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The association between concurrent psychotropic medications and self-reported adherence with taking a mood stabilizer in bipolar disorder

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Objective Multiple psychotropic medications are routinely prescribed to treat bipolar disorder, creating complex medication regimens. This study investigated whether the daily number of psychotropic medications or the daily number of pills were associated with self-reported adherence with taking a mood stabilizer.
Methods Patients self-reported their mood and medications taken daily for about 6 months. Adherence was defined as taking at least one pill of any mood stabilizer daily. Univariate general linear models (GLMs) were used to estimate if adherence was associated with the number of daily medications and the number of pills, controlling for age. The association between mean daily dosage of mood stabilizer and adherence was also estimated using a GLM.
Results Three hundred and twelve patients (mean age 38.4 ± 10.9 years) returned 58,106 days of data and took a mean of 3.1 ± 1.6 psychotropic medications daily (7.0 ± 4.2 pills). No significant association was found between either the daily number of medications or the daily number of pills and adherence. For most mood stabilizers, patients with lower adherence took a significantly smaller mean daily dosage.
Conclusions The number of concurrent psychotropic medications may not be associated with adherence in bipolar disorder. Patients with lower adherence may be taking smaller dosages of mood stabilizers.

KEY WORDS — bipolar disorder; adherence; polypharmacy; mood stabilizer

INTRODUCTION

Multiple psychotropic medications are routinely prescribed in clinical practice for the treatment of bipolar disorder (Baldessarini *et al*., 2007; Frye *et al*., 2000; Ghaemi *et al*., 2006; Kupfer *et al*., 2002). Yet patient non-adherence with physician medication recommendations remains a major obstacle to effective treatment (Baldessarini *et al*., 2008a,b; Sajatovic *et al*., 2006; Scott and Pope, 2002), and is associated with more frequent hospitalizations (Colom *et al*., 2000; Schuepbach *et al*., 2008; Schumann *et al*., 1999; Svarstad *et al*., 2001). Previous evidence shows that a wide range of factors may influence medication adherence in bipolar disorder including age (Baldessarini *et al*., 2008a,b; Perlick *et al*., 2004), current symptoms (Baldessarini *et al*., 2008b; Schumann *et al*., 1999), perceived stigma (Benkert *et al*., 1997; Sirey *et al*., 2001), perceived severity (Clatworthy *et al*., 2009; Greenhouse *et al*., 2000; Keck *et al*., 1997; Trauer and Sacks, 2000), psychiatric comorbidities (Baldessarini *et al*., 2008b; Colom *et al*., 2000; Keck

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et al., 1997; Sajatovic *et al*., 2007), neurocognitive impairment (Martinez-Aran *et al*., 2009), coping skills (Greenhouse *et al*., 2000; Trauer and Sacks, 2000), and medication costs (Piette *et al*., 2004). Many methods have been used to estimate adherence. In clinical settings, most estimates are based on pharmacy refill databases and measure retrospective utilization rates such as the percentage of days a patient has prescribed pills available for a single medication or medication class (Steiner *et al*., 1988). Other measurements in clinical settings are based on self-reports, physician questionnaires, or blood assays, while clinical trials often measure adherence using pill counts or electronic medication monitors (Steiner and Prochazka, 1997).

Despite the frequent use of complex treatment regimens, there are only limited reports about the association between multiple medications and medication adherence in bipolar disorder and results are inconclusive (Baldessarini *et al*., 2008a,b; Gianfrancesco *et al*., 2009; Sajatovic *et al*., 2006, 2007). Since the number of times a day a patient must remember to take medications is widely reported to diminish adherence (Claxton *et al*., 2001), an inverse relationship between the number of medications and adherence is expected. The objective of this study was to investigate whether self-reported adherence with taking a mood stabilizer was associated with the daily number of psychotropic medications or the daily number of pills taken. The problem was analyzed using longitudinal, prospective data from patients who received treatment as usual for bipolar disorder, and recorded the specific medications and number of pills taken daily for 6 months.

METHODS

All data were obtained from an ongoing, long-term naturalistic study in which patients with bipolar disorder recorded mood, sleep, and medications taken daily (Bauer *et al*., 2009). This study has minimal inclusion criteria to better represent routine clinical practice and patient heterogeneity. The participants must have a diagnosis of bipolar disorder by DSM-IV criteria, be at least 18 years old, receive treatment with pharmacologic agents, and be willing to use self-reporting software daily for at least 5 months. The diagnosis of bipolar disorder was made by the prescribing psychiatrist in a clinical interview, and all patients received treatment as usual. All participants were volunteers, and were informed about the study prior to providing written informed consent. The study was approved by each local institutional review board.

Number of patients

To be included in the analysis, patients had to return at least 90 days of data. Of the 411 unique patients, 366 returned sufficient data. Of these 366 patients, 54 did not take a mood stabilizer (three took no medications, 33 took antidepressants, 11 took antipsychotics, and seven took other medications) and were excluded. Data from the 312 patients who took a mood stabilizer were analyzed.

Data collection instrument

All medication and mood-ratings data were self-reported daily using ChronoRecord software in the patient's native language installed on the patient's home computer. The ChronoRecord software was validated and is described in detail elsewhere (Bauer *et al*., 2004, 2008). During patient training, each medication taken for bipolar disorder was selected from a list of psychotropic medications in the software, displayed by brand and generic name for the country where the patient resides. For each selected medication, the pill strength was chosen from a list of available strengths. Every day, for each medication, the patient entered the total number of pills taken. Patients could enter partial pills (1/4, 1/2, or 3/4) for tablets but not capsules. If a medication was not taken, the patient entered zero pills for that drug. The patient could modify the drugs taken throughout the study as needed, and a drug not included in the software list could be added by the patient. Data not entered on one day could be entered later. ChronoRecord includes many error checking steps, such as requiring confirmation for entry of a large number of pills for a drug. The software also prevents modification of previously entered data, and prevents data entry for a future date.

The daily self-ratings for mood were previously validated with clinician ratings on the Hamilton Depression Rating Scale (HAMD) and the Young Mania Rating Scale (YMRS) (Bauer *et al*., 2004, 2008). For rating mood, ChronoRecord uses a 100-unit visual analog scale between the extremes of mania and depression. Based upon the validation studies (Bauer *et al*., 2004, 2008), a mood entry less than 40 was considered depression, 40–60 euthymia, and greater than 60 hypomania/mania.

Concurrent psychotropic medications

For this analysis, mood stabilizers were defined as lithium, valproate, lamotrigine, carbamazepine, or oxcarbazepine. Additional medications included for

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this analysis were antidepressants, antipsychotics, benzodiazepines, insomnia medications, other anticonvulsants (topirimate, gabapentin, pregabalin, tiagabine, levetiracetam, zonisamide, and pregabalin), thyroid hormones, and estrogens. Two medications sold over-the-counter in the US were included as antidepressants (St. John's Wort and *S*-adenosylmethionine).

Mood stabilizer adherence

Since all data being analyzed were self-reported, the ongoing prescribed dosage, dosage timing, and medication changes were not known. For each patient, adherence was defined as taking at least one pill per day of any mood stabilizer. If a patient provided a mood entry but no medication entry, the day was considered non-adherent. Any day missing all data was excluded from the analysis. Previously, no association was found among the days of missing data, the severity of patient mood and patient demographics (Bauer *et al*., 2004). The mean adherence during the study was calculated for each patient as the per cent of days taking a mood stabilizer. This definition of adherence unambiguously measures days taking or not taking a mood stabilizer, but does not distinguish between full and partial adherence. Patients with non-psychiatric illness who have lower adherence usually take the prescribed dosage but at a delayed time interval, typically by hours but sometimes by days (Urquhart, 1998).

Mean daily mood stabilizer dosage

For each patient, the mean daily dosage taken for each mood stabilizer was calculated for all days when the patient took the mood stabilizer. Non-adherent days were removed from the mean daily dosage calculation so that adherence rates would not influence the mean daily dosage. A mean daily dosage was calculated for each mood stabilizer both when taken as a monotherapy, and when taken with at least one other mood stabilizer for $\geq$50% of days.

Statistical analysis

Descriptive statistics for demographic characteristics, mood ratings, and medications taken by the 312 patients were calculated. For each patient, the mean daily number of medications and daily number of pills were determined for all days and for only the days when the patient was adherent. Univariate analyses using general linear models (GLMs) were performed to estimate if any demographic variables were associated with adherence. After controlling for significant demographic variables as covariates, GLMs were used to estimate adherence as a function of the mean daily number of medications and daily number of pills taken when adherent. GLMs were also used to estimate mean mood stabilizer dosage as a function of taking either as monotherapy or with other mood stabilizers, and as a function of adherence and mood. For any GLM estimation to be considered significant, both the corrected model *F*-statistic and the coefficient *t*-statistic had to be significant at the 0.05 level. Means are presented $\pm$SD. SPSS version 16.0 was used for all calculations.

RESULTS

Demographics

The 312 patients had a mean age of 38.4 ± 10.9 years, and returned a mean of 186.24 ± 107.4 days of data (total 58,106 days). The mean per cent of missing mood data for the 312 patients was $7.55\% \pm 0.11$ equivalent to missing about 2 weeks over 6 months, with a median of 1.78% of days missing. The demographic characteristics are shown in Table 1. When considering all days of data, the patients spent 70% of days euthymic, 9% manic, and

Table 1. Patient demographics ($N = 312$)

	N	%
Gender		
Male	96	30.8
Female	216	69.2
Disabled		
Yes	79	27.5
No	208	72.5
Diagnosis		
BP I	198	63.5
BP II	100	32.1
BP NOS	14	4.5
Employment		
Working full-time	135	47.0
Disabled	79	27.5
Other	73	25.4
Marital status		
Married	137	47.6
Divorced	39	13.5
Single	112	38.9
Education		
High school	35	12.3
Some college	98	34.4
College graduate	152	53.3
Country of residence		
US	216	69.2
Outside US	96	30.8

	N	Mean	SD
Age	312	38.4	10.9
Years of illness	283	16.6	10.8
Age of onset	283	22.2	10.2
Prior hospitalizations	286	2.3	3.9

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Table 2. Most frequently taken medications ($N = 312$)[a]

	N	% taking	% not taking
Antidepressants	144	46.2	53.8
Lamotrigine	128	41.0	59.0
Antipsychotics	115	36.9	63.1
Lithium	93	29.8	70.2
Valproate	67	21.5	78.5
Benzodiazepines	64	20.5	79.5
Thyroid hormone	56	17.9	82.1
Carbamazepine/oxcarbazepine	52	16.7	83.3
Estrogens	31	9.9	90.1
Gabapentin/pregabalin	24	7.7	92.3
Insomnia medications	22	7.1	92.9
Fish oil	21	6.7	93.3
Topiramate	15	4.8	95.2

[a]Taken for at least 50% of days by 10 or more patients.

21% depressed. The most frequently taken psychotropic medications are shown in Table 2. Including only days on which a mood stabilizer was taken, one mood stabilizer was taken on 79.4% days, two on 19.7% of days, and three or more on 0.9% of days.

When adherent, the 312 patients took a mean number of medications of 3.3 ± 1.6 (range 1.0–8.0) psychotropic medications per day. Considering all days, the patients took a mean of 3.1 ± 1.6 (range 0.6–7.6) medications per day. The mean per cent of days on which the number of medications taken differed from the patient's mean when adherent was 31.6% (24.2% by one medication, 4.3% by two, and 3.1% by three or more), with no change from the mean number of medications when adherent on the rest of the days. The mean daily number of pills for the patients when adherent was 7.4 ± 4.2 (range 1.0–24.3), while the mean daily number of pills taken on all days was 7.0 ± 4.2 (range 0.2–23.3). The mean per cent of days on which the number of pills taken differed from the patient's mean when adherent was 55% (28.3% by one pill, 10.5% by two, 5.8% by three, 3.5% by four, and 6.9% by five or more), with no change from the mean number of pills when adherent on the rest of the days.

Adherence with taking a mood stabilizer

The mean adherence with taking at least one mood stabilizer pill for all patients was 89.3%. Of the 312 patients, 27 (8.7%) were less than 50% adherent, 15 (4.8%) were between 50% and 75% adherent, 18 (5.7%) were 75–90% adherent, 27 (8.7%) were 90–95% adherent, and 225 (72.1%) were >95% adherent.

All variables that were significantly associated with adherence are shown in Table 3.

Age was positively associated with adherence and was included as a covariate in all GLM models of adherence. None of the other demographic variables (diagnosis, sex, disabled, marital status, education, number of prior hospitalizations, employment status, residing inside or outside the US) were significantly associated with adherence. Euthymic mood was associated with higher adherence, while both mania and depression were associated with lower adherence. Neither the mean daily number of medications nor the daily number of pills taken were significantly associated with adherence.

Mean daily mood stabilizer dosage

No significant difference was found for any mood stabilizer between the mean daily dosage when taken as monotherapy or with one or more additional mood stabilizers. For several mood stabilizers, a higher adherence was associated with a larger daily mean dosage. The GLM estimating mean daily dosage as a function of adherence was significant for lithium ($N = 118$; $F = 8.019$, and $p = 0.005$), valproate ($N = 90$; $F = 7.249$, and $p = 0.008$), and oxcarbazepine ($N = 47$; $F = 4.694$, and $p = 0.036$), and near to significance for lamotrigine ($N = 157$; $F = 3.351$, and $p = 0.069$). Only 17 patients were taking carbamazepine. Figure 1 summarizes dosage by adherence. Mood was not associated with the mean daily dosage of any mood stabilizer. Adherence was not associated with the variance in mean daily dosage of any mood stabilizer.

Table 3. Variables associated with adherence ($N = 312$)

		Corrected model				Estimated coefficient		
Variable	Impact on adherence[a]	*df*1	*df*2	*F*	*p*	Value	*t*-test	*p*
Age[b]	Increase of 3.1% for each additional 10 years of age	1	310	7.111	0.008	0.311	2.667	0.008
Percent days euthymic[c]	Increase of 1.4% for each additional 10% euthymic days	2	309	7.654	0.001	0.137	2.835	0.005
Percent days depressed[c]	Decrease of 2.2% for each additional 10% depressed days	2	309	5.627	0.004	−0.115	−2.018	0.044
Percent days manic[c]	Decrease of 1.9% for each additional 10% manic days	2	309	5.724	0.004	−0.190	−2.065	0.040

[a]The impact is the value of the variable's estimated coefficient.
[b]A GLM with age as a covariate was estimated.
[c]A GLM with both the variable and age covariates was estimated.

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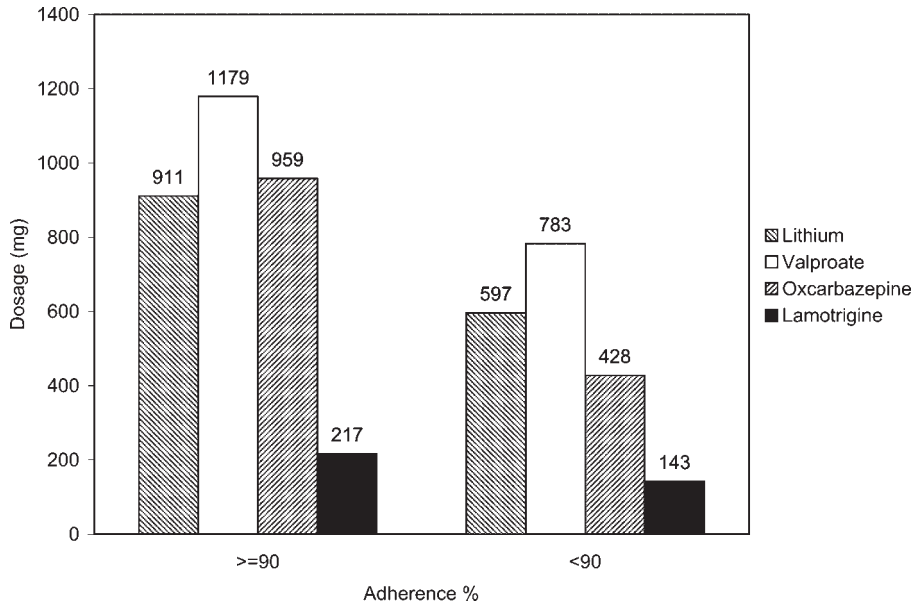

Figure 1. Mean mood stabilizer dosage by adherence, considering only days taking the medication

Considering only the days when the patient was non-adherent, no psychotropic medications were taken on 81% of these days. On 19% of these days, the patient did not take a mood stabilizer but took other psychotropic medications.

DISCUSSION

In this study, the daily number of concurrent psychotropic medications or daily number of pills were not associated with self-reported adherence with taking a mood stabilizer. Previous findings in patients with bipolar disorder based on pharmacy data have been inconsistent. A positive association between the number of medications and adherence was reported (Sajatovic *et al*., 2006), and patients taking two mood stabilizers had higher adherence than those taking one (Sajatovic *et al*., 2007). Conversely, in patients with mixed/manic symptoms, combination therapies were associated with lower adherence with taking an antipsychotic (Gianfrancesco *et al*., 2009). Additionally, no association between the number of medications and adherence was found based on data from a national patient survey (Baldessarini *et al*., 2008b). Inconsistent results have also been reported in chronic non-psychiatric illnesses, including a positive association between the number of medications and adherence (Billups *et al*., 2000; Grant *et al*., 2004; Hamilton and Briceland, 1992; Robertson *et al*., 2008), no association (Corda *et al*., 2000; Grant *et al*., 2003), and a negative association, especially in the elderly (Chapman *et al*., 2005; Col *et al*., 1990; Coons *et al*., 1994; Donnan *et al*., 2002). In agreement with prior studies of bipolar disorder, this study found that increasing age was associated with higher adherence (Baldessarini *et al*., 2008b; Perlick *et al*., 2004; Sajatovic *et al*., 2007) and affective symptoms were associated with lower adherence (Baldessarini *et al*., 2008b; Schumann *et al*., 1999).

Diverse factors may contribute to the lack of association found in this study between the number of concurrent medications and mood stabilizer adherence. The act of daily self-reporting may serve as a visual reminder that increases adherence (van Berge Henegouwen *et al*., 1999). Evidence from electronic monitoring systems shows that patients generally take medications concurrently, so additional medications that do not change the dosage schedule may not seem to increase the burden (Cramer *et al*., 1989). According to health belief models (Rosenstock *et al*., 1988), patients who believe they are ill are more likely to take steps to maintain health and some patients may view the number of medications prescribed as a direct indicator of health status. According to self-regulatory models (Horne and Weinman, 1999), increasing the number of medications may change perception of the disease threat for some patients, such that the necessity of taking medications outweighs concerns such as fear of side effects (Scott and Pope, 2002). Also, there may be an upper limit to the number of daily medications

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beyond which adherence decreases (Robertson *et al*., 2008), and the mean of 3.1 daily medications in this study may be too small to influence adherence.

The high overall adherence rate in this study should not be directly compared with rates estimated by other methodologies. When calculating adherence, this analysis excluded all missing data and all patients who reported taking no mood stabilizers. By defining adherence as taking at least one pill of any mood stabilizer daily, patients taking a lower dose than prescribed were included as adherent. However, for patients with higher adherence, the mean daily dosage of each mood stabilizer was in the expected range, supporting the use of this approach to analyze potential moderators to adherence. Furthermore, there are significant limitations to all common methods used to estimate adherence (DiMatteo, 2004; Steiner and Prochazka, 1997).

Most patients with lower adherence in this study took a smaller mean daily dosage of mood stabilizer on days they took the drug, so the overall percentage of prescribed dosage received may be much less than anticipated. Moreover, on non-adherent days, the patients usually skipped all psychotropic medications rather than selectively avoiding mood stabilizers. Since pharmacokinetic properties have a major impact on maintaining therapeutic blood concentrations and minimizing rate-dependent or rebound side effects (Urquhart, 1998; Urquhart and De Klerk, 1998), formulations of mood stabilizers that are best suited for erratic dosage timing and missed days may be appropriate for patients with lower adherence. Both non-adherence and low mean daily dosages may contribute to the frequent non-responsiveness to mood stabilizers observed in clinical settings (Sajatovic *et al*., 2007; Scott and Pope, 2002).

In this study, the number of medications taken daily differed from the patient's mean on about one-third of the days. In patients with chronic non-psychiatric diseases, having a highly structured daily routine was shown to be an important predictor of adherence (Wagner and Ryan, 2004). In patients with bipolar disorder, difficulty with taking medications in the context of one's daily schedule was also associated with non-adherence (Sajatovic *et al*., 2009). Furthermore, predictable daily routines and social rhythms are important steps for coping with the symptoms of bipolar disorder (Frank *et al*., 2000). Interventions that encourage a structured lifestyle may help to improve adherence and be especially indicated for younger patients.

One strength of this study is that the patients recorded the specific medications and number of pills taken daily. Another strength is that the demographic characteristics of the patients using ChronoRecord were previously shown to be very similar to those who participated in other large, studies of bipolar disorder (Bauer *et al*., 2009). There are also limitations. This observational study design cannot be used to determine causality. A day on which a patient was told to stop taking a mood stabilizer without starting a replacement would incorrectly be considered non-adherent. There was no objective confirmation of the self-reported data. But, as reviewed elsewhere, patient diaries have moderate-to-high concordance with electronic measurement of adherence (Garber *et al*., 2004) and self-report measures of adherence tend not to be overinflated (DiMatteo, 2004). Another drawback was that the length of the study period was relatively short. This analysis also did not include social and psychologic variables, the use of adherence tools like pill boxes, and many factors that may contribute to medication regimen complexity including dosage frequency, dosing instructions such as taking with or without food, the number of medications for non-psychiatric diseases, the number of over-the-counter medications or dietary supplements, and prescription size (Batal *et al*., 2007).

CONCLUSIONS

The number of concurrent psychotropic medications or the daily number of pills may not be associated with adherence with taking a mood stabilizer in patients with bipolar disorder. Patients with lower adherence may take smaller than expected dosages of mood stabilizers, further increasing the likelihood of non-responsiveness.

Further research on the association between concurrent medications and adherence in bipolar disorder is warranted.

CONFLICT OF INTEREST

The ChronoRecord Association is a 501(c)(3) non-profit organization that aims to increase understanding of mood disorders (www.chronorecord.org). None of the authors receive financial compensation from the Association. Tasha Glenn and Peter C. Whybrow share a patent for ChronoRecord software. Michael Bauer, Paul Grof, Natalie Rasgon, and Peter C. Whybrow are on the Medical Advisory Board. There are no other conflicts of interest.

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design, collection, analysis, and interpretation of data, in writing the report, and in the decision to submit for publication.

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