



Factors Affecting Long-term Lithium Compliance in Bipolar Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Author EDP designed the study and wrote the protocol. Authors RL, DRP, LN and NA performed and managed the literature search. Authors EDP and WWI wrote the first draft of the manuscript with assistance from authors RL, DRP, LN and NA. Authors AJS and WWI managed further literature searches and revised the manuscript. The authors read and approved the final manuscript.

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ABSTRACT

Background: Mood stabilizers such as lithium are effective agents to treat bipolar disorder and are known to decrease suicide rates. This paper looks to explore the variables associated with compliance and specifically compare and contrast compliant and non-compliant patient groups.

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Methods: 111 euthymic bipolar patients aged 18-75 that had not been compliant with their lithium therapy completed a phone or paper questionnaire to assess reasons of non-adherence after obtaining informed written consent for this IRB-approved study. Symptoms were also assessed by nurses using the Columbia-Milhauser Mood scale, modified from the Hamilton Depression Inventory and the Biegel Mania Scale. These results were compared to those of 133 euthymic participants that were compliant with their lithium regimen.

Results: Chi-square tests revealed significant differences between the two patient groups regarding factors affecting compliance (P values range: 0.009 - <0.001). T-tests showed patients who discontinued lithium therapy not only had more depressive symptoms when compared with the compliant group, but also the depressive symptoms were more severe ($P=0.02$).

Conclusions: Indefinite length of medication treatment, stigma associated with mental illness, and having one's mood controlled by medication seemed to be associated with patient lack of compliance with lithium. Further research needs to address how to overcome these challenges and improve compliance. The results should be interpreted with caution as naturalistic data and the above results may only apply to the assessed sample.

Keywords: Lithium; compliance; bipolar disorder.

1. INTRODUCTION

Bipolar disorder (BPD) is a chronic relapsing condition with a high prevalence rate. BPD treatment methods have been exorbitantly researched and the effectiveness of mood stabilizers, such as lithium has been well documented. Research has shown that lithium is the most valuable treatment option for long-term treatment of BPD [1]. It has been acknowledged that lithium compliance is still the most successful in reducing manic episodes and preventing recurrent episodes [2-4], Tondo, Baldessarini, Hennen & Floris, 1998) as well as, decreasing depressive symptoms [5]. It has also been well documented that lithium decreases suicidality significantly [6]. Furthermore, treatment leads to fewer hospital admissions, and significantly shorter duration [7]. Overall, medication compliance shows to be the strongest predictor of positive long-term outcomes.

Although an overwhelming amount of research continues to support the benefits of lithium treatment, practical clinical outcomes remain unstable. With a lack of compliance rate ranging from 20% to 60%, patients show a lack of consistency with long-term treatment [2-5,8].

Ample research is being conducted since the appearance of lithium, with varying factors and explanations have been identified as reasons for non-compliance. One of the most common reasons remains the presence of co-morbid substance use disorder [5,9-11]. Another highly mentioned factor is medication side effects, such as weight gain [2]. Along with adverse side effect from the medication, many non-compliant

patients stated that they began to feel less of a need for treatment [12]. Co-morbid medical conditions are commonly seen and might have negative effects on compliance [13]. One of the most preventable reasons for non-compliance established by Even and colleagues in 2007 [14], is psychoeducation with an identified a correlation between patient's level of knowledge of the disorder and treatment, to their compliance of lithium treatment [2,10,15].

Given the information available about the importance of treatment compliance and its potential negative effects there still remains a significant challenge for clinicians: understanding and contributing to potential patient's long-term medication compliance. The purpose of this paper is to further elucidate variables associated with lack of compliance, and specifically to compare and contrast the attitudes compliant and non-compliant stable, euthymic patients with bipolar disorder, who are being treated with long-term lithium.

2. METHODS

2.1 Subjects and Study Design

The study was approved by the Institutional Review Board (IRB), the responsible research ethics committee for our institution. 160 patients aged 18-75 who met DSM-III/III-R/IV criteria for bipolar I illness as determined by their psychiatrist and took lithium for prophylactic treatment that were identified as being euthymic by their treating psychiatrist (based on clinical evaluation) for at least six months and were non-compliant with their medications were selected.

The data were collected between 1987 and 2001. Of the 160 participants who received a questionnaire devised from the research of Jamison and colleagues [16]. To assess their reasons for lack of compliance, 111 (69.4%) gave informed written consent to participate in this IRB-approved study and returned a completed questionnaire or participated via telephone, 49 (30.6%) could not be reached, had moved, or chose not to partake in the research. All research conducted followed the guidelines established in the Declaration of Helsinki for ethical research with human participants.

Patients were asked to rate on a 1 to 7 point scale whether they felt their disorder was a biological illness, caused by life events, or a combination of both. From the medical records of their last visit prior to discontinuation, a rating of the patient's depressive and manic symptoms was ascertained. Symptoms were assessed at each visit by a registered nurse via the Columbia-Milhauser Mood scale, modified from the Hamilton Depression Inventory and the Biegel Mania Scale, which cover DSM criteria for mania, and depression. Additionally, each symptom present was rated from 1-3 as mild, moderate, or severe.

The 111 non-compliant subjects mentioned above were matched by age and by having been euthymic for at least six months with 133 patients diagnosed with Bipolar I that were compliant with their lithium regimen while continuing their care at one of two study clinics: Foundation for Depression and Manic-Depression, New York, New York or Freedom From Fear Clinical Staten Island NY. The same questionnaire (in the form of an interview) and ratings (the number of depressive and manic symptoms was based on the rating given the day of the study's evaluation) were used.

2.2 Statistical Analysis

The two groups were compared using non-parametric Chi-square testing and independent sample t-tests where appropriate. Cross tabulations with chi-square tests were performed to compare the survey responses of patients who discontinued lithium therapy versus patients who were compliant with lithium therapy. *P* values of less than 0.05 were considered to indicate statistical significance. Analyses were performed using SAS software, version 10 (SAS Institute Inc, Cary, NC).

3. RESULTS

3.1 Demographic Characteristics

In the sample of 160 patients, age ranged from 18-75 with a mean age of 41.5 (SD=15.1), with 54% males and 46% females.

3.2 Comparison of Patients Who Continued Lithium vs. Who Discontinued Lithium

There were statistically significant differences between patients who discontinued lithium therapy versus patients who were compliant with lithium therapy on all but one of the survey items as depicted in Table 1.

3.3 Frequency Analysis of the Reasons Why Patients Discontinued Lithium Therapy

The most commonly endorsed reasons for discontinuing lithium therapy were aversion to the indefinite length of medication treatment (18.9%), the stigma associated with mental illness (12.6%), having their moods controlled by medication (12.6%) as seen in Table 2.

3.4 Comparing Bipolar Symptoms between Patients Who Continued Lithium vs. Who Discontinued

T-tests were performed to compare symptoms of bipolar disorder between patients who discontinued lithium therapy versus patients who were compliant with their lithium regime as detailed in Table 3. Significant differences were seen in depressive but not manic symptoms. Patients who discontinued lithium therapy not only had more depressive symptoms but additionally more severe depressive symptoms than patients who remained compliant with lithium therapy (*P* = .02).

4. DISCUSSION

In comparison to lithium compliant patients, bipolar patients who discontinued lithium therapy were significantly more likely to feel averse to the indefinite length of medication treatment, the stigma associated with mental illness, having their moods controlled by medication, receiving purely pharmacologic treatment, the side effects of medication, and the idea of having a chronic illness with the first three being the most common reasons.

Several studies support the current findings and provide additional evidence to the current results. Long-periods of treatment constituted a reason for non-compliance in several research studies [2,10,17]. Furthermore, the stigma commonly associated with lithium treatment has been continuously prevalent [18]. Several researchers went further to state that those with higher social support tend to have higher rates of compliance; while absence of emotional support is associated with non-compliance [3,10,19,20]. Lastly, Rosa and associates stated that mood control was a major factor to non-compliance [2], and more studies have shown that non-compliant participant didn't like the lack of control over one's life while being treated [21].

Patients who stopped taking their medication were significantly more likely to have had trouble paying the clinic, endorse they missed the "high", felt less creative, and less attractive while on medication. They were also more likely to say that they no longer experienced depression and

no longer needed medication than patients who remained on their medication. Interestingly, patients who stopped taking their medication had significantly more severe depressive symptoms on the last day before stopping their medication in comparison to lithium compliant patients. These results are similar to those found in previous studies, where participants stated that they no longer saw the need for lithium [21-25]. Gonzalez-Pinto and colleagues in 2006, found that patients' desire to experience mania episodes, thus leading to higher non-compliance rates [5]. Personality factors as well as the impact of psychotherapy would need to be systematically examined in the future, given the findings by Colom and colleagues, in 2000, that having an underlying personality disorder in euthymic BD patients shared a strong association with non-compliance with medications [26] and the findings by Rothbaum and colleagues in the same year about the positive impact of integrating psychotherapy and psychopharmacology on compliance [27].

Table 1. Comparison of characteristics of patients who continued lithium vs. patients who discontinued lithium therapy

	Patients who continued on lithium (N = 133)	Patients who discontinued lithium therapy (N = 111)	Chi-square p-value
Bothered by indefinite course of medication	29 22%	84 76%	70.62*** <.001
Bothered by stigma	37 28%	76 69%	40.21*** <.001
Bothered that moods are controlled by medication	26 20%	53 48%	21.97*** <.001
Bothered by purely pharmacologic treatment	12 9%	49 44%	39.80*** <.001
Bothered by side effects	22 17%	39 35%	11.16*** .001
Don't like the idea or believe that they have a chronic illness	22 17%	34 31%	6.79** .009
Have trouble paying the fees to the clinic	0 0%	49 44%	73.47*** <.001
Miss the "high"	28 21%	55 50%	21.89*** <.001
Feel less creative	17 13%	44 40%	23.28*** <.001
Feel less attractive	10 8%	34 31%	21.87*** <.001
Have trouble taking the medication	15 11%	20 18%	2.24 ns
No longer feel depressed and don't feel they need medication anymore	6 5%	26 23%	18.99*** <.001
No longer feel they need medication	21 16%	63 57%	44.98*** <.001

Table 2. Primary reason for discontinuing medication

	Patients who stopped taking their medication (N = 111)
Q 1) Bothered by the indefinite course of medication?	21 18.9%
Q 2) Bothered by stigma?	14 12.6%
Q 3) Did you stop because you were bothered by having your moods controlled by medication?	14 12.6%
Q 4) Did you stop because you didn't like the idea that treatment is purely pharmacologic?	10 9%
Q 5) Did you stop because you no longer felt you needed medication?	10 9%
Q 6) Did you stop because you were bothered by medication side effects?	6 5.4%
Q 7) Did you stop because you don't like the fact or believe that you have a chronic illness?	6 5.4%
Q 8) Did you stop because you had trouble paying the fees to the clinic?	6 5.4%
Q 9) Did you stop because you missed the "high"?	6 5.4%
Q 10) Did you stop because you felt less attractive?	6 5.4%
Q 11) Did you stop because you had trouble taking the medication?	5 4.5%
Q 12) Did you stop because you no longer felt depressed and didn't feel you needed medication?	4 3.6%
Q 13) Did you stop because you felt less creative?	3 2.7%

Table 3. Comparison of symptoms of bipolar illness for patients who continued on lithium vs. patients who stopped taking medication (rated on a 1 to 7 point scale where 1=completely disagreed to 7=completely agreed)

	Patients who continued on lithium (N = 133)	Patients who stopped taking their medication (N = 111)	T-value P-value
Total # depressive symptoms (1-7)	M = 0.92 SD = 1.00	M = 1.24 SD = 1.14	2.38* .02
Severity of depressive symptoms	M = 1.39 SD = 1.71	M = 1.95 SD = 1.99	2.39* .02
Total # manic symptoms (1-7)	M = .50 SD = .78	M = .56 SD = .77	.02 ns
Severity of manic symptoms	M = .71 SD = 1.19	M = .80 SD = 1.20	.54 ns
Do you believe bipolar illness is biological (1-7)	M = 5.02 SD = 1.01	M = 4.0 SD = 1.12	7.45*** <.001
Do you believe bipolar disorder is due to life events (1-7)	M = 4.06 SD = 1.03	M = 4.87 SD = 1.15	5.83*** <.001
How much do you believe bipolar disorder is a combination of biology and life events?	M = 4.39 SD = 1.05	M = 4.27 SD = .93	.00 ns

M=Mean; SD=Standard Deviation

Although this study sheds light as to what may lead some patients to not comply with their medications, it does have its limitations. As with all retrospective cohort studies, susceptibility to selection bias and lack of randomization are both important to keep in mind. Also, obtaining post hoc opinions of patients as to why they stopped their medication regimens adds to this studies limitations. It is worth noting that although the same questionnaire was used in both compliant and non-compliant groups, the compliant group was interviewed while the non-compliant group completed the questionnaire over the phone or by mail.

5. CONCLUSION

Accordingly, further research must look at all potential factors affecting compliance, differences in attitudes toward different mood stabilizers, past medical and psychiatric histories, opinions of patients throughout the diagnosing and treatment processes, and must address ways to improve compliance in general, especially long-term compliance [28-30].

From a clinical standpoint, compliance with medication regimens, especially well researched mood stabilizers like lithium in bipolar patients is of utmost importance.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Severus E, Taylor M, Sauer C, Pfennig A, Ritter P, Bauer M, Geddes JR. Lithium for

prevention of mood episodes in bipolar disorders: Systematic review and meta-analysis. *Int J Bipol Disord.* 2014;20(2):15. DOI: 10.1186/s40345-014-0015-8

2. Rosa AR, Marco M, Fachel JMG, Kapczinski F, Stein AT, Barros HMT. Correlation between drug treatment adherence and lithium treatment attitudes and knowledge by bipolar patients. *Progress in Neuro-psychopharmacology & Biological Psychiatry.* 2007;31:217-224. [PubMed: 16982121]
3. Col SE, Caykolyu A, Karakas, Ugurlu G, Ugurlu M. Factors affecting treatment compliance in patients with bipolar I disorder during prophylaxis: A study from Turkey. *General Hospital Psychiatry.* 2014; 36:208-213. [PubMed: 24359677]
4. Tondo L, Baldessarini RJ, Hennen J, Floris G. Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. *AM J Psychiatry.* 1998; 155:638-645. [PubMed: 9585715]
5. Gonzalez-Pinto A, Mosquera F, Alonso M, Lopez P, Rameriz F, Vieta E, Baldessarini RJ. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disorders.* 2006; 8:618-624. [PubMed: 17042834]
6. Lewitzka U, Severus E, Bauer R, Ritter P, Müller-Oerlinghausen B, Bauer M. The suicide prevention effect of lithium: More than 20 years of evidence-a narrative review. *Int J Bipolar Disord.* 2015;3(1):32. DOI: 10.1186/s40345-015-0032-2. Epub 2015 Jul 18. PubMed PMID: 26183461; PubMed Central PMCID: PMC4504869.
7. Kessing LV, Hansen HV, Hvenegaard A, Christensen EM, Dam H, Gluud C, Wetterslev J. Early Intervention Affective Disorders (EIA) Trial Group. Treatment in a specialised outpatient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: Randomised clinical trial. *Br J Psychiatry.* 2013;202(3):212-9. DOI: 10.1192/bjp.bp.112.113548. Epub 2013 Jan 24. PubMed PMID: 23349295.
8. Lingam R, Scott J. Treatment non-adherence in affective disorders. *Acta*

- Psychiatr Scand. 2002;105(3):164-72. Review. PubMed PMID: 11939969.
9. Colom F, Vieta E, Tacchi MJ, Sanchez-Moreno J, Scott J. Identifying and improving non-adherence in bipolar disorders. *Bipolar Disorders*. 2005;7:24-31. [PubMed: 16225557]
 10. Dharmendra MS, Eagles JM. Factors associated with patients' knowledge of and attitudes towards treatment with lithium. *Journal of Affective Disorders*. 2003; 75:29-33. [PubMed: 12781347]
 11. Weiss RD, Greenfield SF, Najavits LM, Soto JA, Wyner D, Tohen M, Griffin ML. Medication compliance among patients with bipolar disorder and substance use disorder. *J Clin Psychiatry*. 1998;59:172-174. [PubMed: 9590667]
 12. Clatworthy J, Bowskill R, Parham R, Rank T, Scott J, Horne R. Understanding medication non-adherence in bipolar disorders using a necessity-concerns framework. *Journal of Affective Disorders*. 2009;116:51-55. [PubMed: 19101038]
 13. Duffy A, Alda M, Kutcher S, Fusee C, Grof P. Psychiatric symptoms and syndromes among adolescent children of parents with lithium-responsive or lithium-nonresponsive bipolar disorder. *Am J Psychiatry*. 1998;155:431-433. [PubMed: 9501760]
 14. Even C, Richards H, Thuile J, Freidman S, Rouillon F. Characteristics of voluntary participants versus nonparticipants in a psychoeducation program for euthymic patients with bipolar disorder. *The Journal of Nervous and Mental Disease*. 2007; 195:262-265. [PubMed: 17468688]
 15. Schaub RT, Berghoefler A, Muller-Oerlinghausen B. What do patients in a lithium outpatient clinic know about lithium therapy? *Journal of Psychiatry and Neuroscience*. 2001;26:319-324. [PubMed: 167185]
 16. Jamison KR, Gerner RH, Goodwin FK. Patient and physician attitudes toward lithium: Relationship to compliance. *Arch Gen Psychiatry*. 1979;36:866-869. [PubMed: 454105]
 17. Sajatovic M, Bauer MS, Kilbourne AM, Vertrees JE, Williford W. Self-reported medication treatment adherence among veterans with bipolar disorder. 2006; 57:56-62. [PubMed: 16399963]
 18. 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;50:100-107. [PubMed: 19216885]
 19. Aagaard J, Vestergaard P, Maarbjer K. Adherence to lithium prophylaxis: II. Multivariate analysis of clinical, social, and psychosocial predictors of nonadherence. *Pharmacopsychiatry*. 1988;21:166-70. [PubMed: 3205885]
 20. Baldessarini RJ, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. *Human Pharmacology*. 2007;23:95-105. [PubMed: 18058849]
 21. Cousins DA, Young AH. The armamentarium of treatments for bipolar disorder: A review of the literature. *Int J Neuropsychopharmacol*. 2007;10(3): 411-31. Epub 2006 Dec 19. Review. PubMed PMID: 17176493.
 22. Maj M, Pirozzi R, Magliano, L. Late non-response to lithium prophylaxis in bipolar patients: Prevalence and prediction. *Journal of Affective Disorders*. 1996;39: 39-42. [PubMed: 8835652]
 23. Berghofer A, Alda M, Baethge C, Bauer M, Bschor T, Grof P, Muller-Oerlinghausen B, Rybakowski JK, Suwalska A, Pfennig A. Stability of lithium treatment in bipolar disorder – long-term follow-up of 346 patients. *International Journal of Bipolar Disorders*. 2013;1. [PubMed: 25505678]
 24. Cochran SD. Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders. *Journal of Consulting and Clinical Psychology*. 1984; 52:873-878. [PubMed: 6501672]
 25. Gitlin MJ, Cochran SD, Jamison KR. Maintenance lithium treatment: Side effects and compliance. *J Clin Psychiatry*. 1989;50:127-31. [PubMed: 2925600]
 26. Colom F, Vieta E, Martínez-Arán A, Reinares M, Benabarre A, Gastó C. Clinical factors associated with treatment

- noncompliance in euthymic bipolar patients. *J Clin Psychiatry*. 2000;61(8):549-55.
PubMed PMID: 10982196.
27. Rothbaum BO, Astin MC. Integration of pharmacotherapy and psychotherapy for bipolar disorder. *J Clin Psychiatry*. 2000; 61(Suppl 9):68-75.
28. Jin J, Sklar GE, Min Sen Oh V, Chuen Li, S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag*. 2008; 4:269-286.
[PubMed: 18728716]
29. Lenzi A, Lazzerini F, Placidi GF, Cassano GB, Akiskal HS. Predictors of compliance with lithium and carbamazepine regimens in the long-term treatment of recurrent mood and related psychotic disorders. *Pharmacopsychiatry*. 1989;22:34-7.
[PubMed: 2652160]
30. Horne R, Weinman J. Predicting Treatment Adherence: An overview of theoretical models. In: Midence K, Myers L, editor. *Adherence to Treatment in Medical Conditions*. Amsterdam, Netherlands: CRC Press. 1998;1-25.

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