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 preformed 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.

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 predicator 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 aversive 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 | 84 | 70.62*** <.001 |
| | 22% | 76% | |
| Bothered by stigma | 37 | 76 | 40.21*** <.001 |
| | 28% | 69% | |
| Bothered that moods are controlled by medication | 26 | 53 | 21.97*** <.001 |
| | 20% | 48% | |
| Bothered by purely pharmacologic treatment | 12 | 49 | 39.80*** <.001 |
| | 9% | 44% | |
| Bothered by side effects | 22 | 39 | 11.16*** .001 |
| | 17% | 35% | |
| Don’t like the idea or believe that they have a chronic illness | 22 | 34 | 6.79** .009 |
| | 17% | 31% | |
| Have trouble paying the fees to the clinic | 0 | 49 | 73.47*** <.001 |
| | 0% | 44% | |
| Miss the “high” | 28 | 55 | 21.89*** <.001 |
| | 21% | 50% | |
| Feel less creative | 17 | 44 | 23.28*** <.001 |
| | 13% | 40% | |
| Feel less attractive | 10 | 34 | 21.87*** <.001 |
| | 8% | 31% | |
| Have trouble taking the medication | 15 | 20 | 2.24 ns |
| | 11% | 18% | |
| No longer feel depressed and don’t feel they need medication anymore | 6 | 26 | 18.99*** <.001 |
| | 5% | 23% | |
| No longer feel they need medication | 21 | 63 | 44.98*** <.001 |
| | 16% | 57% | |
Table 2. Primary reason for discontinuing medication

| Reason                                                                 | 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       | 14 (12.6%)                                             |
| controlled by medication?                                              |                                                        |
| Q 4) Did you stop because you didn’t like the idea that treatment is  | 10 (9%)                                                |
| purely pharmacologic?                                                  |                                                        |
| 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        | 6 (5.4%)                                               |
| effects?                                                              |                                                        |
| Q 7) Did you stop because you don’t like the fact or believe that you  | 6 (5.4%)                                               |
| have a chronic illness?                                                |                                                        |
| Q 8) Did you stop because you had trouble paying the fees to the      | 6 (5.4%)                                               |
| clinic?                                                               |                                                        |
| 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    | 4 (3.6%)                                               |
| feel you needed medication?                                            |                                                        |
| 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)

| Symptom                        | 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 | M = 1.24 | 2.38* | .02     |
| Total # manic symptoms (1-7)     | M = .50 | M = .56 | .02  |         |
| Severity of depressive symptoms | M = 1.39 | M = 1.95 | 2.39* | .02     |
| Severity of manic symptoms      | M = .78 | M = .77 | ns   |         |
| Do you believe bipolar illness is biological (1-7) | M = 5.02 | M = 4.0 | 7.45*** | <.001   |
| Do you believe bipolar disorder is due to life events (1-7) | M = 4.06 | M = 4.87 | 5.83*** | <.001   |
| How much do you believe bipolar disorder is a combination of biology and life events? | M = 4.39 | M = 4.27 | .00   |         |

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.

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