Published in final edited form as:

Am J Geriatr Psychiatry. 2008 November ; 16(11): 922–933. doi:10.1097/JGP.0b013e318187135f.

Prescription Patterns of Psychotropic Medications in Elderly Compared to Younger Participants Who Achieved a “Recovered” Status in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

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Abstract

Objectives—This study aims at comparing prescription patterns between young adults and elderly with bipolar disorder who achieved a recovery status during the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).

Design—STEP-BD is a multicenter National Institute of Mental Health (NIMH)-funded project designed to evaluate the longitudinal outcome of patients with bipolar disorder. The STEP-BD study involved extensive assessment across multiple domains including demographic data, diagnosis,

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Disclosures:

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Grant/Research Funding: Cyberonics, Stanley Foundation, National Institute of Mental Health, Suicide Prevention Internationals, Mental Illness Research, Education and Clinical Center, Cephalon, American Foundation for Suicide Prevention, NARSAD.

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Financial disclosure information:

Research Grants: Glaxo-Smith Kline, MIMH, Ohio Department of Mental Health, Lutheran Hospital Foundation

Consultant: AstraZeneca, Cognition Group

Speaker Bureau: AstraZeneca

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Grant and research Support: Bristol-Myers Squibb Company, Eli Lilly and Company, Cyberonics Inc., Neuronetics, Stanley Foundation, Aspect Medical Systems and Sanofi Aventis. As of 11/19/07: Employee and Stock owner for Eli Lilly. Dr. Marangell is currently an employee of Eli Lilly. The work presented here was conducted while Dr. Marangell was an employee of Baylor College of Medicine and does not reflect the views of Eli Lilly and Company.

Melissa Martinez, M.D.

Grant and research Support: Eli Lilly and Company, Cyberonics Inc., Stanley Foundation, Neuronetics, Sanofi-Aventis, Bristol-Myers Squibb Company, Aspect Pharmaceuticals, Glaxo-Smith Kline and NIMH.

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Grant and research support: NIMH

Speaker Bureau: Abbott Laboratories, AbbCom

symptom severity, treatment and clinical status. Patients achieved “recovered” status when they experienced eight consecutive weeks without significant symptoms.

Participants—we analyzed data of all subjects who achieved a recovered status at least once in their participation.

Measurements—We compared treatment regimes and doses between young participants to middle age (n=3,364), 20 to 59 years old, and older participants 60 and above (n=246).

Results—Of the 3,615 STEP-BD participants who had a lifetime diagnosis of bipolar subtypes I or II, 67.6% (n=2442) achieved a recovered status during their participation. 78.5% (n=193) of older patients recovered compared to 66.8% of the younger cohort. On average, participants who reached a recovered status took 2.05 medications with no difference between age groups. Lithium was prescribed to 37.8% of younger patients compared to only 29.5% of older participants. The mean dosages taken by younger and older patients differed significantly only for lithium, valproate and risperidone with elderly individuals prescribed lower daily dosages. Significant reduction in lithium dosing was observed among individuals age 50 and older and among individuals 60 and older for valproate. Although valproate was more often prescribed, 42.1% of recovered bipolar elder achieved recovery with lithium alone compared to only 21.3% of the younger cohort.

Conclusion—This data shows recovery is achievable in the elderly though more than one medication is often needed regardless of age.

Keywords

Bipolar disorder; elderly; valproate; lithium; recovery

Introduction

It is estimated that by 2030 more than 20% of the US population will be 65 or older¹. Many of these individuals will require psychiatric care. Unfortunately, the needs of elderly patients with bipolar disorder (BD) are not well understood. It has been reported that standard treatments for mania are less effective in elderly patients and that elderly patients with BD treated with standardized care had decreased symptoms although the majority did not achieve complete recovery^{2,3}. A long term study by Angst et al. reported that only 16% of elderly patients with BD had fully recovered with usual treatment⁴. There are no current evidence-based recommendations for managing affective episodes in elderly persons with BD and little is known about recommended medications or doses in older patients⁵. Data from younger patients may not be applicable given metabolic changes that occur with age.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is a multicenter National Institute of Mental Health (NIMH)-funded project designed to evaluate the longitudinal outcome of patients with bipolar disorder⁶. This large database was well suited to evaluate the difference in prescriptions of psychotropic medications between younger and older patients with BD. We were especially interested, in whether older adults use lower doses and less number of medications than their younger cohort.

Method

STEP-BD Methods

STEP-BD is a multicenter study funded by the NIMH that included 4,360 individuals with bipolar disorder. The overall study combines a large prospective naturalistic study and a series of randomized controlled trials⁶, and was active between 1998–2005. STEP-BD was approved by the institutional review boards of all participating treatment centers and coordinating

centers. Oral and written informed consent was obtained from patients prior to any study related procedures.

Since STEP-BD was designed as an effectiveness study, subjects received pharmacological interventions as clinically indicated. Study clinicians completed training in the principles of evidence based treatment. This approach did not demand strict compliance to a specific treatment algorithm. Instead, it emphasized application of evidence-based treatments at every decision point in treatment, according to the current priorities for a given patient.

STEP-BD involved extensive assessment across multiple domains. Demographic data collected at baseline includes age, gender, race, education, income, marital status, and whether participants lived independently. Prescription information was entered on the Clinical Monitoring Form (CMF), a one-page standardized record-keeping form designed for use as a routine progress note⁷. Simple recording conventions were used to score symptoms and record medication doses.

Clinical status was assigned at each clinical contact, and included eight categories that encompassed the full affective episodes (depression, mania, hypomania, or mixed), subsyndromal symptoms (continued symptomatic or roughening), recovering or recovered. A “recovered” status was defined if a participant reported less than two affective symptoms with moderate or greater severity for eight weeks or more, while “recovering” if a participant reported less than two affective symptoms with moderate or greater severity for less than eight weeks. The categories of “continued symptomatic” and “roughening” were viewed as subsyndromal states in which patients have at least three moderate affective symptoms, but did not meet episodic criteria. Continued symptomatic was coded if the patient had not reached recovered status following a full mood episode, whereas roughening was coded if the patient had previously recovered from the most recent fully syndromal mood episode.

Clinical course characteristics were obtained from the Affective Disorders Evaluation (ADE), an assessment tool that utilizes versions of the mood and psychosis modules from the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), which was modified for routine use by practicing clinicians^{8,9}. Information about the presence or history of psychosis or rapid cycling and BP with other psychiatric co-morbidities was drawn from responses to ADE and CMF items. Patients were considered to have current psychosis if they had delusions or hallucinations at baseline. A lifetime history of rapid cycling was defined as having 4 or more phases in any 12 month period, including the past 12 months.

The Mini International Neuropsychiatric Interview (MINI, Version 4.4) which was administered by MINI-certified study clinicians on study entry was used to confirm bipolar diagnosis and establish comorbid axis I illness¹⁰. A patient was classified as having an anxiety disorder if they had a current diagnosis of generalized anxiety disorder, panic disorder, panic disorder with agoraphobia, social anxiety disorder, obsessive-compulsive disorder, or post traumatic stress disorder. The information was obtained from baseline and follow-up MINI forms. For this analysis, we extracted comorbidity information from the data collected at the time point closest and prior to the state at which the patient achieved a clinical status of “recovered”.

Treating psychiatrists underwent training for up to 20 hours in an accredited Continuing Medical Education (CME) program that offered instruction in Model Practice Procedures (MPPs), that included strategies for routine care of patients with BP with updated evidence based treatment guidelines. CME accredited virtual conference series, a series of videos, in-person training, and the STEP-BD Clinician’s Handbook were used as part of physicians training. Clinicians are certified in use of the AED and CMF after completion of a set of training

steps, including reaching minimum standards of competency when rating several videotaped interviews.

Medication selection and the need for laboratory testing and imaging were decided by treating physicians. Participants were not provided with medications or free care and the majority had insurance or private funding.

Study Sample

The current analyses include all participants with a lifetime diagnosis of bipolar subtypes I or II. Study entry required administration of both the ADE and MINI, and consensus on the presence of a STEP-BD eligible Axis I diagnosis.

The current cohort includes all individuals who were classified as “recovered” at any point in the study, including at baseline. Eighty-six patients aged between 15 and 19 year - 3.4% of all eligible participants - were excluded. All other patients were classified into age categories by decade (20–29, 30–39, 40–49, 50–59, 60–69, 70 and older) based on their age at study entry. Because the main objective was the comparison of younger versus older patients, we also grouped patients into two age groups for comparison: 20–59 and ≥ 60 years old.

Psychotropic medications that were frequently prescribed to participants by the time they met “recovered” status were classified into seven groups – lithium (Li), valproate (VPA), carbamazepine, lamotrigine, antidepressants, atypical antipsychotics, and benzodiazepines. We examined nine individual antidepressants (bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazepine, paroxetine, sertraline, and venlafaxine), five individual atypical antipsychotics (aripiprazole, olanzepine, quetiapine, risperidone and ziprasidone), and seven individual benzodiazepines (alprazolam, clonazepam, clorazepate, diazepam, lorazepam, oxazepam and triazolam). The total number of medications and total doses prescribed were assessed. A participant’s total time in the study was defined as the number of days since the patient consented to participate in STEP BD until the date of the last clinical monitoring form.

Statistical Analysis

All patients in the sample were included in the analyses except those who were 19 year old or younger. For categorical variables, we tested if there were differences among younger (ages 20–59) and older (60 and above) patients using Fisher’s exact test for 2-by-2 tables and chi-square tests for variables with more than two levels¹¹. For continuous variables, we tested whether the distribution was normally distributed using the Shapiro-Wilk test¹². We tested for differences between the 2 age groups using a two-sided t-test to determine the number of days in the study and the number of psychotropic medications taken at time of recovered status. For comparisons of the mean doses of the medications, we used the normal approximation for a two-sided non-parametric Wilcoxon two-sample rank sum test.

In addition to the mean and standard deviation (sd) that were calculated for all continuous variables, we also reported minimum, maximum, range and mode for those medications for which there were significant differences between the age groups. Additionally, we graphed the mean dosages and 95% confidence intervals by age decade. We used analysis of variance to test for differences among age decades, and if the overall F test was significant, we performed pairwise comparisons to determine at which age reductions in the dose prescribed occurred. To control the overall level of significance, we adjusted p values using a Bonferroni correction with an individual significance level of $\alpha = .05/k$, where k is the number of comparisons being made¹³. Thus, we considered p values $< .0023$ as significant when comparing mean medications dosages ($k=22$), and $p < .001$ as significant for the remaining comparisons.

One concern was whether patients who were recovered at baseline (STEP-BD-entry) differed from those who required active treatment in STEP-BD to reach recovered status. We tested for differences between these two groups of patients on their demographic and clinical characteristics as well as on medication usage and medication dosages. As above, Fisher's exact test was used for categorical variables with 2 levels, chi-square tests were used for categorical variables with more than 2 levels, and t-tests were used for continuous variables. In addition, we repeated all analyses that compared the younger and older patients, using only patients who recovered during active treatment, excluding those who were recovered at baseline.

Results

Demographics

Table 1 shows the recovery status by age group among eligible male and female patients age 20 and older. Of the 3,615 STEP-BD participants 20 and older who had a lifetime diagnosis of bipolar subtypes I or II, 67.6% (n=2442) overall were considered recovered either at their initial baseline measurement (n=874) or at some point during study participation (n= 1568). Of the older patients, 78.5% were recovered at baseline or during the course of the study compared to 66.8% of those 20–59 (Fisher's exact test, $p<.0001$).

One hundred and ninety three participants, aged 60 and above were recovered at baseline or recovered after baseline during the study, of which 39 (20%) were 70 or older. Demographic and clinical characteristics of the recovered STEP-BD participants are shown in Table 2. Patients in the older age group differed significantly from those in the younger age group on several characteristics. A higher percentage of men 60 and older (56.0%) recovered, compared to 42.3% of men under 60 (Fisher's exact test, $p<.0001$). As would be expected, significantly higher percentages of older participants were married (51.6%) and were divorced, widowed or separated (41.4%) compared to younger participants (38.9% married and 24.4% divorced, widowed or separated) (Chi-square test, $\chi^2=69.8$, 2 df, $p<.0001$).

The two age groups did not differ significantly on race (Fisher's exact test, $p=.6946$), education (chi-square test, $\chi^2=5.2$, 2df, $p=.0741$), income (chi-square test, $\chi^2=1.3$, 2df, $p=.5124$), mean time in the study (two-sided t-test, $t=.83$, $p=.4062$) and whether or not they lived independently (Fisher's exact test, $p=.7290$). They also did not differ on bipolar subtype (Fisher's exact test, $p=.3581$), on current anxiety disorder (Fisher's exact test, $p=.7333$), history of an anxiety disorder (Fisher's exact test, $p=.8725$), alcohol dependence (Fisher's exact test, $p=.1222$) or alcohol abuse (Fisher's exact test, $p=.1366$), drug dependence (Fisher's exact test, $p=.9999$) or drug abuse (Fisher's exact test, $p=.5720$), history of rapid cycling (Fisher's exact test, $p=.0813$), and current psychosis (Fisher's exact test, $p=.5720$). The number of psychotropic medications taken at the time of recovery was not different between the age group (two-sided t-test, $t=.07$, $p=.9481$). On average, patients under 60 took 2.05 medications (sd 1.12), whereas those 60 and older took 2.06 medications (sd 1.02). Five percent of our cohort were not taking psychotropic medications at the time of recovery, while one-third were on three or more.

Difference in Prescription Rate by Age

Table 3 reflects the psychotropic medications taken by patients who reached recovered status. In our sample, the least prescribed medication was carbamazepine with approximately 5% of prescriptions. About 20% of patients in each age group took benzodiazepines, followed by 20% – 25% taking lamotrigine. Atypical antipsychotics were used by 30–33% of participants. Valproate was prescribed to 34.0% of younger patients compared to 39.4% of older participants (Fisher's exact test, $p=.1340$). Of those 20–59, 37.8% took Li whereas only 29.5% of the older group were prescribed this medication (Fisher's exact test, $p=.0243$). Further analysis of the

data revealed that 42.1% of recovered elderly were on Li alone compared to only 21.3% of the younger cohort (Fisher's exact test, $p < .0001$). Anti-depressants were prescribed to more than 40% for all of the recovered participants, although there was no significant difference by age (Fisher's exact test, $p = .2571$).

Dosing of Commonly Prescribed Psychotropic Medications by Age

Detailed information about the dosages of the medications is shown in Table 4. Of the 25 individually examined medications, the mean dosages taken by younger and older patients differed significantly only for lithium (Wilcoxon two-sample test normal approximation, $Z = -6.81$, $p < .0001$), valproate (Wilcoxon two-sample test normal approximation, $Z = -5.01$, $p < .0001$) and risperidone (Wilcoxon two-sample test normal approximation, $Z = -3.09$, $p = .0020$).

The minimum dose in those 60 and older was equal to or greater than the minimum dose in the younger age group for all of the individual medications. For all medications, the maximum dose in the elderly group was less than the maximum in the younger group, except for bupropion with the same maximum dose in both age groups and citalopram in which the maximum dose was higher for the older group. Accordingly, the differences in the mean doses are not due to outliers in the elderly group.

Figure 1 shows the mean dose of Li and DVP across age groups. For Li, the mean dose in mg was substantially higher in younger than in older patients (1006 mg/day, sd 340, for those 20–59 versus 689 mg/day, sd 265, for those 60 and older; ANOVA, $F_{1,896} = 64.86$, $p < .0001$). The maximum daily dose for younger patients was 2400 mg compared to 1350 mg for older patients. The most common dose (mode) in both age groups was 900 mg. Further analysis of the data showed that mean dose of Li differed significantly among the age decades (overall $F_{5,896} = 14.32$, $p < .0001$). Specifically the mean dose of Li was significantly lower in patient aged 50 and above (mean 855, sd 296) compared to patient under age 50 (mean 1031, sd 348) ($F_{1,896} = 64.86$, $p < .0001$).

The values of the F tests for the pairwise contrasts of differences in means between the age decades were as follows: 20–29 vs. 50 and older, $F_{1,896} = 46.33$, $p < .0001$; 30–39 vs. 50 and older, $F_{1,896} = 63.10$, $p < .0001$; 40–49 vs. 50 and older, $F_{1,896} = 46.9$, $p < .0001$. The doses of Li decreased from age 20–29 through age 70 and older. Patients 20–29, 30–39, and 40–49 had average daily doses of 1019 mg (sd 322), 1060 mg (sd 365), and 1013 mg (sd 354), respectively. The mean daily doses decreased from 909 mg (sd 286) for those 50–59 to 735 mg (sd 251) for participants 60–69 and 574 mg (sd 273) for persons 70 and older. Pairwise comparisons of the age decades found no differences in mean dose among patients 20–29, 30–39, and 40–49 (20–29 vs. 30–39, $F_{1,896} = 1.63$, $p = .2025$; 20–29 vs. 40–49, $F_{1,896} = .03$, $p = .8553$; 30–39 vs. 40–49, $F_{1,896} = 2.32$, $p = .1281$). However, there were significant differences between patients in the age decades under 50 compared to participants 50–59, 60–69 and 70 and older, indicating that a significant reduction in lithium dosage occurs at age 50 and older (20–29 vs. 50–59, $F_{1,896} = 10.23$, $p = .0014$; 20–29 vs. 60–69, $F_{1,896} = 24.43$, $p < .0001$; 20–29 vs. 70 and older, $F_{1,896} = 26.59$, $p < .0001$; 30–39 vs. 50–59, $F_{1,896} = 20.25$, $p < .0001$; 30–39 vs. 60–69, $F_{1,896} = 32.56$, $p < .0001$; 30–39 vs. 70 and older, $F_{1,896} = 31.96$, $p < .0001$; 40–49 vs. 50–59, $F_{1,896} = 9.93$, $p = .0017$; 40–49 vs. 60–69, $F_{1,896} = 24.10$, $p < .0001$; 40–49 vs. 70 and older, $F_{1,896} = 26.22$, $p < .0001$). Moreover, there was a statistically significant difference between patients aged 50–59 and 60 and older in Li daily doses, with mean daily doses of 909 mg (sd 286) and 689 mg (sd 265) respectively (ANOVA, $F_{1,896} = 21.2$, $p < .0001$).

Of the 840 participants who recovered and were on DVP, 189 (22.5%) were prescribed DVP alone. The mean dose was also significantly higher in younger patients (1218 mg/day, sd 503, compared to 956 mg/day, sd 588, in patients 60 and older; ANOVA $F_{1,833} = 12.54$, $p = .0004$). The maximum daily dose in both age groups was 3000 mg, with a modal dose of 1000 mg.

Both groups had comparable maximum and minimum doses with a dose range of 2875 mg – 2750 mg in younger and older group respectively. The mean daily dose by age decades remained fairly constant at approximately 1200 mg for ages 20–29, 30–39, 40–49, and 50–59. The mean dose then declined to 966 mg/day (sd 565) in patients 60–69 and 904 mg/day (sd 711) in those 70 and older. The overall F test for the comparison of the age decades was $F_{5,833}=4.20$, $p=.0009$. Pairwise comparisons of age decades found no differences in mean dose among patients 20–29, 30–39, 40–49, and 50–59 (20–29 vs. 30–39, $F_{1,833}=.53$, $p=.4686$; 20–29 vs. 40–49, $F_{1,833}=.37$, $p=.5433$; 30–39 vs. 40–49, $F_{1,833}=.1579$, $p=.1579$; 20–29 vs. 50–59, $F_{1,833}=.37$, $p=.5423$; 30–39 vs. 50–59, $F_{1,833}=1.86$, $p=.1731$; 40–49 vs. 50–59, $F_{1,833}=0.00$, $p=.9698$).

For four of the five atypical antipsychotics (olanzapine, quetiapine, risperidone and ziprasidone), younger patients were prescribed higher mean doses. Those in the younger group who were prescribed risperidone received doses twice as high as those used in the older group (mean dosage of 1.95 mg (sd 1.39) versus 0.98 mg per day (sd 1.37) respectively; two-sided t-test, $t_{18,4}=4.08$, $p=.0007$). However, only 5.7% of the recovered subjects were on risperidone alone. Of interest is that 12.5% were on risperidone and Li, 11.5% on risperidone and DVP and 9.4% on risperidone, Li and DVP.

Sub-analysis by Time of Recovery

We found that patients who were recovered at baseline differed on some characteristics from those who achieved a recovered status later in the study. This included age, lifetime history of rapid cycling, mean number of psychotropic medications taken when recovered, and mean days in the study. Specifically, 11.1% of those who were recovered at the time of the baseline assessment were age 60 and older, compared to 6.1% of those who recovered later in the study (Fisher's exact test, $p<.0001$). Of those who were recovered at baseline, 75.8% had no history of rapid cycling compared to 57.8% of those who recovered during study follow-up (Fisher's exact test, $p<.0001$). On average, the number of medications taken at the time of recovery was 1.9 (sd 1.1) for those who were recovered at baseline and was 2.2 (sd 1.1) for those who recovered later (two-sided t-test, $t_{2440}=-6.12$, $p<.0001$). The mean number of days participants were in the study was 573 (sd 481) for the group who was in a recovered status at baseline and was 710 days (sd 438) for those who required change in treatment during follow-up to reach recovery (two-sided t-test, $t_{1669}=-6.97$, $p<.0001$). Using the stricter Bonferroni-adjusted p-value of $<.001$ as significant, we found that lower percentages of those who were recovered at baseline were taking lamotrigine compared to those who recovered during follow-up (16.5% versus 30.1%; Fisher's exact test, $p<.0001$), antidepressants (38.3% of those who were recovered at baseline compared to 46.0% of those who recovered at follow-up, Fisher's exact test, $p=.0002$), and atypical antipsychotics (28.7% of those who were recovered at baseline compared to 35.7% of those who recovered during follow-up, Fisher's exact test, $p=.0005$). In terms of differences in mean doses, the two groups did not differ statistically for any of the medications.

Despite these differences, the results of analyses comparing younger and older patients were similar, whether we used patients who recovered at follow-up or used the combined set of all recovered patients (those who were recovered at baseline and those who recovered later). The only difference in outcomes in our analyses that excluded participants who were recovered at baseline, was a significantly higher percentage of older patients who recovered (46.9%) used DVP compared to those under 60 (34.2%) (Fisher's exact test, $p=.0148$).

Discussion

This data constitutes one of the largest samples of elderly BD patients ($n=246$) followed in standardized care in 11 different sites. Depp and Jeste critically reviewed the literature of BD

in older adults and cited a total of 35 descriptive studies². In their review article, 85% of studies came from one site or institution and the largest study sample constituted 92 participants.

In spite of limitations due to study design and methods, our results add new information to a grossly understudied area of psychiatry. The results, however, can not be fully discussed and interpreted without considering the limitations of this prospective longitudinal study.

First, for those patients prescribed Li and DVP, serum levels were not consistently available in the database as would be the case in a study prospectively designed to evaluate mood stabilizer serum levels at regular intervals. Blood levels were often assessed only when introducing a new medication or changing dosages. When patients were stable or “recovered”, as in the case of this cohort, blood levels may not have been obtained.

Medication serum level may differ widely across patients even when the same mg/day doses of a given compound is utilized, depending on multiple clinical factors such as age and medical comorbidity. Older individuals, perhaps with some degree of renal insufficiency, may have higher serum lithium levels at relatively lower daily lithium doses¹⁴. Individuals with medical comorbidity and reduced serum protein may have higher circulating amount of free valproate that would be undetected or under-detected if the care provider was only measuring total serum valproate¹⁵. Although blood levels are relevant, patient reported symptoms based on clinical evaluation remain crucial to determining any needed effective intervention and medication changes.

Second, this study captures patients experiencing an eight-week period of stable euthymia, but provides no information regarding what symptoms participants had when their treatment was initiated or lastly changed. For example, previous reports suggested that Li has a higher efficacy than DVP in treating acute classic mania^{16,17}. The clinical status (i.e. depressed, mixed or manic) of patients before they reached recovery could have affected outcome and response to specific medications. In addition, patients who have concomitant psychotic symptoms are most likely to have an antipsychotic used as a primary mood stabilizer or as adjunct therapy. We do, however, plan to pursue such finer analysis in future manuscripts.

The duration of recovery for this cohort was not assessed and participants’ previous responses and failures to medications were not captured. We did not assess if the two subgroups differed in their history regarding hospitalizations or failure to respond to treatment.

The older adult patients in this study may represent a “survivor cohort” of elders with bipolar disorder. Individuals, who are more medically ill, reside in nursing homes/non-community settings as well as individuals who died prematurely due to causes related to whether bipolar illness and/or medical comorbidity represent the more severely ill spectrum of later-life bipolar disorder outcomes, and are not included in this elderly sample. In addition, STEP-BD participants may have had less medical comorbidity than other geriatric cohorts. Participants were not provided with medications or free care and the majority had insurance or private funding. This may suggest that this cohort population has easier accessibility to medical care and is generally healthier than those reported in other studies.

Moreover, adherence was not directly addressed in STEP-BD data. Medications were recorded at each visit based on information provided by patients rather than from a prescription database. Accordingly, there might be a significant difference of what participants were actually taking on regular basis and what has been prescribed to them. However, it has been suggested that adherence with maintenance medication treatment for bipolar disorder is somewhat better (in the order of 10% for full adherence) in older vs. younger patients¹⁸, and this could potentially account for at least part of the differences in a higher proportion of recovery among older adults in this STEP-BD sample.

Lastly, more than 90 percent of the patients in this analysis were Caucasian, limiting the ability to generalize the results to all persons with bipolar disorder.

Our analysis indicates that more 78.5% of elderly participants reached recovery (n=193). This is higher than what have been reported in literature¹⁹. However, in a meta-analysis, Sneed et al. had recently reported increased treatment effect of studies containing active comparators versus those with a placebo-controlled design in elderly with depression. Response rates were 60% in active arms studies compared to only 46% in the placebo control ones. STEP-BD design of standardized approach to diagnosis and evidence based treatment strategies with active comparators could have enhanced response.

While monotherapy is always preferable, 2/3 of participants achieved full recovery on at least two psychotropic medications. This is consistent with other studies including Gilderger's where 31 elderly participants took a mean of 2.4 mood stabilizers, 1.6 antidepressants and 1.3 sedative-hypnotics³.

Only one third of elderly patients were on Li. This is lower than cited in a report by Umapathy, where 2/3 of elderly BD patients were on Li, and consistent with Shulman et al. recent report regarding shifts in prescription patterns towards DVP^{20,21}. This shift is also documented in our providers' prescription tendency as the study progressed with less elderly being prescribed Li and more DVP.

The mean dose of Li in elderly of 689 mg/day (sd 265) was within the range suggested by Gebretsadik of 600–1200 mg/day²². Li usage pattern in the elderly, the maximum dose of Li used and Li daily dosage range are significantly lower compared to the younger cohort subgroups. This data supports previous findings which suggest a decrease in tolerability of Li in the elderly^{23–26}. However, with 40 % of recovered elderly prescribed Li only, suggests that Li is effective as monotherapy in this patient population if it is well tolerated.

The statistically significant decrease in Li dosage with age has been previously observed^{24–26}. This is mostly due to age related decrease in Li glomerular filtration rate and clearance. Li dosage requirements remain fairly constant until the early fifties where the Li requirement to maintain same serum concentration drops significantly.

Valproate was frequently used in this sample as it was prescribed to almost 1/3 of the participants in each age group. Though the mean daily dose of DVP was significantly lower in the older population, the mean daily dose is within the reportable recommended range for elderly with BD of 500–1500 mg per day²². Both groups had comparable dose range suggesting similar tolerability and efficacy in both subgroups, as has been reported previously in the literature^{14,15}.

Antipsychotics are often added to mood stabilizers for treatment of acute mania. A third of the participants were on atypical antipsychotics which often with symptoms of irritability, psychosis and hyperactivity when used as add-on or as monotherapy^{30–36}.

The STEP-BD data shows that recovery in elderly with BD is achievable. Based on our study Li, DVP and atypical antipsychotics are used regularly in patients with BD regardless of age. Though quite effective in treating BD in elderly, Li is less tolerated by elderly patients and is being used less by practitioners. With better tolerability, DVP on the other hand, is becoming a more preferable option. Atypical antipsychotics are progressively being used more in elderly. However, the literature continues to be scarce regarding evidence-based guidelines for treatment of BD in elderly. Given changing global demographics and the substantial humanitarian and financial burden of bipolar disorder, there is a critical need for further research in this area.

Acknowledgements

This project has been funded in whole or in part with federal funds from the National Institute of Mental Health (NIMH), National Institutes of Health, under Contract N01MH80001. Any opinions, findings, conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the NIMH. This article was approved by the publication committee of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). This material is also the result of work supported in part with resources and the use of facilities at the Houston Center for Quality of Care and Utilization Studies, Houston Veterans Affairs Medical Center and by funding from the Department of Veterans Affairs South Central Mental Illness Research, Education and Clinical Center. The views expressed herein are those of the authors and do not necessarily reflect those of the Department of Veterans Affairs or Baylor College of Medicine.

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Figure 1.
Mean Dose of Lithium and Valproate by Age

Table 1

Number of Eligible Male and Female Patients Age 20 and Older with a Lifetime Diagnosis of Bipolar Subtype I or II by Whether or Not They Were Recovered¹.

	20–59		60 and older		Total		p-value ³
	% ²	n	% ²	n	% ²	n	
In recovered status at baseline or attained recovered status during the study	66.8	2,249	78.5	193	67.6	2,442	<.0001
Were not in recovered status at baseline and did not attain recovered status during the study	33.2	1,120	21.5	53	32.4	1,173	
Total	100	3,369	100	246	100	3,615	

¹ Recovered includes patients who were recovered at baseline and those who reached recovered status during the study after baseline.

² This is the percentage of all participants in the age group who had the listed characteristic.

³ p-value indicates if there was a difference between the 2 age groups in whether or not they were recovered, based on Fisher's exact test.

Demographic and Clinical Characteristics by Age for Participants who were in Recovered Status at Baseline or who Reached Recovered Status during Follow-up¹.

	20-59		60 and older		Total		p-value ³
	% ²	n	% ²	n	% ¹	n	
Sex: Male	42.3	952	56.0	108	43.4	1,060	<.0001
Race							.9183
White	90.9	1,955	90.0	171	90.8	2,126	
African American	5.0	107	5.3	10	5.0	117	
All Other	4.2	90	4.7	9	4.2	99	
Education							.0741
High school or less	13.8	297	15.1	28	13.9	325	
High school graduate with < post- high school degree	25.9	555	18.3	34	25.2	589	
Associate, technical, college or post - graduate degree	60.3	1,295	66.7	124	60.8	1,419	
Income							.5124
< \$30,000	69.0	1,443	64.8	114	68.7	1,557	
\$30,000 - \$74,999	21.1	442	23.9	42	21.3	484	
\$75,000 or higher	9.9	207	11.4	20	10.0	227	
Marital Status							<.0001
Married	38.9	838	51.6	96	40.0	934	
Never married	36.6	788	7.0	13	34.3	801	
Divorced, separated	23.5	506	31.7	59	24.2	565	
Widowed	0.9	20	9.7	18	38	1.6	
Independence status							.7290
Live independently	98.7	2,124	98.4	184	98.7	2,308	
Bipolar Subtype							.3581
BP I	71.8	1,614	75.1	145	72.0	1,759	
BP II	28.2	635	24.9	48	28.0	683	
Current anxiety disorder	33.2	632	34.5	58	33.3	690	.7333
Lifetime anxiety disorder	51.2	975	52.1	88	51.2	1,063	.8725
Current alcohol abuse	8.3	158	4.7	8	8.0	166	.1366
Current alcohol dependence	7.7	146	4.1	7	7.4	153	.1222
Lifetime alcohol dependence	27.7	528	24.3	41	27.4	569	.3690
Current drug abuse	4.9	94	3.6	6	4.8	100	.5720
Current drug dependence	3.7	70	3.6	6	3.7	76	1.000
Lifetime drug dependence	16.8	321	16.7	28	16.8	349	1.000
Current psychosis	1.7	27	2.3	3	1.8	30	.4914
Lifetime history of rapid cycling	49.3	744	41.1	53	48.6	797	.0813
Number of psychotropic medications prescribed at time of recovery ^{**}							.2225
0	5.6	126	2.1	4	5.3	130	
1	28.3	636	32.6	63	28.6	699	
2	33.9	762	32.6	63	33.8	825	
3	22.0	495	23.3	45	22.1	540	
4 or more	10.2	230	9.3	18	10.2	248	
	Mean [*]	sd	Mean [*]	sd	Mean [*]	sd	t _{df}
Mean number of psychotropic medications taken when recovered	2.05	1.12	2.06	1.02	2.05	1.11	p-value
Mean days in study	663.7	456.1	635.1	489.4	661.4	458.8	t ₂₄₄₀ = -.079481
							t ₂₄₄₀ = .834062

¹This includes patients who were recovered at baseline and those who reached recovered status during the study after baseline.

²This is the percentage of all participants in the age group who had the listed characteristic.

³p-value indicates if there was a difference between the age groups in the listed characteristic. This is based on Fisher's exact test for categorical variables with 2 levels (sex, race, independence status, bipolar subtype, current anxiety disorder, lifetime anxiety disorder, current alcohol abuse, current alcohol dependence, lifetime alcohol dependence, current drug abuse, current drug dependence, lifetime drug dependence, current psychosis, lifetime history of rapid cycling), chi-square test for categorical variables with more than 2 levels (education, income, marital status, number of psychotropic medication prescribed at time of recovery), and two-sided t-test for continuous variables (mean number of psychotropic medications taken when recovered, mean days on study).

* sd = standard deviation

** From a total of 25 possible psychotropic medications

Table 3

Psychotropic Medications Taken by Subjects who were in Recovered Status at Baseline or who Reached Recovered Status during Follow-up¹, by Age.

	20-59		60 and older		Total		p-value ³
	% ²	n	% ²	n	% ²	n	
Lithium	37.8	849	29.5	57	37.1	906	.0243
Valproate	34.0	764	39.4	76	34.4	840	.1340
Carbamazepine	5.1	115	6.7	13	5.2	128	.3132
Lamotrigine	25.6	575	21.2	41	25.2	616	.1960
Antidepressants ⁴	42.9	965	47.2	91	43.2	1,056	.2571
Atypical antipsychotics ⁵	33.4	752	30.6	59	33.2	811	.4736
Benzodiazepines ⁶	19.6	441	21.8	42	19.8	483	.4528

¹ This includes patients who were recovered at baseline and those who reached recovered status during the study after baseline.

² This is the percentage of all participants in a given age group who were taking the listed medication.

³ p-value indicates if there was a difference between the age groups in the percentage who were taking the listed medication, based on Fisher's exact test.

⁴ bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazepine, paroxetine, sertraline, and venlafaxine

⁵ aripiprazole, olanzepine, quetiapine, risperidone and ziprasidone

⁶ alprazolam, clonazepam, clorazepate, diazepam, lorazepam, oxazepam and triazolam

Table 4
Medication¹ Dosages in Subjects who were in Recovered Status at Baseline or who Reached Recovered Status during Follow-up² by Age. **

Medication	20-59			Age 60 and older			Total			Z p-value ³
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
Lithium	846	1006.11	340.02	56	689.06	265.12	902	986.43	344.35	Z=-6.81 <.0001
Valproate	763	1218	502.65	76	955.59	587.97	839	1194.08	516.09	Z=-5.01 <.0001
Carbamazepine	114	669.32	327.80	12	608.33	144.38	126	663.51	315.11	Z=-.31 .7563
Lamotrigine	570	196.23	124.59	41	162.80	105.49	611	193.99	123.61	Z=-1.69 .0945
Antidepressants										
Paroxetine	131	29.87	15.28	16	28.75	14.43	147	29.74	15.15	Z=-.19 .8468
Citalopram	106	28.70	15.56	16	31.25	22.18	122	29.04	16.49	Z=-.06 .9559
Sertraline	117	111.11	61.87	10	120.00	67.49	127	111.81	62.09	Z=.40 .6897
Fluoxetine	100	38.75	19.53	7	32.86	26.28	107	35.56	19.90	Z=-.75 .4520
Fluvoxamine	9	138.89	82.07	3	125.00	66.14	12	135.42	75.72	Z=-.10 .9243
Escitalopram	44	15.95	8.69	2	20.00	14.14	46	16.13	8.79	Z=.52 .6032
Bupropion	360	261.15	107.48	27	240.74	105.87	387	259.72	107.36	Z=-.96 .3345
Vanlafaxine	175	195.83	117.36	14	167.76	108.11	189	193.75	116.66	Z=-.81 .4203
Mirtazepine	30	38.47	21.76	6	35.00	18.17	36	37.89	21.00	Z=-.22 .8274
Atypical Antipsychotics										
Olanzapine	255	9.33	6.39	30	8.13	5.46	285	9.20	6.30	Z=-.85 .3941
Quetiapine	219	235.50	229.95	18	147.92	126.04	237	228.85	224.79	Z=-1.37 .1698
Risperidone	176	1.95	1.39	13	0.98	0.77	189	1.88	1.37	Z=-3.09 .0020
Ziprasidone	62	90.81	57.61	2	70.00	14.14	64	90.16	56.83	Z=-.39 .6963
Aripiprazole	46	15.76	7.67	2	21.25	1.77	48	15.99	7.59	Z=1.53 .1248
Benzodiazepines										
Lorazepam	134	1.41	1.01	13	1.04	0.59	147	1.37	0.99	Z=-1.00 .3169
Clonazepam	233	1.41	1.09	21	1.55	0.96	254	1.42	1.08	Z=1.01 .3146
Diazepam	19	14.82	12.61	3	6.25	3.31	22	13.64	12.10	Z=-1.15 .2466
Alprazolam	57	1.60	1.59	5	0.80	0.33	62	1.53	1.54	Z=-.77 .4413
Oxazepam	5	47.00	42.66	0	-	-	5	47.00	42.66	-

Medication	20-59			Age 60 and older			Total			Z p-value ³
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
Clorazepate	2	15.00	10.61	0	-	-	2	15.00	10.61	-
Triazolam	2	0.31	0.27	0	-	-	2	0.31	0.27	-

¹ From a total of 25 possible psychotropic medications

² This includes patients who were recovered at baseline and those who reached recovered status during the study after baseline.

³ p-value indicates if there was a difference between the age groups in the mean dose of the listed medication, based on the normal approximation for a two-sided non-parametric Wilcoxon two-sample rank sum test.