, respectively). There were no differences in use of specific psychotropic classes by comorbid SUD (all $ps = 0.08 - 0.90$) or by any other comorbid axis I disorder (all $ps = 0.14 - 0.91$).

3.4. Patterns of medication use by cardiometabolic comorbidity

There were no differences in patterns of specific medication use between those with or without a cardiometabolic illness (all $ps = 0.31 - 0.76$), with the exception of lower rates of Lithium use (18% vs. 33%; $\chi^2(1) = 6.99, p = 0.008$), lower rates of stimulant use (3% vs. 11%; $\chi^2(1) = 5.32, p = 0.021$), and greater rates of anticonvulsant use (60% vs. 43%; $\chi^2(1) = 6.94, p = 0.008$) in the medically comorbid group. Effects for Lithium (B(SE) = -0.82(0.31), $\chi^2(1) = 6.77, p = 0.009$, OR = 0.44), stimulant (B(SE) = -1.28(0.59), $\chi^2(1) = 4.72, p = 0.030$, OR = 0.28), and anticonvulsant (B(SE) = 0.69(0.27), $\chi^2(1) = 6.43, p = 0.011$, OR = 2.00) treatment remained significant after controlling for mood episode polarity. Presence of a comorbid cardiometabolic illness was also significantly associated with increased *total* medication use ($F(1, 229) = 11.70, p = 0.001$), including both psychotropic and non-psychotropic medication.

3.5. Patterns of medication use by other demographic and clinical variables

Additional analyses of specific medication use revealed that women were significantly more likely than men to be prescribed any antidepressant (43% vs. 23%; $\chi^2(1) = 10.33, p = 0.001$) and any SSRI (27% vs. 11%; $\chi^2(1) = 9.25, p = 0.002$). Women were also significantly more likely than men to be prescribed benzodiazepines (49% vs. 31%; $\chi^2(1) = 7.43, p = 0.006$) and stimulants (11% vs. 3%; $\chi^2(1) = 4.30, p = 0.038$). These effects remained significant after controlling for mood episode, with evidence for increased rates of any antidepressant (B(SE) = 0.79(0.31), $\chi^2(1) = 6.27, p = 0.012$, OR = 2.19), SSRI (B(SE) = 0.97(0.39), $\chi^2(1) = 6.06, p = 0.014$, OR = 2.64), benzodiazepine (B(SE) = 0.78(0.29), $\chi^2(1) = 7.08, p = 0.008$, OR = 2.17) and stimulant use (B(SE) = 1.28(0.66), $\chi^2(1) = 3.78, p = 0.052$, OR = 3.59) among the female versus male patients.

There were no differences in use of specific psychotropic classes by race (all $ps = 0.14 - 0.88$), ethnicity (all $ps = 0.08 - 0.92$), civil status (all $ps = 0.09 - 0.75$), insurance status (all $ps = 0.17 - 0.96$), history of previous hospitalization (all $ps = 0.06 - 0.84$), history of suicide attempt (all $ps = 0.06 - 0.99$), or presence of psychosis at hospital admission (all $ps = 0.06 - 0.91$). Age was not significantly associated with the use of any psychotropic medication class (all $ps = 0.09 - 0.88$), with the exception of increased likelihood of hypnotic use (B(SE) = 0.03(0.01), $\chi^2(1) = 6.08, p = 0.014$, OR = 1.03). This effect held after controlling for any effects of mood episode, (B(SE) = 0.03(0.13), $\chi^2(1) = 5.75, p = 0.016$, OR = 1.03). Age was also significantly associated with average total (psychotropic and non-psychotropic) medication use ($F(1, 229) = 19.5, p < 0.001$) in this sample.

4. Discussion

Complementing existing studies from primarily outpatient samples, current study data provide further evidence for the high rates of complex polypharmacy in BD, and extend findings to those patients in an acute mood episode. Even after accounting for the 20% of patients who were not engaged in any pharmacologic treatment prior to hospitalization, 55% were on 3 or more psychotropic medications at the time of hospital admission and 36% were on 4 or more. This latter figure is exactly double the rate reported from the outpatient STEP-BD sample (Goldberg et al., 2009), though more consistent with rates of polypharmacy reported by Levine et al. (2000) in their voluntary BD registry. Differences across studies may be attributable to a number of factors. For example, certain classes of psychotropic medication (i.e., benzodiazepines, hypnotics, stimulants) were not included in the operationalization of complex polypharmacy in STEP-BD, as they were in the current study, and STEP-BD recruited a larger, more diverse sample of patients including those with BDI, BDII and BDNOS, as well as some with schizoaffective disorder. It should also be noted that STEP-BD relied upon a largely outpatient sample, whereas the current study was designed to evaluate trends in polypharmacy among acutely ill patients presenting for inpatient hospitalization, who may simply be more likely to experience aggressive pharmacotherapy.

Evaluation of demographic and clinical variables revealed that those receiving complex polypharmacy for BD were more likely to be female, to be depressed, to have a comorbid anxiety disorder, and to have a history of suicide attempt. Notably, female sex, anxiety comorbidity, and suicide attempt history remained significant predictors of complex polypharmacy, even after accounting for their shared variance with depression, suggesting that presence of depression alone was not sufficient to explain increased rates of polypharmacy among these patient subgroups. Despite differences in study design, it should be noted that these results were largely consistent with the demographic and clinical correlates reported in the STEP-BD analysis (Goldberg et al., 2009), in which female sex, depressive illness burden, and history of suicide attempt were all found to be higher in the complex polypharmacy group. In STEP-BD, however, history of psychosis was associated with increased likelihood of complex polypharmacy, whereas current study analyses revealed that active psychosis was associated with a *decreased* likelihood of complex polypharmacy. This pattern of results may reflect a growing trend toward the use of antipsychotic monotherapy to treat psychosis in BD, in comparison to a combined treatment approach (Yatham et al., 2005). Yet it is also important to note that this effect was fully accounted for by shared variance with mania at the time of hospitalization, which may also reflect overall poor adherence with community treatment, or disengagement altogether, when patients are actively manic and more likely to experience psychotic symptoms (Copeland et al., 2008). Although evaluation of specific medication classes revealed significantly increased odds of complex polypharmacy across all agent classes, it is not surprising that effect sizes were especially high for those medications that are typically augmented (e.g., anticonvulsant, antipsychotic) and those that are typically used for augmentation (e.g., antidepressant, benzodiazepine) in general clinical practice (Baldessarini et al., 2007). Strikingly, in our sample, a complex polypharmacy regimen for BD was associated with a 12 times increased odds of benzodiazepine use.

Additional study analyses revealed that average number of prescriptions almost doubled (from 3.3 to 5.9) when both psychotropic and non-psychotropic medications were taken into account, further highlighting the high overall medication burden experienced by patients with BD, especially as they age, and the increasingly complex interplay between mental health and physical health needs of this population (Krishnan, 2005; Kupfer, 2005). This concern was further reflected in the presence of cardiometabolic illness in roughly 50% of

all study patients. Although cardiometabolic illness was *not* associated with increased risk for complex polypharmacy in the current study, it was associated with increased use of anticonvulsant medication, which is consistent with some prior reports in both psychiatric and non-psychiatric samples (Newcomer, 2006). Perhaps reflecting clinician hesitancy to prescribe certain agents for individuals with complex medical conditions, cardiometabolic illness was also associated with decreased use of Lithium and stimulant medication. Yet when both psychotropic and non-psychotropic medications were evaluated together, cardiometabolic illness was associated with greater *total* number of medications prescribed. Future research will be necessary to more thoroughly evaluate the contribution of non-psychotropic medication, including certain agent classes, to the overall burden of polypharmacy experienced by patients with BD.

By and large, additional analyses of the use of specific medication classes revealed little correspondence with demographic and clinical variables such as age, race, ethnicity, civil status, insurance status, axis I comorbidity, history of suicide attempt, or presence of psychosis at the time of hospital admission. One interesting finding was the relatively low rate of Lithium use across the study sample, regardless of suicide attempt history and other relevant clinical factors, which is consistent with prior reports of decreased trends in Lithium prescribing over time (Blanco et al., 2002). Not surprisingly, patients presenting in a depressed or mixed episode were significantly more likely to be prescribed antidepressants and benzodiazepines than those presenting with mania. Yet even after statistically controlling for depression, women were found to be significantly more likely than men to be prescribed antidepressants, particularly SSRIs, as well as benzodiazepines and stimulants. These data are consistent with a recent analysis of over 13,000 outpatient visits in a general psychiatric sample, which revealed significantly higher rates of polypharmacy, antidepressant, and sedative-hypnotic prescribing for women versus men (Mojtabai & Olfson, 2010). Although the current study was not designed to evaluate potential reasons for such effects, it may be that women are more accepting of such medications or, consistent with greater rates of mental health treatment seeking in women more generally (Oliver et al., 2005), have more frequent contact with medication providers and hence greater opportunity for pharmacotherapy augmentation. It may also be that women are perceived by providers as having greater need for augmentation with these agents. Future research will be necessary in order to better clarify potential explanations for this pattern of results.

Future research will also be necessary in order to address other limitations of this research study. Most notably, the study relied upon retrospective chart review, which benefits from data collected in the context of routine clinical care, but also has a number of limitations. Although we were conservative in selecting those cases that had a BDI diagnosis at both admission and discharge, thereby reducing heterogeneity of the sample, chart diagnoses were not confirmed by structured interview, secondary axis I conditions may not have always been assessed or documented in the electronic medical record, and medication use was primarily self-reported. Further, although medication prescription data could be obtained via chart review, the stability of and adherence to community pharmacotherapy could not be assessed in the current study. Thus, it is unclear to what extent patterns of pharmacotherapy in the current study reflect long-standing regimens vs. medication regimens that were adjusted in the period immediately prior to hospitalization. Further, given poor rates of medication adherence reported in the BD literature (Gaudiano et al., 2008), it is unclear to what extent patients had been adherent to outpatient medication regimens. Finally, the study sample was primarily Caucasian and the majority of participants carried some level of health insurance, either through private or public sources. Thus, generalizability to more diverse patient groups with BD, and to those without health insurance coverage, remains unclear.

Nevertheless, the current study provides important descriptive data that extend the literature on psychotropic medication use in BD in a number of ways. Primarily, study data confirm prior reports (Frye et al., 2000; Levine et al., 2000; Baldessarini et al., 2007; Goldberg et al., 2009) of a high medication burden among individuals with BD, and further suggest that this burden may be even higher among those who are most acutely ill. Indeed, complex polypharmacy was evident in 36% of the study sample. This finding is especially striking, as patients presented as acutely symptomatic despite high rates of polypharmacy. Study data further extend the literature by highlighting the particularly high medication burden experienced by women with BD (Bjerrum et al., 1998; Goldberg et al., 2009; Mojtabai & Olfson, 2010); a burden that was associated with – but not fully accounted for by – higher rates of depression in this patient group, and one that appeared to be driven by more frequent use of adjunctive (i.e., antidepressant, benzodiazepine, stimulant) medications with mixed efficacy support (Yatham et al., 2005; Sachs et al., 2007; McIntyre, 2009) for the treatment of BD.

Altogether, findings from this study reflect the enormous challenge of symptom management in BD (Ketter, 2010) and do not discount the many instances of “rational” or evidence based polypharmacy that may yield clinical benefit (Solomon et al., 1996; Post, 2007). Yet study data also highlight the “fine line between help and harm” that clinicians face in light of the current limited effectiveness of monotherapy for BD (Werder & Preskorn, 2003) and the increased trend toward polypharmacy (Solomon et al., 1996; Frye et al., 2000; Levine et al., 2000; Baldessarini et al., 2007; Goldberg et al., 2009) with both psychotropic and non-psychotropic medications. In addition to increased risk of adverse side effects, drug interactions, medication error, and poor treatment adherence (Kingsbury et al., 2001), it is also worth noting that complex polypharmacy carries high cost burden to both patients and the healthcare system. With the unknown effects of combining several different medications off label, especially those that may be working cross-purpose, study data highlight a clear need for additional research on the patterns and quality of outpatient prescribing for BD and on the potential risks, especially for women, of iatrogenic complications without evidence of potential benefits.

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Table 1

Demographic and clinical characteristics of the study sample (N = 230)

	n (%)	M (SD)	Range
Age		42.2 (12.6)	18 – 77
Sex (female)	134 (58)		
Race (White)	217 (94)		
Ethnicity (Non-Hispanic)	210 (91)		
Civil status			
Single, never married	97 (42)		
Married/cohabiting	61 (27)		
Divorced/separated/widowed	72 (31)		
BD episode upon admission			
Depressed	85 (37)		
Manic	96 (42)		
Mixed	44 (19)		
Unspecified	5 (2)		
GAF upon admission		46.7 (9.7)	15 – 65
Index hospitalization			
Inpatient hospitalization	163 (71)		
Partial hospitalization	67 (29)		
History of previous hospitalization	185 (80)		
Psychosis upon admission	105 (47)		
History of suicide attempt	101 (44)		
Comorbid anxiety disorder	76 (33)		
Comorbid substance use disorder	93 (40)		
Other axis I comorbidity	28 (12)		
Any cardiometabolic disease	116 (50)		
Insurance status (public) [†]	85 (37)		

Note. GAF = global assessment of functioning.

[†] Due to existing hospital policies, a small proportion ($n = 5$; 2%) of the study sample was uninsured.

Table 2

Characteristics associated with complex polypharmacy (≥ 4 psychotropic medications) for BD

	Complex Polypharmacy (n = 82)	No Complex Polypharmacy (n = 148)		
	<i>M (SD) or n (%)</i>	<i>M (SD) or n (%)</i>	χ^2	<i>p</i>
Age	42.6 (11.3)	41.9 (13.4)	-0.42 [†]	0.678
Sex (female)	56 (68)	78 (53)	5.03	0.025
Race (White)	79 (96)	142 (96)	0.03	0.873
Ethnicity (Non-Hispanic)	77 (97)	133 (94)	1.56	0.212
Civil status			0.56	0.755
Single, never married	34 (42)	63 (43)	--	--
Married/cohabiting	20 (24)	41 (28)	--	--
Divorced/separated/widowed	28 (34)	44 (30)	--	--
BD episode upon admission			9.87	0.002
Depressed	38 (46)	47 (32)	4.03	0.045
Manic	24 (29)	72 (49)	9.47	0.002
Mixed	20 (24)	24 (16)	1.68	0.195
Unspecified	0 (0)	5 (3)	2.83	0.092
GAF upon admission	46.4 (9.1)	46.5 (10.0)	0.09 [†]	0.933
Index hospitalization			0.41	0.522
Inpatient hospitalization	56 (68)	107 (72)	--	--
Partial hospitalization	26 (32)	41 (28)	--	--
History of previous hospitalization	68 (83)	117 (79)	0.50	0.478
Psychosis upon admission	30 (37)	75 (51)	5.27	0.022
History of suicide attempt	49 (60)	52 (35)	6.63	0.010
Comorbid anxiety disorder	39 (48)	37 (25)	12.14	<0.001
Comorbid substance use disorder	29 (35)	64 (43)	1.36	0.244
Other axis I comorbidity	14 (17)	14 (10)	2.86	0.091
Any cardiometabolic disease	44 (54)	72 (49)	0.53	0.467
Insurance status (public)	30 (37)	55 (37)	0.03	0.864

Note. GAF = global assessment of functioning.

[†] For purposes of comparison of continuous data, t-tests were employed.

Table 3

Odds of complex polypharmacy by specific medication class

Complex Polypharmacy (<i>n</i> = 82)		No Complex Polypharmacy (<i>n</i> = 148)					
	<i>n</i> (%)		<i>n</i> (%)	<i>B</i> (<i>SE</i>)	χ^2	<i>p</i>	OR
Lithium	31 (38)		28 (19)	0.96 (0.31)	9.56	0.002	2.61
Anticonvulsant	66 (81)		53 (36)	2.00 (0.33)	37.39	<0.001	7.39
Any antipsychotic	69 (84)		52 (35)	2.28 (0.35)	43.03	<0.001	9.80
Atypical antipsychotic	62 (76)		48 (32)	1.87 (0.31)	35.89	<0.001	6.46
Typical antipsychotic	16 (20)		6 (4)	1.75 (0.50)	12.14	<0.001	5.74
Any antidepressant	50 (61)		28 (19)	1.90 (0.31)	37.94	<0.001	6.70
SSRI	31 (38)		15 (10)	1.68 (0.36)	22.51	<0.001	5.39
SNRI	11 (13)		4 (3)	1.79 (0.60)	8.16	0.004	5.58
Other antidepressant	20 (24)		11 (7)	1.39 (0.41)	11.77	0.001	4.02
Any benzodiazepine	63 (77)		32 (22)	2.49 (0.33)	57.05	<0.001	12.02
Any stimulant	37 (45)		20 (14)	1.59 (0.55)	8.30	0.004	4.90
Any hypnotic	12 (15)		5 (3)	1.66 (0.33)	25.76	<0.001	5.26