

Depressive Illness Burden Associated With Complex Polypharmacy in Patients With Bipolar Disorder: Findings From the STEP-BD

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Background: Many patients with bipolar disorder receive multi-drug treatment regimens, but the distinguishing profiles of patients who receive complex pharmacologies have not been established.

Method: Prescribing patterns of lithium, anti-convulsants, antidepressants, and antipsychotics were examined for 4035 subjects with bipolar disorder (DSM-IV) immediately prior to entering the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Subjects were recruited for participation across 22 centers in the United States between November 1999 and July 2005. The quality receiver operating characteristic (ROC) method was used to develop composite profiles of patients receiving complex regimens ($p < .01$ for all iterations).

Results: Use of 3 or more medications occurred in 40% of subjects, while 18% received 4 or more agents. Quality ROC analyses revealed that subjects had a 64% risk for receiving a complex regimen (≥ 4 medications) if they had (1) ever taken an atypical antipsychotic, (2) ≥ 6 lifetime depressive episodes, (3) attempted suicide, and (4) an annual income \geq \$75,000. Complex polypharmacy was least often associated with lithium, divalproex, or carbamazepine and most often associated with atypical antipsychotics or antidepressants. Contrary to expectations, a history of psychosis, age at onset, bipolar I versus II subtype, history of rapid cycling, prior hospitalizations, current illness state, and history of alcohol or substance use disorders did not significantly alter the risk profiles for receiving complex regimens.

Conclusion: Complex polypharmacy involving at least 4 medications occurs in approximately 1 in 5 individuals with bipolar disorder. Use of traditional mood stabilizers is associated with fewer cotherapies. Complex regimens are especially common in patients with substantial depressive illness burden and suicidality, for whom simpler drug regimens may fail to produce acceptable levels of response.

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Rapid growth in the pharmacopeia for bipolar disorder has generated more medication alternatives and, perhaps more importantly, a greater potential for patients to receive multiple medications simultaneously. However, little is known about the factors most likely to influence clinicians' decisions to prescribe complex multi-drug regimens for individuals with bipolar disorder.

Intramural studies of patients treated at the National Institute of Mental Health (NIMH) identified a substantial rise in the number of medications being prescribed for patients from 1974 to 1996, but without a greater benefit in outcome.¹ This observation has been interpreted to suggest that either contemporary patients with bipolar

disorder require more elaborate drug regimens to attain symptomatic recovery as compared to patients from a generation ago, or that clinicians often add an increasing number of psychiatric medications as more options become available, even if there is not discernible additional benefit.

The empirical literature on polypharmacy, composed largely of commercially-sponsored, controlled, 2-drug combination trials in acute mania, lags behind clinical practice, in that it has focused mainly on the advantages or disadvantages of combining either a conventional antipsychotic² or atypical antipsychotic (such as olanzapine,³ risperidone,^{4,5} or quetiapine^{6,7}) with a traditional mood stabilizer (such as lithium, divalproex, or carbamazepine) during acute mania or continuation treatment (e.g., using 2 agents vs. 1 following an acute mood episode^{8,9}). One recent study found no acute antimanic advantage, but more weight gain and dyslipidemia with olanzapine plus carbamazepine as compared to carbamazepine alone.¹⁰ Randomized controlled studies involving combinations of traditional mood stabilizers are few in number and limited to relatively small sample sizes (i.e., $N \leq 30$)¹¹⁻¹³ or active comparator combinations (e.g., 2 mood stabilizers vs. mood stabilizer plus antipsychotic¹⁴) that may have been underpowered to detect efficacy and/or tolerability differences between simpler versus more complex regimens. The combination of a traditional mood stabilizer and an antidepressant for acute bipolar depression showed no advantage over mood stabilizer monotherapy in 2 recent randomized placebo-controlled trials,^{15,16} although, for acute bipolar depression, the combination of lithium plus lamotrigine appears to yield greater efficacy than lithium plus placebo,¹⁷ as does the combination of olanzapine plus fluoxetine versus olanzapine monotherapy.¹⁸ Most studies have focused on monotherapy versus 2 antimanic drugs, yet in routine practice, a substantial number of patients with bipolar disorder receive 3 or more medications, regardless of their current illness phase.¹⁹

The present naturalistic study examined the prevalence of complex multi-drug prescriptions (i.e., 4 or more psychotropics) among entrants to the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and developed composite profiles (i.e., combinations of variables) to identify patients who receive such regimens. Efforts to better understand psychiatrists' prescribing behavior, and possible pharmacotherapy objectives, may help identify which aspects of illness complexity (e.g., symptom severity domains, episode recurrence, comorbidities) contribute most to the use of complex pharmacotherapy.

METHOD

The overall design and scope of the multi-site STEP-BD study have been described previously.²⁰ Briefly, sub-

jects were at least 15 years old, met DSM-IV criteria for any type of bipolar disorder (I, II, not otherwise specified [NOS], cyclothymic disorder, or schizoaffective bipolar disorder), and were recruited for participation across 22 centers in the United States between November 1999 and July 2005. Diagnoses were made by research psychiatrists using the STEP-BD Affective Disorders Evaluation (ADE)²¹ and independently confirmed with the Mini-International Neuropsychiatric Interview (MINI, version 5.0),²² administered by a trained master's- or doctoral-level research clinician (psychiatrist, psychologist, social worker, or psychiatric nurse). The current study focused on all STEP-BD entrants who met DSM-IV criteria for bipolar I ($N = 2666$), II ($N = 1084$), or NOS ($N = 285$) disorders at the time of their baseline assessment. Study exclusion criteria were kept to a minimum to enhance the generalizability of findings to patients seen with bipolar disorder under ordinary clinical conditions. Analyses for the current study focused on medications that patients were taking at study entry as well as their past history of medication usage.

Clinical features were rated using the ADE, as this intake assessment tool gathers information regarding present and past psychiatric illness, family histories of psychiatric illness, medical illnesses, and current mental status. Affective or psychotic symptoms and current medications were assessed using the Clinical Monitoring Form (CMF),²³ a 1-page instrument that contains a modified version of the Structured Clinical Interview for DSM-IV current mood modules as well as the Clinical Global Impressions-Severity of Illness (CGI-S) scale. The ADE and CMF were used to determine 1 of 8 clinical states for each subject at the time of enrollment, corresponding to 4 DSM-IV syndromal categories (depression, hypomania, mania, or mixed) and 4 subsyndromal categories (continued symptoms, recovering, recovered, and roughening, the latter term describing subjects with emerging signs of affective relapse after having previously been recovered).

Seven core medications and medication groups were defined: lithium, divalproex, carbamazepine, lamotrigine, other anticonvulsants without definitively established thymoleptic properties (e.g., topiramate, gabapentin, oxcarbazepine), any atypical antipsychotic, or any antidepressant. Data on the use of other medications that are not generally considered to be core treatments for syndromal symptoms in bipolar disorder, including benzodiazepines and other sedative-hypnotics (e.g., zolpidem), were recorded but not used in the current analyses.

All subjects provided written informed consent to participate in the study protocol, which was approved by the respective institutional review board at each of the STEP-BD study sites as well as the Data Safety Monitoring Board of STEP-BD.

Table 1. Characteristics of Subjects Taking Fewer Versus 4 or More Core Psychotropics^a at STEP-BD Entry

Variable	Subjects Taking < 4 Medications ^{b,c}	Subjects Taking ≥ 4 Medications ^{b,c}	χ^2	T	df	p	Cohen d
Female, N/N (%)	1713/3061 (56)	446/676 (66)	22.353	...	1	<.0001	0.09
White, N/N (%)	2737/3324 (82)	637/711 (90)	21.959	...	1	<.0001	0.09
Clinical state at study entry, N/N (%)							
Recovered	580/3324 (17)	116/711 (16)	0.451	...	1	.502	0.00
Manic	90/3323 (3)	12/711 (2)	2.476	...	1	.116	0.07
Hypomanic	129/3323 (4)	24/711 (3)	0.412	...	1	.521	0.03
Mixed	243/3323 (7)	62/711 (9)	1.660	...	1	.198	0.05
Depressed	994/3323 (30)	259/711 (36)	11.609	...	1	.001	0.18
Income ≥ \$75,000/y, N/N (%)	747/3324 (22)	158/711 (22)	0.009	...	1	.925	0.00
Past year rapid cycling, N/N (%)	1046/2152 (49)	264/460 (57)	6.165	...	1	.013	0.13
Alcohol abuse/dependence, N/N (%)	325/3324 (10)	48/711 (7)	6.038	...	1	.014	0.08
Drug abuse/dependence, N/N (%)	461/3324 (14)	84/711 (12)	1.944	...	1	.163	0.05
History of suicide attempt, N/N (%)	1105/3201 (35)	338/686 (49)	52.030	...	1	<.0001	0.05
First episode polarity depressed, N/N (%)	1602/3324 (48)	369/711 (52)	3.069	...	1	.080	0.05
History of psychosis, N/N (%)	309/3324 (9)	96/711 (13)	11.014	...	1	.001	0.02
Age, mean ± SD, y	39.4 ± 13.1	41.3 ± 12.1	...	3.468	3738	<.001	0.11
Age at illness onset, mean ± SD, y	16.2 ± 3.6	16.4 ± 3.3	...	0.907	3913	.182	0.03
No. of lifetime manias, mean ± SD	4.3 ± 1.8	4.5 ± 1.6	...	2.680	3518	.007	0.09
No. of lifetime depressions, mean ± SD	4.5 ± 1.7	4.9 ± 1.4	...	5.820	3544	<.0001	0.20
CGI-S score at entry, mean ± SD	3.0 ± 1.3	3.3 ± 1.3	...	6.230	3980	<.0001	0.20
BMI, mean ± SD	28.2 ± 6.6	29.5 ± 7.1	...	4.078	2942	<.0001	0.15
Bipolar disorder diagnosis, N/N (%)			16.6	...	2	<.0001	...
Bipolar I	2156/3324 (65)	510/711 (72)					
Bipolar II	913/3324 (27)	171/711 (24)					
Bipolar NOS	255/3324 (8)	30/711 (4)					

^aCore medications/medication groups are lithium, divalproex, carbamazepine, lamotrigine, other anticonvulsants, atypical antipsychotics, and antidepressants.

^bPercentages are column percentages.

^cNs vary due to missing data for some analyses.

Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions-Severity of Illness, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

Symbol: ... = not applicable.

Statistical Analyses

Between-group (i.e., complex polypharmacy present or absent) comparisons on dichotomous and continuous variables are presented using χ^2 tests or t tests for the dichotomous and continuous independent variables, respectively, summarized in Table 1. Accompanying effect sizes (Cohen d) were calculated to provide estimates of the clinical significance of univariate analyses for the entire study group. A recursive receiver operating characteristic (ROC) analysis was performed using software available in the public domain, developed at the Sierra Pacific Mental Illness Research, Education, and Clinical Core (<http://mirecc.stanford.edu>; Stanford, Calif.). The event to be predicted, or “gold standard,” was whether a patient was on a complex regimen of 4 or more psychotropic medications. The gold standard was coded as a binary variable.

As described by Kraemer,²⁴ the ROC analysis first identifies the best predictor and then splits patients into subgroups at a cut-point identified by the analysis. Within each subgroup, the remaining variables are searched for the next best predictor. Each time the “best” predictor is found, a χ^2 test is performed and the variable is retained as a predictor if $p < .01$. The process of searching for predictors continues until a predictor is not significant or

until there are fewer than 10 observations in a subgroup. Hence, the technique generates a collection of predictor variables that, taken together as a whole, yield a predictive result.

We chose to examine predictors of complex polypharmacy using ROC analyses rather than more traditional regression analyses in order to provide results that were more readily applicable in a clinical situation than those obtained through regression analyses. Importantly, unlike regression approaches, ROC analyses provide risk profiles that can be used as a focus of future study. While ROC analysis is commonly used to focus on balancing sensitivity and specificity in analyses of medical laboratory tests, this approach has more recently been used to predict composite risk profiles for dichotomous outcome states in clinical populations,²⁵ including patients with bipolar disorder.²⁶

RESULTS

Of the 7 core medications/medication categories studied, the mean ± SD number of medications being taken at study entry was 2.21 ± 1.41 (range, 0–7). Of the 4035 subjects, 472 (12%) were taking none of the core medications upon study entry, while 839 (21%) took

Table 2. Prevalence of Subjects Receiving ≥ 4 Core Medications/Medication Groups, Stratified by Presence of an Individual Agent

Current Agent	N	Subjects	Subjects	Cohen d
		Taking < 4 Medications, N (%)	Taking ≥ 4 Medications, N (%)	
Lithium	266	225 (85)	41 (15)	0.03
Divalproex	1185	934 (79)	251 (21)	0.11
Carbamazepine	767	548 (16)	219 (31)	0.13
Lamotrigine	839	563 (17)	276 (39)	0.18
Other anticonvulsant	629	351 (56)	278 (44)	0.59
Atypical antipsychotic	1262	780 (62)	482 (38)	0.74
Antidepressant	1935	1251 (65)	684 (35)	0.78

1 medication, 1130 (28%) took 2 medications, 883 (22%) took 3 medications, and 711 (18%) took 4 or more core medications. We operationally defined complex polypharmacy as being at least 1 standard deviation greater than the mean; hence, patients receiving 4 or more medications were classified as receiving complex polypharmacy.

Table 1 compares the characteristics of subjects taking fewer than 4 ($N = 3324$) versus 4 or more ($N = 711$) core medications/medication groups at STEP-BD entry, with accompanying effect sizes. As shown in the table, relatively modest effect sizes were associated with each of the univariate relationships examined with respect to polypharmacy prescriptions for the entire sample. Baseline severity at the time of study entry, as reflected by CGI-S scores, was modestly but significantly higher among subjects taking 4 or more core psychotropics ($p < .001$). In order to identify other factors related to the CGI-S, which could in turn potentially mediate the relationship between CGI-S scores and use of complex polypharmacy, we examined Pearson correlations between baseline CGI-S scores and several relevant clinical parameters, including current age, age at onset, gender, history of suicide attempts, income level, and lifetime use of an atypical antipsychotic, lithium, or carbamazepine. All such correlations were low ($r < 0.18$) and none was statistically significant.

Table 2 presents the proportion of subjects taking fewer than 4 medications versus 4 or more based on the presence of lithium, divalproex, carbamazepine, lamotrigine, other anticonvulsants, any atypical antipsychotic, and any antidepressant. Notably, the effect size associated with more extensive polypharmacy (i.e., ≥ 4 core medications/medication groups) was substantially smaller for subjects who were taking lithium ($d = 0.03$), divalproex ($d = 0.11$), or carbamazepine ($d = 0.13$) as compared to other core pharmacotherapies, suggesting the possibility that patients who receive these mood stabilizers may be less likely to receive more elaborate cotherapies. By contrast, antidepressants had the largest effect size ($d = 0.78$) associated with extensive polyphar-

macy, suggesting that individuals who took antidepressants were especially likely to receive more elaborate additional medications.

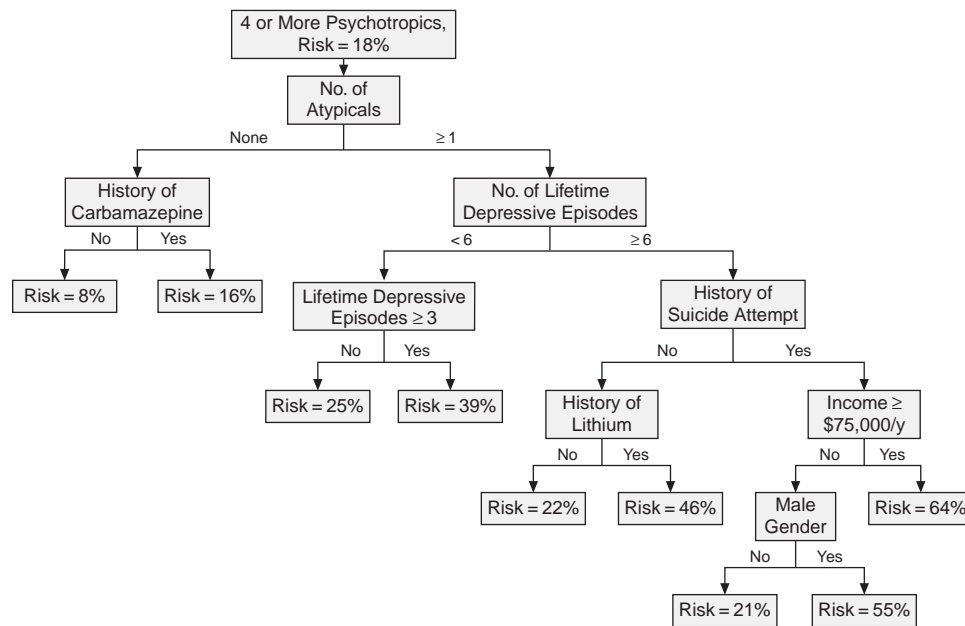
Figure 1 presents the ROC tree generated for identifying the profile of subjects who had been prescribed 4 or more core medications/medication groups. The tree can be read by following the path down to a particular risk. Thus, the profile associated with the greatest risk of receiving a complex polypharmacy regimen included patients who (1) received an atypical antipsychotic, (2) had 6 or more lifetime depressive episodes, (3) made a suicide attempt, and (4) had an annual income of at least \$75,000. This model provided a 64% risk for receiving a complex medication regimen, compared to the overall 18% prevalence rate among all STEP-BD entrants for being prescribed 4 or more medications. By contrast, the risk profile for not receiving an extensive medication regimen was best accounted for by subjects who (1) did not receive an atypical antipsychotic and (2) did receive carbamazepine (risk for complex polypharmacy = 8%). No other clinical features contributed to the low-risk model. Factors that appear in the ROC tree may differ from what one might expect based on the effect sizes reported in Table 1 because the ROC creates subgroups according to risk, whereas the effect sizes were based on the full sample.

DISCUSSION

The present findings indicate that a substantial proportion of individuals with bipolar disorder are prescribed complex polypharmacy regimens, particularly when they present with depression. In particular, bipolar disorder patients appear especially likely to receive more extensive medication combinations if they had been prescribed an atypical antipsychotic, had multiple depressive episodes, and made at least 1 suicide attempt. Inclusion of antidepressants as part of a treatment regimen was associated with the largest effect size leading to extensive polypharmacy with core medications. These observations underscore the extent to which depression in bipolar disorder continues to pose a formidable psychopharmacologic challenge, as also suggested by prior observations that antidepressants remain among the most widely prescribed psychotropic agents for patients with bipolar disorder.²⁷

The previously demonstrated lack of efficacy of adjunctive antidepressants relative to mood stabilizers alone from randomized controlled trials for bipolar depression^{15,16,28} are consistent with prescribing habits observed in the present study, which suggest that clinicians often resort to numerous and more elaborate drug combinations when confronted by serious depression in patients with bipolar disorder. Recent prospective data from the STEP-BD program²⁹ and other studies (e.g., Wehr and

Figure 1. Receiver Operating Characteristic Tree Showing Risk of Receiving a Complex Polypharmacy Regimen for Bipolar Disorder Patients Prescribed 4 or More Core Medications/Medication Groups^a



^aCore medications/medication groups are lithium, divalproex, carbamazepine, lamotrigine, other anticonvulsants, atypical antipsychotics, and antidepressants.

Goodwin³⁰) also indicate that antidepressant use is associated with multiple depressive episodes. In the present study group, it is possible that clinicians added other medications if patients had become unstable as the result of antidepressant use in an effort to regain remission. However, the cross-sectional design of the present study did not permit the chronological assessment of *when* antidepressants were introduced relative to other treatments, leaving open the alternative explanation that antidepressants may have been added to pre-existing complex medication regimens.

Complex polypharmacy was somewhat less prevalent when medication regimens included lithium, divalproex, or carbamazepine rather than other agents, such as atypical antipsychotics, antidepressants, or anticonvulsants with less definitive data, to treat any phase of bipolar disorder. Whereas causal relationships cannot be inferred from these cross-sectional naturalistic data, one possible interpretation is that lithium, divalproex, or carbamazepine confer more robust overall efficacy than other medications for bipolar disorder, prompting a lesser need for additional pharmacotherapies. Alternatively, it is possible that psychiatrists refrain from including lithium, divalproex, or carbamazepine in the regimens of bipolar patients who ultimately receive multiple agents. This is particularly likely for carbamazepine, due to its complex drug interaction profile. In either case, practitioners may underestimate the value and parsimony that might be

derived from incorporating lithium, divalproex, or carbamazepine in routine treatment regimens.

Strikingly, many clinical parameters related to illness severity that had initially been hypothesized to predict receipt of complex polypharmacy regimens did *not* emerge in the ROC analysis as being related to extensive polypharmacy. These variables included a history of psychosis, rapid cycling, number of prior hospitalizations, age at onset, comorbid alcohol or substance use disorders, current illness state (i.e., euthymic versus not euthymic), and bipolar I versus II subtype. The presence of multiple depressive episodes and a history of suicide attempts may especially compel prescribers to intervene with more numerous medications in people with bipolar disorder because clinicians often recognize these features as both difficult to treat and more proximal to morbidity and risk for suicide mortality.³¹ Patients with bipolar II disorder also were as likely as those with bipolar I disorder to receive complex polypharmacy, perhaps because depression in the former group is often frequent and unremitting,³² and suicide risk from depression may be higher in bipolar II than in bipolar I disorder.³³ The observed association between higher income and more complex polypharmacy raises the possibility that prescribers may undertake more extensive, aggressive, and costly treatments (while relatively underutilizing lithium, divalproex, and carbamazepine) for patients with the fewest financial obstacles to them. Because a higher income increased the risk for

complex polypharmacy by 18%, one cannot discount this hypothesis.

Methodologically, the present study illustrates the advantages of an ROC approach for establishing clinical profiles to define distinct patient subgroups. For example, many of the dependent variables distinguished the groups with simple or complex regimens but with small effect sizes. This could lead to the erroneous conclusion that particular variables were not relevant to the risk of complex polypharmacy. However, the ROC analyses revealed that the discriminatory power of variables can be much stronger for particular subgroups of patients. To cite one such instance, a history of suicide attempts alone showed little difference between the simple and complex regimen groups, but for patients who had taken an atypical antipsychotic and had more than 6 depressive episodes, it was important in predicting pharmacologic complexity. It should be noted that a logistic regression approach could also be applied to our data, but its outcome would not be as readily interpretable on a clinical basis. Specifically, logistic regression identifies statistically significant independent contributions of predictor variables for an entire sample, but does not allow for the creation of specific risk profiles as does ROC analysis.²⁴

It remains to be demonstrated whether, and when, more complex regimens are associated with better outcomes than might occur with fewer medications for the average patient with bipolar disorder—or, more precisely, for bipolar disorder patients with histories of multiple depressive episodes and suicide attempts. Denicoff and colleagues¹² previously found that the combination of lithium plus carbamazepine was associated with greater prophylactic efficacy than either monotherapy among bipolar disorder patients with rapid cycling, but not in those without rapid cycling. Although rapid cycling was not a predictor of complex polypharmacy prescriptions in the current study, it is often associated with extensive periods of depression,³⁴ antidepressant use,²⁹ and risk for suicidal behavior.³⁵ Hence, such patients would seem to be a critical group for future studies of combination drug therapy.

Information about the relationship between complex polypharmacotherapy and medication adherence, as well as cumulative adverse effects, was unavailable in the current study, although both treatment complexity and number of medications have been cited in previous work as predictors of nonadherence.³⁶ Relationships between the number of prescribed medications and treatment adherence may differ depending on *which* medications are combined. For example, among bipolar disorder patients taking lithium, divalproex, carbamazepine, or lamotrigine, long-term adherence appears greater with use of 2 rather than 1 of these agents,³⁷ perhaps because combinations of these agents are more effective. In the current

study, patients taking any of these agents were less likely to receive 4 or more core medications, in contrast to those taking atypical antipsychotics or antidepressants. With respect to potential adverse drug effects and complex polypharmacy, some clinicians may prescribe additional medications if adverse drug effects (such as low energy or poor concentration) are mistaken for signs of untreated psychopathology and perceived as targets for additional pharmacotherapy.

Historical exposure to a particular medication may influence subsequent decisions to prescribe that same medication, or other medications, and hence we included past history of psychotropic medications in the ROC model to profile current complex polypharmacy. Unavailability of information regarding response to past medications, or issues related to duration of use or adherence, represents limitations of the current study. Other limitations include the cross-sectional study design and retrospective assessment of prior treatments and historical illness characteristics (e.g., assessing the lifetime number of episodes). The observed lifetime prevalence of comorbid alcohol and drug abuse in the study group was somewhat lower than has been reported in other studies of multi-episode patients with bipolar disorder.³⁸ Although enrollment of STEP-BD participants was intended to optimize generalizability about individuals with bipolar disorder by imposing few study exclusion criteria, subjects were voluntary patients who sought treatment at academically-affiliated specialty centers for the treatment of bipolar disorder and were willing to participate in research-based treatment. Hence, the results may have differed had other types of patients with bipolar disorder been studied.

In summary, the present study indicates that a substantial proportion of individuals with bipolar disorder receive 4 or more core psychotropic agents during routine treatment and that features related to recurrent depression and suicidality may represent driving forces behind clinician decisions to undertake more extensive drug regimens. Conversely, patients appear less likely to receive complex polypharmacy regimens if they do not require an atypical antipsychotic but do receive lithium or an anticonvulsant with demonstrated efficacy in bipolar disorder. These naturalistic observations underscore both the limitations of existing treatments for bipolar depression as well as the need for controlled studies to determine which multi-drug regimens offer greater utility in depressed bipolar patients with suicidal features.

Drug names: carbamazepine (Carbatrol, Equetro, and others), divalproex (Depakote and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), oxcarbazepine (Trileptal and others), quetiapine (Seroquel), risperidone (Risperdal and others), topiramate (Topamax), zolpidem (Ambien and others).

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