Adverse Effects and Nonadherence with Mood Stabilizers

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ABSTRACT:
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Similar to other long-term clinical conditions nonadherence to medications is common in bipolar disorder. It is often under-recognized in clinical practice and greatly under-researched topic in academic psychiatry. Nonadherence to mood stabilizers is in part due to the adverse effects and it is more likely due to certain adverse effects such as weight gain, tremor, and cognitive impairment. Practicing psychiatrists can potentially reduce the nonadherence by vigorous attempts to identify, discuss, and ameliorate these adverse effects.

Key words: adverse effects, nonadherence, mood stabilizers

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Nonadherence is the primary clinical problem associated with the treatment of bipolar disorder (1). Nonadherence to mood stabilizers dates back to the first ever patient treated with lithium who was nonadherent to lithium after six months of treatment and readmitted to the psychiatric ward "manic as ever" (2).

Consequences of nonadherence

Nonadherence in bipolar disorder has significant adverse consequences. Interruption of the treatment increases the risk of recurrence of manic episodes even after several months of stability (3). Nonadherence increases the number of hospitalizations by four times over a period of one year (4). In another study, nonadherent bipolar patients were hospitalized more than twice as often as adherent patients (73% versus 31%), mean hospital days were more than 8 times higher (37.2 versus 4.4), and total hospital costs almost 6 times higher ($9701 versus $1657 over 12 months) (5). Nonadherence in bipolar disorder also increases the number of suicide attempts and completed suicides (6). Discontinuation of lithium, either by the physician for clinical reasons or by the patient unilaterally after a considerable period of stability, may increase the risk of suicidal acts by 13 times in comparison to staying on lithium therapy (7). In the same study, the first year of discontinuation was especially noteworthy because the suicidal risk increased to 20 times in comparison to patients staying in treatment. Therefore, early action by the physician, engaging the nonadherent patient to return back to the treatment is extremely important. It is possible though that the medications that induced remission in the first attempt may not show the same results when used subsequently after the period of nonadherence (8). Overall, nonadherence is responsible for a significant efficacy-effectiveness gap (9).

Nonadherence is greatly under-researched

The lack of research on nonadherence is surprising given how common it is and how significant the consequences are (1). Only 1% of the publications on mood stabilizers specifically look at nonadherence. There are very few randomized control trials about nonadherence. In addition, there isn't even general agreement on definition of nonadherence and the methodology and tools to study it. Many long-term studies about nonadherence failed to report which specific adverse effects led to nonadherence and the time point in the study at which the nonadherence occurred. The reasons for the lack of attention to the problem of nonadherence are not clear (10). It is unlikely that there is lack of awareness of how significant the issue is. To some extent, the hope that new medications with modified adverse effect profiles will ameliorate the problem may promote this neglect.

Prevalence of nonadherence

A review of 25 studies of nonadherence in bipolar disorder treatment (1979–2004) showed the prevalence of nonadherence ranged from 23%–68% with a median of 42% (11). The median duration of continuous use when a patient was first started on lithium is only about 76 days (12). In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, nonadherence (defined as missing 25% or more of doses of any one medication on 20% or more study visits) was found in 23.9% of patients and in another 15.8% on 10–20% of study visits (13).

Of 101 pts with bipolar disorder, based on self-report and serum levels, 41.6% of the patients were completely or partially nonadherent (14).

Role of adverse events in nonadherence

Surprisingly for clinicians, not all studies find adverse effects to predict nonadherence. This may, in part be due to adverse effects not being looked at by some studies of nonadherence, lack of systematic assessment for adverse effects, and lack of standardized reporting of adverse effects.

Nevertheless, adverse effects are one of the important reasons for nonadherence in patients with bipolar disorder (15). A review found that in six out of ten studies of bipolar disorder that reported adverse effects, they were the main or one of the main reasons for nonadherence (16).

In an early paper, 22% of patients who discontinued medication did so due to lack of efficacy and 78% due to adverse effects (17). In a 5-year prospective observational study of 402 bipolar patients on lithium, more than 25% of the nonadherent patients reported discontinuation due to adverse effects (18). Nonadherence can be due to specific adverse effects or to a general fear of adverse effects (19). In a survey of 423 patients, nearly 20% reported missing all their daily doses at least once in the preceding 10 days (20). In the same patient group, 40.2% expressed frustration with the adverse effects, and 13.1% of those who stopped all medications reported adverse effects as the reason for discontinuation. Nonadherence due to adverse effects may be almost four times that due to lack of efficacy, 78% vs. 22% respectively (17). When patients self-reported reasons for nonadherence, in two studies 40% and 13.1% attributed it to adverse effects (20, 21).

Adverse effects associated with nonadherence

Some adverse effects such as weight gain, cognitive effects, emotional effects, nausea, tremors, and lack of coordination are more likely to be associated with nonadherence. In a pooled analysis of two randomized, placebo-controlled trials (N = 638), it was reported that discontinuation rates attributed to tremor (5% vs 1%), nausea (8% vs 1%) and somnolence (4% vs 1%) were significantly higher for lithium than placebo (22). Perceptions of the experts, clinicians and patients regarding specific adverse effects as predictors of nonadherence were assessed in three separate studies. Experts reported weight gain and sedation (23), clinicians reported weight gain (20), and patients reported weight gain and cognitive effects (24) as the most likely predictors of nonadherence due to adverse effects. Sedation and cognitive side effects were self-reported as the reasons for nonadherence by 30% and 27% of patients respectively (21).

In order to test the association of cognitive deficits with nonadherence, cognitive function was systematically assessed in 103 patients with bipolar I or II disorder (25). While an association between poor performance on some cognitive tasks and nonadherence was found, the cause and effect relationship remains unclear. Mood symptoms also may affect how patients perceive and tolerate somatic adverse events (26). Concepts of illness strongly influence subjective impairment caused by the medication (27).

Weight gain is an important adverse effect of mood stabilizers that may lead to nonadherence in bipolar disorder (24). Twenty per cent of patients on lithium reported a weight gain of over 10 kg (28). Lithium, valproate and some second-generation antipsychotics are associated with high incidence of weight gain, whereas lamotrigine, aripiprazole, ziprasidone may cause less weight gain in most patients (29).

Strategies to decrease nonadherence due to adverse effects

Nonadherence is considerably under-recognized by clinicians and physicians wrongly assume patients to be adherent (20,30). Physicians should ask patients about nonadherence at every visit, but in a non-judgmental way.

Simply educating the patient about the medications and the illness (31) and mentioning the adverse effects to the patient (32) are not effective. Interventions that actually do improve adherence to medication are always complex and involve combinations of interventions (32). Clinicians should take time to adequately discuss the potential adverse effects of the medication and should actively identify and manage adverse effects as part of a multifaceted plan to maintain adherence. In particular, clinicians should be watchful for adverse effects such as weight gain, tremors, cognitive impairment and emotional adverse effects that are particularly associated with non-adherence.

Finally, there needs to be a marked increase in research on nonadherence and on methods for the identification and treatment of adverse effects. We also suggest that every clinical trial that measures the efficacy of the medications should also provide detailed data on adverse effects and adherence.

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