Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Nerv Ment Dis. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

J Nerv Ment Dis. 2017 March ; 205(3): 182–187. doi:10.1097/NMD.0000000000000544.

A Reexamination of Non-Psychiatric Medication Adherence in Individuals with Bipolar Disorder and Medical Comorbidities

Jennifer B. Levin, PhD[a,b], **Anna Krivenko, BS**[a], **Ashley Bukach, MA**[a,b], **Curtis Tatsuoka, PhD**[b,c], **Kristin A. Cassidy, MA**[a], and **Martha Sajatovic, MD**[a,b,c]

[a]Department of Psychiatry, Case Western Reserve University School of Medicine and University Hospitals Case Medical Center, 10524 Euclid Avenue, Cleveland, Ohio, 44106, U.S.A

[b]Neurological & Behavioral Outcomes Center, University Hospitals Case Medical Center, 2103 Cornell Rd, Cleveland, Ohio, 44106, U.S.A

[c]Department of Neurology, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, Ohio, 44106, U.S.A

Abstract

Individuals with bipolar disorder (BD) have high rates of non-adherence, medical illness, and premature mortality. This analysis reexamined correlates of poor adherence to non-psychiatric medication in 73 patients with BD and medical comorbidities. The majority was female (74%) and African-American (77%) with mean age of 48.08 (SD = 8.04), mean BD duration of 28.67 years (SD = 10.24), mean years of education of 12.01 (SD = 1.87), and mean proportion of days with missed doses in past week of 43.25 (SD = 31.14). Sex, age, education, race, and living alone did not correlate with adherence. More BD medications and more severe psychiatric symptoms correlated with worse adherence. Specifically, poor adherence correlated with Retardation and Vegetative factors of MADRS and Affect factor of BPRS. Among poorly adherent patients with BD and medical comorbidities, number of BD medications, tension/anxiety and somatic symptoms of depression related to worse non-psychiatric medication adherence.

Keywords

medication adherence; medication non-adherence; medical comorbidities; bipolar disorder; non-psychiatric medication adherence

Introduction

Individuals with bipolar disorder have a mortality rate 2–3 times that of the general population, with the largest number of deaths being from cardiovascular disease (Birkenaes et al., 2007; Ramsey, Leoutsakos, Mayer, Eaton, & Lee, 2010; Ramsey et al., 2013). The higher rate of cardiovascular disease is attributed to unhealthy behaviors, such as poor diet, smoking, inactivity, increased risk for social factors such as poverty and homelessness,

Correspondence concerning this article should be addressed to Jennifer B. Levin, Department of Psychiatry, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center, 10524 Euclid Avenue, Cleveland, OH 44106. jennifer.levin@uhhospitals.org.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

genetic predisposition, and metabolic side effects of psychiatric medication (Birkenaes et al., 2007; Centorrino, Mark, Talamo, Oh, & Chang, 2009). Another important factor impacting health in this population is poor adherence to medication regimens (Busby & Sajatovic, 2010; Sajatovic et al., 2009; Sajatovic, Valenstein, Blow, Ganoczy, & Ignacio, 2007; Scott & Pope, 2002a). The data are sparse regarding the extent of and correlates of poor adherence to non-psychiatric medications in this population. However, the extensive literature on psychiatric non-adherence in patients with bipolar disorder and poor adherence to medications for physical health conditions in the general population may provide insight into the barriers for adherence to non-psychiatric medication for individuals with bipolar disorder.

Correlates of poor adherence to psychiatric medication in individuals with bipolar disorder include denial of illness, symptom severity, cognitive impairment, side effects, lack of illness knowledge, disorganized home environment, lack of social support, problems accessing treatment, and comorbid substance abuse (Clatworthy, Bowskill, Rank, Parham, & Horne, 2007; Hou, Cleak, & Peveler, 2010; Levin, Tatsuoka, Cassidy, Aebi, & Sajatovic, 2015; Pompili et al., 2013; Sajatovic et al., 2011; Sajatovic et al., 2015). Recent reviews also identify several sociodemographic correlates of poor adherence to bipolar disorder medications. These include younger age, female, lower education, family history of bipolar disorder, non-white race, non-married, living in a non-urban region, homelessness, financial hardship, and unemployment (Leclerc, Mansur, & Brietzke, 2013; Pompili et al., 2013).

Factors associated with poorer adherence to non-psychiatric medication in the general population include more medical comorbidities, number of medications prescribed, higher medication cost, less follow-up care, lack of trust and communication between patient and provider, complexity of treatment, lack of social support, cognitive impairment, negative feelings towards medication, and substance use (Rolnick, Pawloski, Hedblom, Asche, & Bruzek, 2013; Tamblyn, Eguale, Huang, Winslade, & Doran, 2014; Wheeler, Roberts, & Neiheisel, 2014). Additionally, a number of sociodemographic correlates of poor adherence to medical therapy have been identified in the general population and include being female, non-white, younger, less education, lower income, living alone, non-married, and having an unstable living environment (Rolnick et al., 2013; Wheeler et al., 2014). There is also extensive evidence that psychological factors, such as depression, are associated with a decline in adherence to medications for various chronic medical conditions (Eze-Nliam, Thombs, Lima, Smith, & Ziegelstein, 2010; King et al., 2012; Osborn & Egede, 2012; Wheeler et al., 2014).

Recently, we reported that there is no significant correlation between psychiatric and non-psychiatric medication adherence in patients with bipolar disorder, that poor adherence to non-psychiatric medication, while still a significant problem, is lower than to bipolar disorder agents, and that there is a significant correlation between general psychiatric symptoms as measured by the Brief Psychiatric Rating Scale (BPRS) and poor adherence to non-psychiatric medication (Levin, Aebi, Tatsuoka, Cassidy, & Sajatovic, 2016). The current study set out to explore in greater detail the sociodemographic variables and specific cluster of psychiatric symptoms associated with poor adherence to non-psychiatric medication in individuals with bipolar disorder.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

It was hypothesized that age (younger), sex (female), lower education, living alone, non-white race, bipolar disorder Type I, and taking more medications would be associated with worse non-psychiatric medication adherence. It was also hypothesized that particular psychiatric symptoms would differentially positively correlate with poor non-psychiatric medication adherence. Specifically, it was hypothesized that the Resistance, Positive Symptoms, Affect, and Negative Symptoms factors but not the Activation factor of the BPRS would correlate with poor non-psychiatric medication adherence. Furthermore, it was hypothesized that the Vegetative and Retardation factors but not the Dysphoria factor of the MADRS would correlate with poor non-psychiatric medication adherence.

Methods

Participants

The demographic, clinical and health characteristics of the sample of 73 patients with bipolar disorder and medical comorbidities are summarized in Table 1. Participants had a mean age of 48.08 (SD = 8.04) and mean years of education of 12.01 (SD = 1.87). The majority of the sample was female (74.0%), African-American (76.7%), unable to work due to a disabling condition (61.6%), and met criteria for bipolar disorder Type I (74.3%). The mean age of bipolar disorder onset was 19.68 (SD = 9.27) and the mean number of years with bipolar disorder was 28.55 (SD = 10.21) Mean MADRS and BPRS scores fell in the moderate range with 19.90 (SD = 8.82) and 36.79 (SD = 7.19) for MADRS and BPRS, respectively. Average lifetime psychiatric hospitalizations was 6.15 (SD = 9.85).

Materials

Tablets Routine Questionnaire—(TRQ) – This self-report measure identifies levels of non-adherence for the past 7 and past 30 days (Scott & Pope, 2002a, 2002b). TRQ has been shown to correlate highly with lithium levels (Scott & Pope, 2002a). The percentage of days with missed doses in the past week was assessed for each prescribed foundational oral medication for the treatment of bipolar disorder. For individuals who were on ≥1 foundational medication, an average was calculated in order to gather information on the full bipolar disorder treatment regimen. We did not measure the level of adherence to antidepressant drugs as they are often prescribed sporadically to target acute symptoms and are not considered to be maintenance medication for bipolar disorder. For individuals who reported being prescribed non-psychiatric medication, the percentage of days with missed doses was calculated for each medication separately and then an average TRQ for all non-psychiatric medications was then calculated. Higher TRQ scores are a reflection of worse medication adherence.

The Brief Psychiatric Rating Scale—(BPRS) measures global psychopathology (Overall & Gorham, 1962). Total scores on the BPRS range from 18 to 126 with higher scores indicative of more severe psychiatric symptoms. We utilized a robust five factor model identified by a meta-analysis of 26 factor analytical studies with a combined sample of 17,620 participants (Shafer, 2005). The five factors include Affect, Positive Symptoms, Negative Symptoms, Resistance, and Activation (see Table 2).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The Montgomery-Asberg Depression Rating Scale—(MADRS) measures depression symptoms (Montgomery & Asberg, 1979). Total scores on MADRS range from 0–60, with higher scores indicating more severe depression. Given the multidimensional nature of depression, several studies examined the factor analytical structure of the MADRS. The most robust model, accounting for 61% of the total variance, was that of a three factor solution (Suzuki et al., 2005). The three factors include Dysphoria, Retardation, and Vegetative Symptoms (see Table 2).

Charlson Comorbidity Index—(CCI) Self Report Version - Data on comorbid medical conditions were collected based on the self-report version of the CCI (Charlson, Pompei, Ales, & MacKenzie, 1987; Chaudhry, Jin, & Meltzer, 2005). The CCI summary score is comprised of the presence of 10 medical conditions including respiratory diseases, rheumatological diseases, cancer, diabetes, digestive problems, heart trouble, HIV or AIDS, kidney disease, liver disease, and stroke. While the original CCI includes dementia, it was excluded from the self-report version given that those with dementia would not be able to provide informed consent. Each disease category is assigned a weight which represents mortality risk with lower scores indicative of lower risk.

Given the high risk of cardiovascular disease in this population, self-reported adherence to antihypertensives, cholesterol lowering agents, and diabetes medications were calculated separately. Self-report data were also gathered via structured interview to identify the presence or absence of hypertension, hyperlipidemia, diabetes, smoking, to identify the number of daily cigarettes, and to calculate Body Mass Index (BMI). Obesity was defined as having a BMI ≥30.

Procedure

These data are part of a larger NIMH-funded randomized control trial testing a psychosocial intervention intended to promote bipolar disorder medication adherence versus an educational control in poorly adherent individuals with bipolar disorder. Study inclusion criteria included having either Type I or Type II bipolar disorder as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Gibbon, Spitzer, & Williams, 2002) or in rare cases when a participant could not provide complete information on the SCID (N=3), the diagnosis was confirmed with their provider, bipolar disorder for at least two years duration, treatment with at least one evidence-based medication to stabilize mood for at least six months (lithium, anticonvulsant, or antipsychotic mood stabilizer) and 20% or more of days with missed doses for current bipolar disorder medication treatment for either the past week or past month as measured by the Tablets Routine Questionnaire (Harvey, 1991). Past week TRQ was utilized as recall for shorter periods are likely to be more accurate. Past month TRQ was utilized to capture individuals who are adherent for relatively short periods of time but may have more difficulty adhering for longer periods of time. The 20% cutoff was chosen based on the expert consensus guidelines on adherence in patients with serious mental illness (Velligan et al., 2009). Only those patients reporting a comorbid medical condition on the CCI were included in the analysis. TRQ was completed for any medication that participants considered to be non-psychiatric based on patient self-report. Study inclusion criteria were purposely

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

broad in order to be generalizable to real-world patients with bipolar disorder. Only individuals who were unable to participate in study procedures, unable/unwilling to provide informed consent, and those at immediate risk of harm to self or others were excluded. In the current descriptive study, the data analyses utilized screening and baseline data only and did not analyze intervention effects.

Data Analysis

Independent samples t-tests were run to identify differences between dichotomous demographic variables including sex, living alone, race, and bipolar disorder type and self-reported average past week TRQ for all non-psychiatric medications. Spearman Rho correlational analyses were then run between continuous demographic variables including age, number of medications for bipolar disorder, number of medications for non-psychiatric medical conditions, and years of education with average past week TRQ for all non-psychiatric medications. Non-parametric correlation analyses were then run to determine the relationship between continuous variables including symptom severity (MADRS and BPRS), Charlson Comorbidity Index and self-reported average past week TRQ for non-psychiatric medications. Factors of the MADRS and BRPS were then correlated with past week non-adherence for psychiatric medications for the whole sample and for African Americans and females separately. All statistical analyses were performed using IBM SPSS Statistics 22.

The study was approved by the local Institutional Review Board and all study participants provided written informed consent. Data were collected between October, 2012 and June, 2015.

Results

As presented in Table 1, the most prevalent health problems in this sample of individuals with bipolar disorder were hypertension (60.3%), rheumatologic diseases (57.5%), hyperlipidemia (47.1%), respiratory diseases (41.1%), and diabetes (31.5%). Seventy-five percent of the sample (N=50) were smokers with an average of 10.58 (SD = 7.67) cigarettes smoked daily, 72% had a lifetime prevalence of alcohol abuse or dependence, and 74% had a lifetime prevalence of drug abuse or dependence. The average BMI (N=64) was 33.20 (SD = 8.23) and 64.1% (41/64) of participants were obese. The average Charlson Comorbidity Index was 2.48 (SD = 2.51) with a range of 14.

The average number of bipolar disorder medications prescribed was 1.48 (SD = 0.82) with 65.8% of the sample prescribed one foundational medication for bipolar disorder and 34.2% prescribed two or more medications. The average number of non-psychiatric medications prescribed was 3.16 (SD = 1.73). A paired-samples t-test was significant for past week TRQ for bipolar disorder medication (M=64.71, SD = 24.81) versus non-psychiatric medication (M=43.25, SD = 31.14), such that participants missed more of their bipolar disorder medication dosages than non-psychiatric medication treatments, $t(71) = 4.80$, $p < .001$, $d = .57$. The average past week TRQ for antihypertensives (N=38), cholesterol lowering medications (N=23), and diabetes medications (N=22) was 43.80 (SD = 34.64), 51.43 (SD = 38.01), and 36.42 (SD = 35.23), respectively. Spearman rho correlations were significant

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

between TRQ for cholesterol lowering medication and antihypertensives (*rs[13]* =.62, $p < .05$), but not between TRQ for diabetes medications and antihypertensives (*rs[16]* = .23, $p > .05$), or between TRQ for diabetes medications and cholesterol lowering medications (*rs[12]* = .15, $p > .05$).

Independent sample t-tests with demographic variables including sex $t(71) = -1.01$, $p > .05$, race (African American versus Caucasian) $t(71) = .43$, $p > .05$, and bipolar disorder type (Type I versus Type II) $t(68) = 1.62$, $p = .110$ being the independent variables and average past week non-psychiatric medication TRQ being the dependent variable did not produce any significant findings. One-tailed non-parametric correlation analyses between continuous demographic variables and average past week TRQ for all non-psychiatric medications yielded no significant correlation for age (*rs[73]* = −.09, $p > .05$), years of education (*rs* = .05[72], $p > .05$), the Charlson Comorbidity Index (*rs[73]*= −.09, $p > .05$), or number of non-psychiatric medications prescribed (*rs[73]* = −.12, $p > .05$). There was a significant correlation for number of foundational medications for bipolar disorder prescribed and average past week TRQ for all non-psychiatric medication (*rs[73]* = .20, $p < .05$) such that more medications for bipolar disorder related to higher TRQ for non-psychiatric medication.

According to one-tailed non-parametric correlation analyses, there was a significant positive correlation between MADRS and average past week TRQ for non-psychiatric medication (*rs[73]* = .28, $p < .01$) as well as for BPRS and average past week TRQ for non-psychiatric medication (*rs[73]* = .29, $p < .01$) such that more severe bipolar disorder symptoms were associated with worse adherence to non-psychiatric medication.

One-tailed Spearman rho correlations between TRQ for non-psychiatric medication and factors of the MADRS and BPRS are presented in Table 3. When examining specific factors of the MADRS, TRQ for non-psychiatric medication was correlated with the Retardation (*rs[73]* = .30, $p < .01$) and Vegetative factors (*rs[73]* = .27, $p < .05$) but not with the Dysphoria factor (*rs[73]* = .08, $p > .05$). When looking at specific factors of the BPRS, TRQ for non-psychiatric medication was correlated with the Affect factor (*rs[73]* = .26, $p < .05$) and there was a trend with the Activation factor (*rs[73]* = .17, $p = .07$) but not with Positive Symptoms (*rs[73]* = .02, $p > .05$), Negative Symptoms (*rs[73]* = .09, $p > .05$), or Resistance (*rs[64]* = .05, $p > .05$).

Given the fact that the literature notes that race and sex may be related to adherence status (Leclerc et al., 2013; Pompili et al., 2013), we examined African Americans and females separately. When examining only African Americans, only the Retardation factor (*rs* [56] =.24, $p < .05$) of the MADRS and the Affect factor (*rs*[56]= .25, $p < .05$) of the BPRS were significantly correlated with past week TRQ for non-psychiatric medication. When examining only females, both the Retardation factor (*rs [54]* = .33, $p < .01$) and the Vegetative factor (*rs[54]* =.30, $p < .05$) of the MADRS and the Affect factor of (*rs[54]* = .27, $p < .05$) of the BPRS were significantly correlated with past week TRQ for non-psychiatric medication.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Discussion

The aim of the current study was to examine the sociodemographic variables and specific cluster of psychiatric symptoms associated with poor adherence to non-psychiatric medication in individuals with bipolar disorder and medical comorbidities known to be poorly adherent to medications for bipolar disorder. The findings show that such individuals are more adherent with medications for physical health compared to bipolar disorder drugs. Additionally, being on a larger number of bipolar disorder medications and having more severe bipolar disorder symptoms is associated with worse adherence to prescribed medications for physical illness. Contrary to our initial hypothesis, many of the demographic variables that are associated in the literature with either poor adherence to psychiatric medications or non-psychiatric medication in the general population did not turn out to be significant in our sample of non-adherent patients with bipolar disorder. Namely, age, education, living alone, and race did not relate to poor adherence to non-psychiatric medication. It is possible that there may not have been enough power to detect significant findings, particularly for race and living alone, given that the sample of Caucasians was relatively small and the majority of the sample lived alone. On the other hand, the non-significant findings for sex may reflect inconsistencies in the adherence literature with some studies reporting more worse adherence in men (Colom, Vieta, Tacchi, Sanchez-Moreno, & Scott, 2005; González-Pinto, Reed, Novick, Bertsch, & Haro, 2010), others reporting worse adherence in women (Colom et al., 2000; Sajatovic et al., 2011), and still others reporting that sex is not correlated to medication adherence (Belzeaux et al., 2013; Gianfrancesco, Rajagopalan, Sajatovic, & Wang, 2006).

The finding that taking more medications for bipolar disorder is associated with worse non-psychiatric medication adherence is consistent with the literature, suggesting that simpler medication regimens are associated with better adherence (de Vries et al., 2014; Ingersoll & Cohen, 2008). It is known that individuals with bipolar disorder have cognitive impairment even in euthymic states (Depp et al., 2014) and it is possible that having fewer medications to remember to take may be easier for individuals who are required to take prescribed medication for physical health conditions. Furthermore, a larger number of medications may be a reflection of increased severity of illness. The finding that more severe bipolar disorder symptoms are associated with worse adherence has also been reported by others (Barraco, Rossi, Nicolò, & Group, 2012; Leclerc et al., 2013; Sajatovic et al., 2015) and does not seem surprising given the likelihood that symptoms of both depressive episodes such as lack of motivation and symptoms of manic episodes including distractibility and lack of focus could both impede an individual’s ability to take medications on a regular basis.

Our findings of significant correlations between specific psychiatric symptoms and poor adherence to non-psychiatric medication could help inform future approaches to enhance adherence among people with bipolar disorder. For depression, our results suggest that it is not the feeling of sadness or negative thoughts that relate to poor adherence but rather the physiological manifestations of depression including reduced appetite and sleep and inner tension as well as lassitude, inability to feel, apparent sadness, and difficulty concentrating. With regard to the factors of the BPRS associated with non-psychiatric medication adherence, it is not hostility and uncooperativeness, making up the Resistance factor as we

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

predicted, but rather anxiety, guilt, depressed mood, and somatic concern as well as a trend suggesting that excitement and tension play a role. Taking our findings collectively, specific bipolar disorder symptoms that seem to be most strongly associated with poor non-psychiatric medication adherence are inner tension/anxiety and the somatic symptoms of depression. Perhaps care approaches need to target and specifically address factors that can help individuals with these problems in order to help individuals adhere to medications more effectively. For example, the individual with anxiety might benefit from targeted behavioral interventions that can help reduce anxiety, while individuals with pervasive vegetative symptoms could potentially benefit from approaches that make it easier to remember to access and take medications, such as technology-facilitated prompts or long-acting drug formulations that require less frequent administration.

In African Americans, symptoms including lassitude, inability to feel, apparent sadness, difficulty concentrating, anxiety, guilt, depressed mood, and somatic concern related to poor non-psychiatric medication adherence while for females, in addition to these cluster of symptoms, vegetative symptoms of depression also related to poor non-psychiatric medication adherence. The fact that different sociodemographic groups evidence differences in correlates to medication adherence suggests that interventions to improve illness self-management including adherence should be tailored to specific groups.

Another finding which speaks to the question of illness self-management is that there is not always an association between taking one type of medication and another. This can be seen in both the finding that the proportion of doses missed of psychiatric medications is not associated with the proportion missed for non-psychiatric medications as well as in the finding that there is no relationship between patterns of adherence with diabetes medications compared to either cholesterol lowering agents or antihypertensives. These results suggest that an important part of improving illness self-management will be to address knowledge about specific chronic illnesses, psychiatric and medical, and to identify and target barriers to adherence to specific types of medications.

There are a number of limitations to the current study which may impact the generalizability of the results. First, the sample was made up largely of African American females. Furthermore, given that the sample was recruited for poor adherence to psychiatric medications, the correlates of poor non-psychiatric adherence may be different than in patients with bipolar disorder who are adherent to their bipolar disorder medications. Also, certain sociodemographic groups had relatively small samples and thus the non-significant results may reflect a lack of power to detect differences between groups. Additionally, the results are based solely on self-reported non-adherence, which may lack reliability given the tendency for people to overestimate non-adherence. In future studies, it will be important to include at least one other method to measure adherence such as pill counts or electronic monitoring devices. It should be noted, however, that since these individuals did acknowledge poor adherence to their psychiatric medication, they may have been less likely to inflate adherence behavior overall. Finally, given that the determination for non-psychiatric medications was based on participant self-report, it is possible that a psychiatric medication was prescribed for a non-psychiatric use (such as sleep) yet could have psychotropic effects. Furthermore, it is recommended that future studies collect larger

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

samples in order to differentiate between types of non-psychiatric medications, allowing for more specific analyses as well as the ability to address the potential for psychotropic effects from non-psychiatric medications.

Conclusions

In summary, given the extensive medical morbidity and premature mortality in individuals with bipolar disorder, the results of the current study may provide useful information to advance the understanding of differences in adherence that may occur with treatments for bipolar disorder versus adherence with medications for physical illness as well as the impact of symptoms of one type of illness on another. Among individuals with bipolar disorder, medication treatment regimen, sex, ethnicity and specific bipolar disorder symptoms appear to be related to adherence status. Future studies might use personalized approaches to optimize treatment adherence for mental and physical health based upon an individual's unique clinical status.

Acknowledgments

Conflicts of Interest and Source of Funding This work was supported in part by the National Institute of Mental Health [R01MH093321], the Neurological and Behavioral Outcomes Center, University Hospitals Case Medical Center, Cleveland, Ohio, and the Clinical and Translational Science Award (CTSC) - UL1TR 000439. Jennifer Levin receives partial salary support from the following research grants: Reuter Foundation, Reinberger Foundation, Woodruff Foundation, Janssen Scientific Affairs, and National Institutes of Health (NIH). Martha Sajatovic receives partial salary support from the following research grants: Pfizer, Merck, and Ortho-McNeil Janssen, Janssen, Reuter Foundation, Woodruff Foundation, Reinberger Foundation, National Institute of Health (NIH), and Centers for Disease Control and Prevention (CDC). She has also been a consultant for Bracket, Prophase, Otsuka, Pfizer, Neurocrine and Sunovion and has received royalties from Springer Press, Johns Hopkins University Press, Oxford Press, UpToDate, and Lexicomp.

References

Barraco A, Rossi A, Nicolò G, Group ES. Description of study population and analysis of factors influencing adherence in the observational Italian study "Evaluation of Pharmacotherapy Adherence in Bipolar Disorder" (EPHAR). CNS Neurosci Ther. 2012; 18(2):110–118. [PubMed: 21199448]

Belzeaux R, Correard N, Boyer L, Etain B, Loftus J, Bellivier F. collaborators, F. A. C. o. E. f. B. D. F.-B. Depressive residual symptoms are associated with lower adherence to medication in bipolar patients without substance use disorder: results from the FACE-BD cohort. J Affect Disord. 2013; 151(3):1009–1015. [PubMed: 24051101]

Birkenaes AB, Opjordsmoen S, Brunborg C, Engh JA, Jonsdottir H, Ringen PA, Andreassen OA. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Clin Psychiatry. 2007; 68(6):917–923. [PubMed: 17592917]

Busby KK, Sajatovic M. REVIEW: Patient, treatment, and systems-level factors in bipolar disorder nonadherence: A summary of the literature. CNS Neurosci Ther. 2010; 16(5):308–315. [PubMed: 21050421]

Centorrino F, Mark TL, Talamo A, Oh K, Chang J. Health and economic burden of metabolic comorbidity among individuals with bipolar disorder. J Clin Psychopharmacol. 2009; 29(6):595–600. [PubMed: 19910727]

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]

Chaudhry S, Jin L, Meltzer D. Use of a self-report-generated Charlson Comorbidity Index for predicting mortality. Med Care. 2005; 43(6):607–615. [PubMed: 15908856]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Clatworthy J, Bowskill R, Rank T, Parham R, Horne R. Adherence to medication in bipolar disorder: a qualitative study exploring the role of patients' beliefs about the condition and its treatment. Bipolar Disord. 2007; 9(6):656–664. [PubMed: 17845282]

Colom F, Vieta E, Martinez-Aran A, Reinares M, Benabarre A, Gasto C. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. J Clin Psychiatry. 2000; 61(8):549–555. [PubMed: 10982196]

Colom F, Vieta E, Tacchi MJ, Sanchez-Moreno J, Scott J. Identifying and improving non-adherence in bipolar disorders. Bipolar Disord. 2005; 7(Suppl 5):24–31. [PubMed: 16225557]

de Vries ST, Keers JC, Visser R, de Zeeuw D, Haaijer-Ruskamp FM, Voorham J, Denig P. Medication beliefs, treatment complexity, and non-adherence to different drug classes in patients with type 2 diabetes. J Psychosom Res. 2014; 76(2):134–138. [PubMed: 24439689]

Depp CA, Harmell AL, Savla GN, Mausbach BT, Jeste DV, Palmer BW. A prospective study of the trajectories of clinical insight, affective symptoms, and cognitive ability in bipolar disorder. J Affect Disord. 2014; 152–154:250–255.

Eze-Nliam CM, Thombs BD, Lima BB, Smith CG, Ziegelstein RC. The association of depression with adherence to antihypertensive medications: a systematic review. J Hypertens. 2010; 28(9):1785–1795. [PubMed: 20531223]

First MB, Gibbon M, Spitzer RL, Williams JB. User's Guide for the Structured Clinical Interview for DSM-IV-TR Axis I Disorders - Research Version - (SCID-I for DSM-IV-TR, November 2002 Revision): Biometrics Research. 2002

Gianfrancesco FD, Rajagopalan K, Sajatovic M, Wang RH. Treatment adherence among patients with bipolar or manic disorder taking atypical and typical antipsychotics. J Clin Psychiatry. 2006; 67(2):222–232. [PubMed: 16566617]

González-Pinto A, Reed C, Novick D, Bertsch J, Haro JM. Assessment of medication adherence in a cohort of patients with bipolar disorder. Pharmacopsychiatry. 2010; 43(7):263–270. [PubMed: 20842617]

Harvey NS. The development and descriptive use of the Lithium Attitudes Questionnaire. J Affect Disord. 1991; 22(4):211–219. [PubMed: 1939930]

Hou R, Cleak V, Peveler R. Do treatment and illness beliefs influence adherence to medication in patients with bipolar affective disorder? A preliminary cross-sectional study. Eur Psychiatry. 2010; 25(4):216–219. [PubMed: 20005683]

Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med. 2008; 31(3):213–224. [PubMed: 18202907]

King RM, Vidrine DJ, Danysh HE, Fletcher FE, McCurdy S, Arduino RC, Gritz ER. Factors associated with nonadherence to antiretroviral therapy in HIV-positive smokers. AIDS Patient Care STDS. 2012; 26(8):479–485. [PubMed: 22612468]

Leclerc E, Mansur RB, Brietzke E. Determinants of adherence to treatment in bipolar disorder: a comprehensive review. J Affect Disord. 2013; 149(1–3):247–252. [PubMed: 23489403]

Levin JB, Aebi ME, Tatsuoka C, Cassidy KA, Sajatovic M. Adherence to Psychotropic and Nonpsychotropic Medication Among Patients With Bipolar Disorder and General Medical Conditions. Psychiatr Serv. 2016; 67(3):342–345. [PubMed: 26695494]

Levin JB, Tatsuoka C, Cassidy KA, Aebi ME, Sajatovic M. Trajectories of medication attitudes and adherence behavior change in non-adherent bipolar patients. Compr Psychiatry. 2015; 58:29–36. [PubMed: 25617964]

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979; 134:382–389. [PubMed: 444788]

Osborn CY, Egede LE. The relationship between depressive symptoms and medication nonadherence in type 2 diabetes: the role of social support. Gen Hosp Psychiatry. 2012; 34(3):249–253. [PubMed: 22401705]

Overall JA, Gorham DR. The Brief Psychiatric Rating Scale. Psychological Reports. 1962; 10:799–812.

Pompili M, Venturini P, Palermo M, Stefani H, Seretti ME, Lamis DA, Girardi P. Mood disorders medications: predictors of nonadherence - review of the current literature. Expert Rev Neurother. 2013; 13(7):809–825. [PubMed: 23898852]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ramsey CM, Leoutsakos JM, Mayer LS, Eaton WW, Lee HB. History of manic and hypomanic episodes and risk of incident cardiovascular disease: 11.5 year follow-up from the Baltimore Epidemiologic Catchment Area Study. J Affect Disord. 2010; 125(1–3):35–41. [PubMed: 20570367]

Ramsey CM, Spira AP, Mojtabai R, Eaton WW, Roth K, Lee HB. Lifetime manic spectrum episodes and all-cause mortality: 26-year follow-up of the NIMH Epidemiologic Catchment Area Study. J Affect Disord. 2013; 151(1):337–342. [PubMed: 23835104]

Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. Clin Med Res. 2013; 11(2):54–65. [PubMed: 23580788]

Sajatovic M, Ignacio RV, West JA, Cassidy KA, Safavi R, Kilbourne AM, Blow FC. Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinic. Compr Psychiatry. 2009; 50(2):100–107. [PubMed: 19216885]

Sajatovic M, Levin J, Fuentes-Casiano E, Cassidy KA, Tatsuoka C, Jenkins JH. Illness experience and reasons for nonadherence among individuals with bipolar disorder who are poorly adherent with medication. Compr Psychiatry. 2011; 52(3):280–287. [PubMed: 21497222]

Sajatovic M, Levin J, Sams J, Cassidy K, Akagi K, Aebi M, Tatsuoka C. Symptom severity, self-reported adherence, and electronic pill monitoring in poorly adherent patients with bipolar disorder. BIPOLAR DISORDERS. 2015; 17(6):653–661. [PubMed: 26529124]

Sajatovic M, Valenstein M, Blow F, Ganoczy D, Ignacio R. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. Psychiatr Serv. 2007; 58(6):855–863. [PubMed: 17535948]

Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. J Clin Psychiatry. 2002a; 63(5):384–390. [PubMed: 12019661]

Scott J, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. Am J Psychiatry. 2002b; 159(11):1927–1929. [PubMed: 12411230]

Shafer A. Meta-analysis of the brief psychiatric rating scale factor structure. Psychol Assess. 2005; 17(3):324–335. [PubMed: 16262458]

Suzuki A, Aoshima T, Fukasawa T, Yoshida K, Higuchi H, Shimizu T, Otani K. A three-factor model of the MADRS in major depressive disorder. Depress Anxiety. 2005; 21(2):95–97. [PubMed: 15884092]

Tamblyn R, Eguale T, Huang A, Winslade N, Doran P. The incidence and determinants of primary nonadherence with prescribed medication in primary care: a cohort study. Ann Intern Med. 2014; 160(7):441–450. [PubMed: 24687067]

Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, Persistent Mental I. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009; 70(Suppl 4):1–46. quiz 47–48. [PubMed: 19686636]

Wheeler KJ, Roberts ME, Neiheisel MB. Medication adherence part two: predictors of nonadherence and adherence. J Am Assoc Nurse Pract. 2014; 26(4):225–232. [PubMed: 24574102]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Demographic, Clinical and Health Characteristics of a Sample of 73 Poorly Adherent Patients with Bipolar Disorder

Characteristics	N (%)
Sex	
Female	54 (74.0)
Male	19 (26.0)
Race[a]	
White	19 (26.0)
African-American	56 (76.7)
Marital Status	
Single/Never Married	36 (49.3)
Married	12 (16.4)
Separated/Divorced/Widowed	25 (34.2)
Diagnoses	
Bipolar Disorder Type I	52 (74.3)
Bipolar Disorder Type II	18 (25.7)
Medical Comorbidities	
Hypertension	41 (60.3)
Arthritis or rheumatism	42 (57.5)
Hyperlipidemia	32 (47.1)
Asthma, emphysema, or chronic bronchitis	30 (41.1)
Diabetes	23 (31.5)
Digestive problems (e.g. ulcer, colitis, gallbladder disease)	15 (20.5)
Heart trouble (e.g. angina, heart failure, coronary heart disease)	6 (8.2)
Stroke	5 (6.8)
HIV or AIDS	5 (6.8)
Cancer, diagnosed in the past 3 years	3 (4.1)
Liver problems (e.g. cirrhosis)	2 (2.7)
Kidney Disease	0 (0)

[a]Participants endorsed identification with each category separately; race categories were not mutually exclusive.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Factor Structure for the Montgomery-Asberg Depression Rating Scale (MADRS) and the Brief Psychiatric Rating Scale (BPRS)

Scale Items	Factors
MADRS	
(9) Pessimistic thought	Dysphoria
(10) Suicidal thought	
(2) Reported sadness	
(7) Lassitude	Retardation
(8) Inability to feel	
(1) Apparent sadness	
(6) Concentration difficulties	
(4) Reduced sleep	Vegetative Symptoms
(5) Reduced appetite	
(2) Inner tension	
BPRS	
(1) Somatic concern	Affect
(2) Anxiety	
(5) Guilt feelings	
(9) Depressed mood	
(4) Conceptual disorganization	Positive Symptoms
(8) Grandiosity	
(12) Hallucinatory behavior	
(15) Unusual thought content	
(3) Emotional withdrawal	Negative Symptoms
(13) Motor retardation	
(16) Blunted affect	
(10) Hostility	Resistance
(11) Suspiciousness	
(14) Uncooperativeness	
(6) Tension	Activation
(7) Mannerisms-posturing	
(17) Excitement	
(18) Disorientation	

Note. MADRS factor structure based on Suzuki's three-factor model (Suzuki et al., 2005). BPRS factor structure based on a five-factor model (Shafer, 2005).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Summary of Correlations between Past Week Tablets Routine Questionnaire (TRQ) to Non-psychiatric Medications and Factors of the Montgomery-Asberg Depression Rating Scale (MADRS) and the Brief Psychiatric Rating Scale (BPRS)

	TRQ for Non-Psychiatric Medication	
Measure	**Spearman's Rho Correlation**	**P-value**
MADRS	**.279**	**.008**
Dysphoria	.076	.262
Retardation	**.300**	**.005**
Vegetative	**.269**	**.011**
BPRS	**.293**	**.006**
Affect	**.258**	**.014**
Positive Symptoms	.024	.421
Negative Symptoms	.093	.216
Resistance	.054	.335
Activation	.171	.073