# Nonadherence With Mood Stabilizers: Prevalence and Predictors

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***Background:*** The prevalence of nonadherence with mood stabilizers ranges from about 18% to 52%. Only 1% of publications on mood stabilizers address this issue. This study aimed to explore the prevalence and predictors of nonadherence in a cohort of individuals with affective disorders receiving long-term treatment with mood stabilizers.

***Method:*** Subjects receiving lithium, carbamazepine, and/or valproate were identified from biochemistry laboratory data. Ninety-eight of these subjects had major depressive disorder (N = 20) or bipolar disorder (N = 78) (DSM-IV) and gave informed consent to participate in a structured clinical interview to assess their medication adherence and the factors that influenced it.

***Results:*** Just under 50% of subjects (46/98) acknowledged some degree of medication nonadherence in the previous 2 years, and 32% (29/92) reported only partial adherence in the last month (missing 30% or more of their prescribed medication). Backward stepwise logistic regression demonstrated that partially adherent subjects were best distinguished from adherent subjects by a more frequent past history of nonadherence, denial of severity of illness, and greater duration of being prescribed a mood stabilizer.

***Conclusion:*** Rates of mood stabilizer nonadherence are high. Attitudes and behaviors are better predictors of nonadherence than side effects from medication. Clinicians need to inquire routinely about problems with adherence.

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Mood stabilizers such as lithium, valproate, and carbamazepine are the mainstay of treatment of severe recurrent affective disorders. However, there is a significant efficacy-effectiveness gap.[1–3] Schou[4] noted that about 66% of subjects respond to lithium under research conditions, but only about 33% show an equivalent benefit in clinical settings. Publications exploring the reduced efficacy of prophylaxis in affective disorders tend to focus on illness characteristics, treatment resistance, or individual physiology rather than medication nonadherence. Indeed, Guscott and Taylor[2] noted that only 1% of publications on mood stabilizers specifically explored this issue. This finding is disappointing, as the reported prevalence of nonadherence with mood stabilizers is between 18% and 52%[4–6] and a study of over 1000 patients prescribed lithium found that the median duration of continuous adherence before an individual chooses to stop their medication for the first time was only 76 days.[7]

This project is part of a larger study of psychobiosocial aspects of unipolar and bipolar disorders. The aims of this article are to explore (1) the prevalence of nonadherence with mood stabilizers and (2) the variables that best differentiate adherent from partially adherent subjects.

## METHOD

### Sample

The authors applied for and received ethical approval for the study from the Joint Hospital and University ethics committee. To identify potential recruits for the study, a list of case numbers for people with a probable diagnosis of affective disorder who were having routine serum drug level monitoring of mood stabilizers was obtained from records held at the local biochemistry laboratory. This laboratory was contracted to undertake blood assays for a mental health service caring for a population of just under 300,000. The area included a large conurbation of about 190,000 people combined with surrounding semi-rural commuter areas with a population of about another 100,000 people. The laboratory provided services to National Health Service (NHS)–funded general adult psychiatry clinics in the area. As with most areas of Britain, more than 90% of individuals use the NHS as compared

with private health care services. The local mental health service guidelines suggested that individuals receiving regular prescriptions of mood stabilizers should have routine serum drug level assays at 3-month intervals.

Patient charts were screened initially by the authors to identify individuals aged 18 years or over with a history of affective disorder who were currently in contact with general adult psychiatric outpatient services and who had at least 1 plasma drug level check within the last 3 months. Two hundred thirty-three case records were identified, but 51 were immediately excluded because the diagnosis recorded in the case notes indicated that the patient did not meet DSM-IV criteria for major depressive disorder (MDD) or bipolar disorder or was not receiving the identified medication as a mood stabilizer (e.g., some individuals with epilepsy were receiving carbamazepine). The possible sample for inclusion was therefore 182 subjects. Letters were sent to the treating psychiatrists seeking permission to approach these individuals. A further 36 patients were excluded at this stage (some individuals were currently inpatients, some were deemed too unwell or were unable to participate, and in a few cases no response was received from the psychiatrist despite repeated attempts at contact by the researchers). The remaining 146 subjects were contacted by mail and invited to participate in a study exploring psychological and social aspects of affective disorders, the treatments they were offered, and their attitudes toward both the treatments and services they were receiving. Subjects were informed in advance that the interview might last 1 to 2 hours, but that the data collected for the study would not lead to any changes in the current services that they received. Each individual who gave written informed consent was then offered a maximum fee of £40 (about U.S. $60) to cover travel costs and other expenses incurred as a result of their participation in the study.

## Measures

A semistructured clinician-administered interview was undertaken in person (by M.P.) with subjects at a time convenient to them. The following data were collected:

1. **Basic demographic and illness information.** Using a schedule employed in our previous studies of adherence,[8] we used subject, significant other, and case note information to record DSM-IV diagnosis (according to the affective disorders section of the Structured Clinical Interview for DSM-IV[9]), current age, gender, employment status, age at onset of affective disorder, duration of disorder and number of previous episodes, and duration of treatment with currently prescribed mood stabilizers.
2. Each subject was then asked to complete the following:

***Tablet Routines Questionnaire.*** The Tablet Routines Questionnaire (TRQ)[10] was read to the subjects. It assesses daily routines for taking medication and the proportion of medication an individual has missed in the previous week and previous month. We also asked whether and how many times the individual had stopped treatment (without medical advice) in the last 2 years. Adams and Scott[8] adapted the TRQ to include 3 additional questions: Do you have any trouble taking all of the medication prescribed? (shown to have a specificity for nonadherence of 90%[11]) Do you know if your serum mood stabilizer level was as expected when you last had it checked? and If it was not, was any action suggested or taken?

***Side Effects Questionnaire.*** The lithium Side Effects Questionnaire (SEQ)[12] rates the presence and severity of recognized side effects on a 0-to-4 rating scale (0 = not present to 4 = present and severe). Total scores range from 0 to 72. Equivalent scales were constructed for carbamazepine and valproate. If patients were taking more than 1 mood stabilizer, the rating for the one they had been prescribed for the longest duration was included in the statistical analysis.

***Lithium Knowledge Test.*** The Lithium Knowledge Test (LKT)[13] is a brief questionnaire to test knowledge essential for safe and effective use of lithium. The LKT comprises 20 questions, with 1 point added for a correct answer and 1 point deducted for a wrong answer. Previous studies suggest that mean scores for patients range from about 4.0 to 11.5, with higher scores recorded in those participating in psychoeducation sessions.[13] Only subjects being prescribed lithium completed this rating, since no reliable and valid equivalent questionnaire was available for other medications.

***Attitudes Toward Mood Stabilizers Questionnaire.*** We made minor adjustments to the wording of the Lithium Attitudes Questionnaire[13] to ensure it assessed attitudes toward all mood stabilizers. The Attitudes Toward Mood Stabilizers Questionnaire (AMSQ)[8] comprises 19 items grouped into 7 subscales: general opposition to prophylaxis (4 items), denial of therapeutic effectiveness (2 items), fear of side effects (2 items), difficulty with medication routines (4 items), denial of illness severity (3 items), negative attitudes toward drugs in general (3 items), and lack of information about mood stabilizers (1 item). Higher scores on each subscale represent more negative attitudes toward mood stabilizers. Reported mean total scores in small patient samples range from about 4.0 to 6.0.[13]

The different self-report ratings of adherence included in these questionnaires were then compared to determine the most robust measure of adherence status.

3. Data on plasma levels of mood stabilizers were obtained from the biochemistry laboratories. Data from assays (date of test and plasma levels) were collated blind to information on adherence status and recorded in 2 ways:

   ***Below/within therapeutic range.*** The serum drug level from the assay undertaken within the 3 months prior to the research interview was reviewed to see if it was within or below the recognized therapeutic range. The local laboratory ranges used in this study were 0.4 to 1.0 mmol/L for lithium, 6 to 10 μg/mL for carbamazepine, and 50 to 100 μg/mL for sodium valproate.

   ***Mean plasma level.*** Data for all assays in the year prior to the research interview were collated. Where 2 or more consecutive assay results were available, the mean serum drug level was calculated for that individual.



### Statistical Analysis

All analyses were undertaken using SPSS (version 9.0, SPSS Inc., Chicago, Ill.). Our primary goal was to compare 2 groups: individuals who were adherent with mood stabilizers and individuals who missed some or all of their medication (partially adherent). Given the predominant use of lithium, we also undertook some separate analyses on lithium adherence/partial adherence.

To determine a robust self-report measure of partial nonadherence, we assessed the sensitivity and specificity of different categories of mood stabilizer adherence. The categories were as follows: any reported nonadherence in the past 2 years, missing 30% or more of medication in the last month, and missing any medication in the last week.

Chi-square tests and odds ratios (ORs) were calculated for between-group differences in categorical variables. Analyses of covariance (ANCOVAs) were used to explore differences between adherent and partially adherent subjects on continuous measures such as the SEQ, LKT, and AMSQ, with age, gender, diagnosis, and duration of illness as covariates. Backward stepwise logistic regression was used to explore which variables best classified subjects into adherent and partially adherent groups.

## RESULTS

### Sample Characteristics

Of 146 potential participants, 41 individuals did not respond to our letter of invitation, declined to participate, or did not attend the interview appointment. A further 7 subjects were excluded at the interview for the following reasons: diagnosis of schizoaffective disorder (N = 4), currently not taking mood stabilizer with agreement of treating psychiatrist (N = 2), and plasma lithium level above the therapeutic range (2.1 mmol/L; N = 1).

The final sample comprised 20 individuals with MDD and 78 with bipolar disorder (bipolar I = 68; bipolar II = 10). The mean ± SD age of the subjects was 43.1 ± 11.4 years, 57 were female, 48 were living with a partner, and 30 were in paid employment. The mean age at onset of affective disorder was about 27 years (MDD, 29.3 ± 12.7 years; bipolar, 25.9 ± 10.1 years), and the mean duration of illness was about 15.5 years (MDD, 15.1 ± 12.1 years; bipolar, 15.9 ± 10.6 years). The median number of affective episodes was 5 (range, 1–14), and 89% of the sample (87/98) had been hospitalized on at least 1 occasion. Subjects had been prescribed a mood stabilizer for 2.1 to 17.2 years, with a mean duration according to diagnosis of 6.3 ± 5.2 years in subjects with bipolar disorders and 4.3 ± 3.5 years in subjects with MDD.

Seventy-two subjects were being prescribed lithium either alone (N = 50), with carbamazepine (N = 5), with valproate (N = 2), or in combination with other mood stabilizers (N = 15). Twelve other subjects were being prescribed carbamazepine, and a further 14 subjects were being prescribed valproate. Only 5 subjects were receiving mood stabilizers as the only pharmacologic treatment, and the most commonly prescribed other medications were antidepressants (34% [32/98]), antipsychotic medications (37% [38/98]), and benzodiazepines (19% [18/98]). Information on current dosage of each prescribed medication (from patient self-report, biochemistry, or case note recordings) was available for only 58% of the sample (56/98). Mean dosage of prescribed mood stabilizers was about 838 ± 299 mg for lithium, 926 ± 182 mg for carbamazepine, and 2300 ± 467 mg for valproate.

Mean plasma levels of mood stabilizers were 0.55 ± 0.19 mmol/L (range, 0.1–1.0 mmol/L) for lithium, 6.12 ± 2.91 μg/mL (range, 2.9–9.8 μg/mL) for carbamazepine, and 56.9 ± 24.3 μg/mL (range, 29–78 μg/mL) for valproate. Thirty-seven subjects had a most recent plasma drug level below the range set by the study parameters.

For subjects being prescribed lithium (N = 72), the mean score on the LKT was 4.8 ± 2.3. The sample mean SEQ score for all treatments was 28.6 ± 14.2, and the mean AMSQ score was 4.9 ± 2.7.

### Prevalence of Self-Reported Nonadherence

Twelve subjects agreed to answer some but not all of the TRQ questions about adherence, so for the purposes of the analysis were regarded as adherent (since we had no evidence that they were nonadherent). A further 6 subjects answered no TRQ items. As it was not possible to reliably assess their adherence, they were excluded from the rest of the comparison of adherent and partially adherent subjects. (Five of the 6 were later noted to have subtherapeutic plasma levels of mood stabilizer.)

**Table 1. Significant Differences Between Subjects Adherent and Partially Adherent to Mood Stabilizer Treatment**

| Variable | Adherent (N = 63) | Partially Adherent (N = 29) | p Value |
|---|---|---|---|
| Subtherapeutic level of mood stabilizer, N | 13 | 18 | .04 |
| Plasma lithium level, mean (SD), mmol/L[a] | 0.58 (0.17) | 0.45 (0.18) | .03 |
| Number of years prescribed a mood stabilizer, mean (SD)[b] | 3.8 (3.5) | 6.9 (5.5) | .04 |
| Attitudes Toward Mood Stabilizers Questionnaire[b] | | | |
| Total score, mean (SD) | 4.2 (2.6) | 6.8 (3.1) | .03 |
| Subscale scores, mean (SD) | | | |
| Resistance to prophylaxis | 1.6 (0.8) | 2.3 (1.1) | .03 |
| Fear of side effects | 0.7 (0.6) | 1.0 (0.4) | .04 |
| Denial of severity | 1.1 (0.8) | 1.8 (1.0) | .01 |
| General negative attitudes toward medication | 1.1 (0.7) | 1.5 (0.8) | .02 |

[a]Means based only on subjects prescribed lithium; adherent, N = 47; partially adherent, N = 25 (analysis of variance; df = 1,70).
[b]Analysis of covariance (df = 1,5,85) with age, gender, diagnosis, and duration of illness as covariates.

From the modified TRQ, we established that 47% (N = 46) of the 98 subjects had been nonadherent against medical advice within the last 2 years, with 1 in 5 in the sample (N = 21) admitting to stopping their medication against or without advice on 2 or more occasions. Current difficulties in taking all medication as prescribed were reported by 49% (N = 45) of 92 subjects , 42% (N = 40) had been nonadherent at some point in the last month, and 29 subjects had missed taking ≥ 30% of their prescribed medication in this period. In the week prior to interview, 27% (N = 25/92) reported some nonadherence, with almost half of this group (N = 12) stating that they missed more than 50% of their prescribed medication. Eighty-four percent (N = 38) of the 45 subjects with a past history of nonadherence acknowledged that they had been nonadherent for some time within the last month, and 47% (N = 20), within the last week. Of the 37 subjects who had a recent plasma level of mood stabilizer below the recommended therapeutic range, 25 had a past history of nonadherence in the past 2 years.

## A Working Definition of Partial Adherence

Adherence is rarely an all-or-nothing phenomenon, so it was important to try to determine a robust self-report measure of adherence/partial adherence that would allow comparison of individuals who do or do not take most of their prescribed medication. When self-report ratings were compared, the best measure of partial adherence was failure to take ≥ 30% of prescribed medication in the last month. This rating demonstrated statistically significant associations with past nonadherence, repeated past nonadherence, any nonadherence in the past month, and nonadherence in the last week ($\chi^2 = 7.2$, df = 6, p = .03). Compared with nonadherence in the past 2 years, missing ≥ 30% of prescribed mood stabilizers in the past month had a specificity of 100% and a sensitivity of 65%. Compared with nonadherence in the past week, it had a specificity of 87% and a sensitivity of 84%.

## Comparison of Adherent and Partially Adherent Subjects

Adherence status (≥ 30% nonadherence in the past month, N = 29; adherent, N = 63) was compared with biochemical data. As shown in Table 1, partially adherent subjects were significantly more likely than adherent subjects to have a plasma level of mood stabilizer below the recommended level (62% vs. 21%; $\chi^2 = 3.9$, df = 1, p = .04). The OR that a subject with a subtherapeutic plasma level was partially adherent as compared with adherent was 3.7 (95% confidence interval = 1.53 to 23.5). In those subjects with data from more than 1 biochemistry assay, the mean serum levels of lithium (adherent = 0.58 ± 0.17 mmol/L, partially adherent = 0.45 ± 0.18 mmol/L; F = 4.7, df = 1,70; p = .03) were statistically significantly different in adherent and partially adherent subjects. This was also true of carbamazepine (adherent = 7.12 ± 2.12 μg/mL, partially adherent = 4.15 ± 3.13 μg/mL; F = 6.1, df = 1,9; p = .04), but the number of subjects was considerably smaller and some individuals in this subgroup were on treatment with more than 1 mood stabilizer. There was a similar trend in subjects receiving valproate, but only 7 patients (partially adherent = 1) had more than 1 biochemistry assay result available.

Adherent and partially adherent subjects did not differ significantly in demography or on illness parameters such as age at onset or diagnosis (MDD vs. bipolar disorder). ANCOVA (with age, gender, diagnosis, and duration of illness as covariates) showed that the mean SEQ scores (adherent = 27.4 ± 12.8; partially adherent = 30.8 ± 16.5) and, in those prescribed lithium, mean LKT scores (adherent = 4.8 ± 2.2; partially adherent = 4.7 ± 2.3) were similar in both groups. As shown in Table 1, in comparison to adherent subjects, partially adherent subjects had been prescribed a mood stabilizer for nearly twice as many years (F = 5.9, df = 1,5,85; p = .04). Partially adherent subjects also demonstrated more negative attitudes toward the treatment as shown by higher mean scores on the AMSQ (6.8 vs. 4.2), with significant differences on 4 AMSQ subscale scores: resistance to prophylaxis, fear of side effects, denial of severity of illness, and general negative attitudes toward medication.

## Classification

Backward stepwise logistic regression was used to explore factors that best classified individuals into adherent and partially adherent groups. Age at onset, duration of

Table 2. Classification of Subjects Into Adherent and Partially Adherent Groups Using Backward Stepwise Logistic Regression[a]

| Independent Variable | Exp (β) | 95% Confidence Interval | p Value |
|---|---|---|---|
| History of nonadherence in the past 2 years | 6.8 | 2.6 to 18.2 | .001 |
| Denial of severity | 2.3 | 1.2 to 4.3 | .02 |
| Number of years on treatment with mood stabilizers | 1.1 | 1.01 to 1.3 | .03 |

[a]Cases correctly classified: adherent, 84%; partially adherent, 72%.



illness, gender, and diagnosis were entered first, followed by past history of nonadherence, length of time on treatment with mood stabilizer, subtherapeutic plasma level of mood stabilizer, and ratings on the SEQ and AMSQ subscales. As shown in Table 2, 80% of cases (73/92) were correctly classified ($\chi^2 = 16.6$, df = 3, p = .001) using 3 factors: history of nonadherence in the last 2 years, denial of severity of illness (AMSQ subscale score), and greater length of time on treatment with a mood stabilizer. However, it could be argued that nonadherence in the last 2 years was used to help select the most robust self-report measure of nonadherence, so the analysis was repeated excluding this measure. Denial of severity of illness (AMSQ subscale score), greater length of time on treatment with a mood stabilizer, and younger age at onset correctly classified 74% of subjects (69/92).

The same parameters plus LKT scores were then used in a separate logistic regression analysis to classify individuals being prescribed lithium into adherent and partially adherent groups. The logistic regression analysis for lithium users showed exactly the same pattern (denial of severity, longer time on treatment with a mood stabilizer, and younger age at onset), although slightly fewer cases were correctly assigned (71% [68/92]). In this analysis, subtherapeutic plasma drug level just failed to reach statistical significance.

## DISCUSSION

### General Comments

Before discussing the results of this study in detail, it is important to highlight methodological issues. As with any study of treatment adherence, we are hampered by the likelihood that the sample includes some but not all of the individuals who are partially or totally nonadherent. Such methodological problems afflict all studies in this field, as individuals who are nonadherent with medication are also likely to fail to agree to participate in or fail to adhere with research protocols. However, it is important to acknowledge several potential sources of bias in our sample selection that may affect the generalizability of the results. First, although we attempted to select subjects by using biochemistry records rather than asking clinicians to identify suitable research subjects, the participants recruited represented only 67% (98/146) of the potential sample. We do not know which individuals from those excluded were more or less likely to be medication adherent. We could speculate that those currently hospitalized may be at greater risk of recent nonadherence or that those unable to give informed consent may include individuals whose severe symptoms were undertreated because of adherence problems. Likewise, if individuals had no recorded serum drug level check within the 3-month period, was this because of their nonadherence with having plasma assays or because of some other, unrecorded practical problem? Second, we did not assess current symptom severity or comorbidity of affective disorder with other psychiatric or physical disorders. Colom et al.[14] recently suggested that the presence of personality disorder might adversely affect adherence rates. Third, data on all aspects of the medication regimen were available on only 58% of the sample. Although the issue of limited data is similar for other nonpsychiatric studies (e.g., Ross[15]), it may have influenced our analysis of the impact of treatment regimen on adherence. Fourth, we assessed attitudes and beliefs about medication on only 1 occasion. As yet, there is no research on the stability or variability of such beliefs over time.

Although the study does have weaknesses such as those highlighted, there is considerable agreement between the rates of nonadherence with mood stabilizers reported here and in previous studies undertaken over the last 25 years.[5,8,16,17] The 3-fold variation (15%–55%) in the reported prevalence of nonadherence in such studies is partially explained by the differing definitions of nonadherence employed. For example, those studies[1,3,5,7,8] defining nonadherence as "stopping medication against medical advice in the last 2 years" show rates of about 50% (in the current study, 47%). Those studies[4,10] recording only *total* nonadherence demonstrate rates of less than 20%. However, it is increasingly recognized that such a strict definition misrepresents adherence behavior, as nonadherence is rarely an "all-or-nothing" phenomenon.[3,5] Some researchers have focused on biochemistry data rather than self-report ratings to measure adherence rates. For example, Dickson and Kendall[1] reported "inadequate" lithium levels in 38% of their sample. Although this was not our primary measure of adherence, our data are highly comparable, with 37 of 98 subjects having subtherapeutic serum levels of mood stabilizers.

### Defining Adherence Status

Self-report measures of nonadherence are often treated with suspicion. This suspicion is perhaps misplaced, as Stephenson et al.[11] demonstrated that these measures have a specificity of 90%, although they may overestimate actual adherence rates by about 15%. Interestingly, self-report appears much more reliable than clinician predictions (50%–60% accuracy).

In our study, we compared several self-report ratings to try to determine the most robust measure of adherence status. Our definition of partial adherence was an individual missing 30% or more of his or her prescribed mood stabilizer in the past month. This definition may seem rather arbitrary, but the 30% cutoff compares favorably with definitions used in studies of nonadherence with antidepressants, mood stabilizers, and antipsychotics.[8,18–20] Furthermore, this rating has a specificity against current and past nonadherence of 87% and 100%, respectively, and if compared with therapeutic/subtherapeutic serum mood stabilizer levels, the specificity of the rating is 83%. The sensitivity is lower at 65% to 84% (62% against serum levels), but is still acceptable, particularly if taking into account the possibility that serum levels of mood stabilizer may be lower than laboratory recommendations for reasons other than nonadherence (such as clinician and patient preference). Further studies will verify whether comparing self-report with a single serum drug assay is reliable and whether measures of fluctuation in levels or the mean level over an extended period is more useful. More data will also help ascertain whether this 30% cutoff represents a clinically useful definition. In this study, this definition gave a prevalence of partial adherence of 32%.

**Predicting Nonadherence**

A major problem with previous research into nonadherence is that it focused on isolated demographic, illness, or treatment variables. As such, studies have identified demographic (e.g., young males),[4,16] illness (bipolar I disorder),[6,17] or treatment (side effects)[10,18] factors that may increase the general risk of nonadherence. The studies rarely assessed specific attitudes toward treatment, and they did not identify which individuals from these "high-risk" groups would go on to be nonadherent. Our study has tried to take these issues into account and, as such, contributes some interesting insights into risk factors for nonadherence. It was not surprising that past history of nonadherence was more common in partially adherent subjects. However, it was interesting to note that being prescribed a mood stabilizer for longer was associated with a greater risk of nonadherence. In this study, length of time prescribed a mood stabilizer was greatest in subjects with early-onset bipolar I disorder and may indicate a particular need for psychoeducation for this group of individuals.

From the AMSQ, it became clear that in our sample, it was not the actual experience of side effects but the *fear* of side effects that increased the risk of nonadherence. Likewise, generally negative attitudes toward any medications as well as specific resistance to the idea of prophylaxis differentiated adherent from partially adherent subjects. Finally and very importantly, denial of the severity of the disorder increased the possibility that an individual would be nonadherent. This latter factor is usually viewed as assessing psychological reactions to the disorder. However, it could also reflect individuals' general insight or awareness about their disorder or even aspects of their neuropsychological functioning. Denial of severity, along with previous experimentation with nonadherence and being on treatment with mood stabilizers for a longer period of time, allowed 4 out of 5 subjects to be correctly classified according to adherence status. The importance of this finding is that these 3 factors can be assessed routinely in day-to-day clinical practice, without recourse to research questionnaires.

In summary, this study suggests that 1 in 3 individuals prescribed mood stabilizer prophylaxis is not fully adherent with medication. Over 60% of these partially adherent subjects have subtherapeutic serum levels of mood stabilizers. This nonadherence rate is comparable with that reported for individuals with long-term physical problems such as diabetes, hypertension, and asthma.[3] To individual patients, this nonadherence appears to be largely a result of their own views and attitudes toward their disorder, the benefits of treatment, and the potential impact on their life (as described by "health belief models"). In psychiatry, this level of nonadherence goes a considerable way toward explaining the efficacy-effectiveness gap for mood stabilizers. Furthermore, clinical questioning about difficulties in taking tablets and comparing these responses with biochemistry data or asking directly about attitudes and beliefs toward medications could detect nonadherence. This simple clinical approach does not seem to be part of routine clinical practice. In our assessment, we asked all subjects if they had ever been asked about any difficulties with medication adherence. Only 3 subjects reported that their clinician had ever inquired about this aspect of their treatment. As Guscott and Taylor[2] highlight, perhaps clinicians need to develop a greater awareness of how to identify and manage this treatment problem. If a risk factor for poor outcome is present in up to 50% of patients, it is vital that clinicians are encouraged to ask proactively about problems with adherence and create an atmosphere where such issues can be discussed openly.

*Drug name:* carbamazepine (Tegretol and others).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.



## REFERENCES

1. Dickson WE, Kendall RE. Does maintenance lithium therapy prevent recurrences of mania under ordinary clinical conditions? Psychol Med 1986;16:521–530
2. Guscott R, Taylor L. Lithium prophylaxis in recurrent affective illness: efficacy, effectiveness and efficiency. Br J Psychiatry 1994;164:741–746
3. Scott J. Psychotherapy for bipolar disorder. Br J Psychiatry 1995;167: 581–588
4. Schou M. The combat of non-compliance during prophylactic lithium treatment. Acta Psychiatr Scand 1997;95:361–363
5. Jamison KR, Gerner RH, Goodwin FK. Patient and physician attitudes toward lithium. Arch Gen Psychiatry 1979;36:866–869

6. Jamison KR, Akiskal HS. Medication compliance in patients with bipolar disorder. Psychiatr Clin North Am 1983;6:175–192
7. Johnson R, McFarland B. Lithium use and discontinuation in a Health Maintenance Organization. Am J Psychiatry 1996;153:993–1000
8. Adams J, Scott J. Predicting medication non-adherence in severe mental disorders. Acta Psychiatr Scand 2000;101:119–124
9. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV. New York, NY: Biometric Research, New York State Psychiatric Institute; 1995
10. Peet M, Harvey N. Lithium maintenance, 1: a standard education programme for patients. Br J Psychiatry 1991;158:197–200
11. Stephenson BJ, Rowe BH, Haynes RB, et al. Is this patient taking the treatment as prescribed? JAMA 1993;269:2779–2781
12. Ghose K. Lithium salts: therapeutic and unwanted effects. Br J Hosp Med 1977;18:578–583
13. Harvey N. The development and descriptive use of the Lithium Attitudes Questionnaire. J Affect Disord 1991;22:211–219
14. Colom F, Vieta E, Martinez-Aran A, et al. Clinical factors associated with treatment non-compliance in euthymic bipolar patients. J Clin Psychiatry 2000;61:549–555
15. Ross F. Patient compliance: whose responsibility? Soc Sci Med 1991;32:89–94
16. Frank E, Prien RF, Kupfer DJ, et al. Implications of non-compliance on research in affective disorders. Psychopharmacol Bull 1985;21:37–42
17. Maj M, Pirozzi R, Magliano L. Long term outcome of lithium prophylaxis in bipolar disorders: a 5-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry 1998;155:30–35
18. Buchanan A. Maudsley Monograph 37: Compliance With Treatment in Schizophrenia. London, England: Psychology Press; 1996:13–41
19. Paykel ES. Psychotherapy, medication combinations, and compliance. J Clin Psychiatry 1995;56(suppl 1):24–30
20. Keck PE Jr, McElroy SL, Strakowski SM, et al. Factors associated with pharmacological noncompliance in patients with mania. J Clin Psychiatry 1996;57:292–297

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