

Antidepressant-Induced Rapid Cycling: Another Perspective

JEFFREY A. MATTES, MD

Psychopharmacology Research Association of Princeton, Princeton, NJ, USA

Background. Depressive symptoms are the main cause of morbidity in bipolar patients, but concern about antidepressant-induced rapid cycling has limited antidepressant use in such patients. This paper evaluates the validity and the prevalence of antidepressant-induced rapid cycling.

Methods. The literature regarding antidepressant induced rapid cycling is reviewed, focusing on two issues: 1) does antidepressant-induced rapid cycling occur only in patients who become manic or hypomanic on antidepressants; 2) can the apparent shortening of cycle length on antidepressants be attributable simply to the fact that antidepressants alleviate depression and can precipitate mania or hypomania.

Results. The suggestion that antidepressants can induce rapid cycling is derived primarily from patients who become manic or hypomanic on antidepressants. The fact that antidepressants alleviate depression and precipitate mania can explain most of the available data, without invoking the poorly defined concept of antidepressant-induced rapid cycling.

Conclusions. Bipolar patients who are stable on mood stabilizers, who don't become manic or hypomanic on antidepressants, can be safely treated with antidepressants without excessive concern about inducing rapid cycling.

Keywords Antidepressant, Rapid Cycling, Bipolar, Review

INTRODUCTION

Bipolar patients are sometimes not given antidepressant medication because of concern that it might induce rapid cycling. The belief that antidepressants can induce rapid cycling is quite widespread. For example, a recent review by Montgomery et al. (1) states "rapid cycling is often induced by tricyclic antidepressants although this association is often not recognized" [they cite Wehr et al. (2)]. A review of the clinical practice guidelines from the Department of Veterans Affairs (3, page 16) states "antidepressant treatment may have a negative impact on the natural course of bipolar disorder by inducing rapid cycling." Similarly, Ghaemi et al. (4) state "the available evidence supports the widely accepted view that use of an antidepressant alone, and perhaps even adding one to ongoing mood-stabilizing treatment, can increase affective instability or cycling rates and the risk of switching into mania." Also, Nemeroff et al. (5, page 10) state "There is considerable evidence supporting the association of antidepressants

and the induction of mania and rapid cycling in patients with bipolar disorder."

However, the validity of antidepressant-induced rapid cycling has always been somewhat controversial (6–8), partly because prior to this concern being raised (in 1979), bipolar patients were often treated with a combination of lithium and an antidepressant, without creating any awareness that rapid cycling was being induced. The safety of antidepressants in bipolar patients is of considerable clinical importance, since it is fairly well established that mood stabilizers (except lamotrigine) are better at preventing manic episodes than they are at preventing depressive episodes (9); many bipolar patients on mood stabilizers periodically become depressed. Therefore, it seemed worthwhile to again review the literature regarding antidepressant-induced rapid cycling, to determine how much evidence exists that this phenomenon occurs. This review focuses on several issues not emphasized in prior papers, to attempt to integrate disparate findings and conclusions (of note, this review does not consider the relative value of lamotrigine for bipolar depression).

Other reviews are available (2,6,7), each with its own, slightly different, perspective. There have not been any large scale studies to evaluate the validity of antidepressant-induced rapid cycling, though there have been numerous

Address correspondence to Jeffrey A. Mattes, MD, Psychopharmacology Research Association of Princeton, 601 Ewing Street, Suite A-12, Princeton, New Jersey 08540. E-mail: jmattesmd@msn.com

articles and letters arguing about its validity. To put this paper in a historical context, there has been some concern in the past (10) that psychiatrists were not sufficiently concerned about the risk of mania with antidepressants, and were too ready to treat bipolar depressed patients with antidepressants without prescribing a concomitant mood stabilizer to prevent mania. It may be, however, that the pendulum has now swung too far in the other direction, and that many patients who could benefit from concomitant antidepressants are not receiving them (my clinical impression that this is the case led to this review).

Several issues must be kept in mind when reviewing the available literature. One issue which has often not been discussed is whether or not patients who demonstrate apparent antidepressant-induced rapid cycling also demonstrate antidepressant-induced mania (though Altshuler et al. (6) reported that patients with antidepressant-induced mania were more likely to have antidepressant-induced rapid cycling). A related question is whether the rapid cycling which may or may not be induced by antidepressants always involves cycling between mania (or hypomania) and depression, or whether it can refer to cycles of depression and euthymia (without periods of mania or hypomania). In fact, a complicating factor in integrating the literature is that the definition of rapid-cycling varies. Calabrese et al. (9), for example, review evidence that most cycling involves recurrences of depressions, not mania, and Oppenheim (11) reported one case of unipolar depressive rapid cycling in a patient on an antidepressant; but this is not the type of rapid cycling that has generally been described. Coryell et al. (7), in a study and a review, found unipolar (depressed) rapid cycling to be essentially nonexistent; only patients with mania or hypomania were at risk for rapid cycling, suggesting that prevention of mania or hypomania would eliminate the risk of rapid cycling.

Another perspective which has not been considered is the possibility that antidepressant-induced rapid cycling may be an artifact, consequent to antidepressant-induced manic (or hypomania). If one uses the Wehr et al. (12) definition of cycle length, that is, the number of weeks from mania to depression back to mania (possibly with intervening periods of euthymia), and if antidepressants help to alleviate the depressive periods and move a patient more quickly into mania (or hypomania), then any calculation of cycle length will appear to show reduced cycle length with antidepressants when, in actuality, the only parts of the cycle which are being shortened are the periods of depression and the intervals from depression to mania. In other words, since antidepressants are known to alleviate depression and induce mania, it can be assumed that they will shorten cycle length even if all they do is alleviate depression and induce mania; and this effect will be prominent since depressive episodes tend to last longer than manic episodes (2,13–16).

The following brief review looks at the literature from these perspectives. Specifically, it addresses these questions:

1. Does antidepressant-induced rapid cycling only occur in patients who become manic or hypomanic on antidepressants, regardless of the use of concomitant mood stabilizers?
2. If a patient's manic and hypomanic episodes are adequately prevented with mood stabilizers, can he/she safely take an antidepressant to treat or prevent recurrences of depression, without concern about inducing rapid cycling?
3. Can the rapid cycling which has been attributed to antidepressants be understood, more parsimoniously, as being due to the fact that antidepressants alleviate depression and can precipitate mania?

REVIEW

The evidence that antidepressants can induce rapid cycling has never been very strong. The original report (12,17) emanated from NIMH; it involved only five atypical patients, that is patients who did not respond well to prior treatment attempts in primary or secondary care settings. Patients were involved in a series of double-blind placebo controlled crossover studies, using patients as their own controls; they were hospitalized at NIMH, "on" or "off" antidepressants, and their cycle length was monitored, for over a year. Antidepressants were continued even during manic episodes; this would almost never be done clinically, that is to continue antidepressants after a patient has become manic or hypomanic. In fact, Wehr et al. (2) subsequently state that drug-induced rapid cycling "cannot be observed if antidepressants are stopped or observations cease as soon as they become manic." Thus subsequent authors who did not keep manic or hypomanic patients on antidepressants have apparently meant something different than the originators of the concept of antidepressant-induced rapid cycling.

The five patients in the original report (12) were not homogeneous: for example, patient number 2 was eventually stabilized on an antidepressant, with chlorpromazine and lithium to control mania. All patients became manic on antidepressants first (cycle length was defined as the time from one manic period to the next), indicating no reason for concern in bipolar patients who do not become manic on antidepressants (i.e., whose tendency to mania is controlled by mood stabilizers).

Three studies evaluating maintenance treatment of bipolar disorder [Prien et al. (18); Prien et al. (19); Quitkin et al. (20)] [reviewed in the Wehr et al. (2) article and by Coryell et al. (7)] represent the strongest evidence that antidepressant-induced rapid cycling is not a problem for most bipolar patients. In all of these controlled studies, bipolar patients were given antidepressants. In the Prien et al. (18) study, 44 bipolar patients were treated with lithium, imipramine, or placebo; 13 received imipramine. In this study, an attempt was made to keep patients on their assigned treatment even after their first relapse, for two years. While significantly more patients on imipramine became manic, rapid cycling did not occur on imipramine (7% of the imipramine group had more than one

episode (either manic or depressed), compared with 8% of the lithium group and 27% of the placebo group).

In the Quitkin et al. (20) study [also described in Kane et al. (21)], lithium plus placebo was compared to lithium plus imipramine in 75 bipolar patients, who were followed for an average of 19 months. In the third study, Prien et al. (19) evaluated 117 bipolar patients randomly assigned to lithium, imipramine, or a combination of the two drugs, followed for up to two years. While these studies indicated that imipramine can induce mania in some bipolar patients, there was no evidence of imipramine-induced rapid cycling.

Wehr et al. (2), in the 1987 review, concluded that antidepressants probably can cause mania in some bipolar patients, and can probably also cause rapid cycling in "a few" bipolar patients. However, they also concluded, since most of the literature reporting antidepressant-induced rapid cycling consists of anecdotal reports [cited in Wehr et al. (2)], that the original NIMH study (with N of only 5) is probably the best evidence for antidepressant-induced rapid cycling. Although the authors [Wehr et al. (2)] mention the possibility that more frequent depressive episodes (without mania) may be induced by antidepressants, the majority of the evidence they present concerns patients who became manic or hypomanic on antidepressants and proceeded to cycle rapidly (as shown in their Figure 2). As Wehr et al. (2) point out, the maintenance studies (18,19,20,21) systemically excluded patients who could not be stabilized on medication prior to the maintenance phase; thus unstable patients, who are probably those most likely to show antidepressant-induced rapid cycling, were excluded. On the other hand, it seems fair to conclude that for patients who can be stabilized on medication, there is relatively little risk of antidepressant-induced rapid cycling.

Wehr et al. (22) later summarize data from 51 patients who had periods of rapid cycling (some of these were patients who had been described in prior papers by the Wehr and Goodwin group); again, evidence is presented that tricyclic antidepressants can induce rapid cycling in some patients, but nothing is presented that would disagree with the thesis that patients who don't become manic or hypomanic on antidepressants will not develop rapid cycling. In fact, Wehr et al. (22) cite Winokur et al. (23) in indicating that manic episodes tend to be "immediately preceded or followed by depressive episodes, with no intervening normal period," suggesting the drugs that induce mania will induce rapid cycling.

Other studies are also relevant; some have been cited as supporting the concept of antidepressant-induced rapid cycling (6,22), but the support is weak, at best. Kupfer et al. (24) prospectively systematically studied 33 patients with bipolar II depression treated with imipramine at a median dose of 200 mg./day for 20 weeks; there was no evidence of drug-induced rapid cycling. Horowitz et al. (25) and Simpson et al. (26) presented anecdotal reports of 12 patients who they felt had antidepressant-induced rapid cycling; however, this was a diverse group of patients (e.g., one was schizoaffective), and the response to treatment (including a variety of mood stabilizers,

antidepressants and T4) was quite variable. Coryell et al. (7,8), in a prospective study following 345 bipolar patients for a mean of 13.7 years, concluded that rapid cycling tends to be a transitory phase in bipolar patients which remits spontaneously, regardless of treatment; that is, a relationship between antidepressant use and rapid cycling was not found.

Altshuler et al. (6), in a review and an additional report on patients from NIMH, used life charts (though without controlled treatment) to estimate that 26% of bipolar patients might have cycle acceleration on antidepressants. However, this (again) was an atypical group; for example, most patients had a history of lithium-refractory illness, so the results may not be applicable to patients whose manic or hypomanic episodes are prevented by mood stabilizers; also, 55% of the sample were rapid cyclers. In this sample, cycle acceleration, if it occurred, generally was evident within two months of beginning the antidepressant, suggesting that there is less risk of cycle acceleration in patients who are stabilized for more than two months on an antidepressant and a mood stabilizer. Also, only three patients judged to have antidepressant-induced rapid cycling did not also have antidepressant-induced mania. Given that treatment was not controlled, and given the Coryell conclusions noted previously (that rapid cycling can be a transitory phase of bipolar disorder unrelated to antidepressants), it is impossible to draw definitive conclusions from this study.

Angst et al. (27) studied 63 patients with Affective Illness (only 17 were bipolar) in a "mirror image" design, comparing cycle length before and after an average of 19 months of imipramine. There was evidence of reduced cycle length on imipramine, but the authors reported that in their population cycle length decreased with time, unrelated to medication. They did not find evidence that cycle length on imipramine decreased more than would have been expected in affectively ill patients (in their population) without medication (they did not mention whether episodes were manic or depressive).

Kukopulos et al. (16) and Tondo et al. (28), in an uncontrolled study, reported evidence of antidepressant-induced rapid cycling in up to 86 of 434 bipolar patients followed for an average of 18 years (about 13 years retrospectively and about 5 years prospectively). However the rapid cycling they noted was due to mania or hypomania induced by the antidepressants; the authors note a "clinical fact that most manias are followed by a depression" [Kukopulos et al. (16), page 256]; thus these authors would apparently agree that if one can prevent the development of mania or hypomania on antidepressants, one would also prevent antidepressant-induced rapid cycling. The authors also noted that "unipolar rapid cyclers are rare and are probably only apparently unipolar" [Kukopulos et al. (16), page 250].

Akiskal et al. (29) has written extensively about the risks of antidepressants in bipolar patients. However, he focuses on the risk of not recognizing "soft" evidence of bipolarity and treating bipolar patients with antidepressants alone, not on patients stabilized on mood stabilizers who are given antidepressants. Calabrese et al. (9) focused on the difficulty in treating depressed rapid cycling bipolar patients, but did not specify

whether patients were manic or hypomanic between depressive episodes.

Ghaemi et al. (14), in a more recent naturalistic study, reported that 23% of 35 bipolar patients appeared to develop new or accelerated rapid cycling on antidepressants, but many of these patients were not receiving concomitant mood stabilizers, and there was no evidence that patients who did not become manic developed rapid cycling. More recently Ghaemi et al. (4) reviewed the long-term (at least six months) use of antidepressants in bipolar patients. Six of the seven studies reviewed were prophylactic (not acute treatment) studies. They conclude that there is little evidence that antidepressants are of any prophylactic value (for preventing a recurrence of depression) for patients on lithium. Their clinical recommendations, that long-term antidepressant use should be reserved for patients who repeatedly have depressive recurrences on mood stabilizers alone, seems sound. But they do not critically evaluate the belief that antidepressants can induce rapid cycling.

Altshuler et al. (30), based on a retrospective chart review, present evidence that bipolar patients on a mood stabilizer and an antidepressant are more likely to have a depressive relapse if the antidepressant is discontinued, supporting the prophylactic use of antidepressants in appropriate patients.

CONCLUSIONS

In some respects, this review will not significantly affect treatment recommendations, in that antidepressants must still be used sparingly and cautiously in bipolar patients, because of the risk of inducing mania. However, psychiatrists might be somewhat more comfortable prescribing antidepressants if it is appreciated that there is no evidence that antidepressants induce rapid cycling in bipolar patients who do not become manic or hypomanic on them. If a patient becomes manic or hypomanic on antidepressants, and if this cannot be prevented by mood stabilizers, one should avoid antidepressants if at all possible. However, if patients on mood stabilizers do not become manic or hypomanic on antidepressants, there is no evidence that antidepressants will shorten the cycle length. Thus a more accurate summary statement, rather than maintaining that antidepressants can induce rapid cycling, is that patients who become manic or hypomanic on antidepressants, despite concomitant use of mood stabilizers, may become unstable or cycle more rapidly if antidepressants are given.

REFERENCES

- Montgomery SA, Keck PE: First international exchange on bipolar disorder. *J Affect Disord* 2000; 59:S81–S88
- Wehr TA, Goodwin FK: Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry* 1987; 144:1403–1411
- Bauer MS, Callahan AM, Jampala C, Petty F, Sajatovic M, Schaefer V, Wittlin B, Powell BJ: Clinical practice guidelines for bipolar disorder from the Department of Veterans Affairs. *J Clin Psychiatry* 1999; 60:9–21
- Ghaemi SN, Lenox MS, Baldessarini RJ: Effectiveness and safety of long-term antidepressant treatment in bipolar disorder. *J Clin Psychiatry* 2001; 62:565–569
- Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD: Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am J Psychiatry* 2001; 158:906–912
- Altshuler LL, Post RM, Leverich GS, Mikalaukas K, Rosoff A, Ackerman L: Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry* 1995; 152:1130–1138
- Coryell W, Endicott J, Keller M: Rapidly cycling affective disorder, demographics, diagnosis, family history, and course. *Arch Gen Psychiatry* 1992; 49:126–131
- Coryell W, Solomon D, Turvey C, Keller M, Leon A, Endicott J, Schettler P, Judd L, Mueller T: The long-term course of rapid-cycling bipolar disorder. *Arch Gen Psychiatry* 2003; 60:914–920
- Calabrese JR, Shelton MD, Bowden CL, Rapport DJ, Suppes T, Shirley ER, Kimmel SE, Caban SJ: Bipolar rapid cycling: Focus on depression as its hallmark. *J Clin Psychiatry* 2001; 62(suppl 14):34–41
- Baldessarini RJ: Drugs and the treatment of psychiatric disorders: Psychosis and anxiety. In J. Hardman, L. Limbird, P. Millinoff, R. Ruddon eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York, NY: McGraw-Hill Press: 2002: 431–460
- Oppenheim G: Drug-induced rapid cycling: Possible outcomes and management. *Am J Psychiatry* 1982; 139:939–941
- Wehr TA, Goodwin FK: Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 1979a; 36:555–559
- Freedman AM, Kaplan HI, Sadock BJ: *Comprehensive Textbook of Psychiatry/II*. Vol. 1, 2nd ed. Baltimore, MD: The Williams & Wilkins Company: 1975:1021
- Ghaemi SN, Boiman EE, Goodwin FK: Diagnosing bipolar disorder and the effect of antidepressants: A naturalistic study. *J Clin Psychiatry* 2000; 61:804–808
- Kolb LC: *Modern Clinical Psychiatry*, 8th ed. Philadelphia, PA.: WB Saunders Company: 1973:38
- Kukopulos A, Caliairi B, Tundo A, Minnai G, Floris G, Reginaldi D, Tondo L: Rapid cyclers, temperament and antidepressants. *Compr Psychiatry* 1983; 24:249–258
- Wehr TA, Goodwin FK: Rapid cycling between mania and depression caused by maintenance tricyclics. *Psychopharmacol Bull* 1979b; 15:17–19
- Prien RF, Klett J, Caffey EM: Lithium carbonate and imipramine in prevention of affective episodes. *Arch Gen Psychiatry* 1973; 29:420–425
- Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE: Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. *Arch Gen Psychiatry* 1984; 41:1096–1104
- Quitkin FM, Kane J, Rifkin A, Ramos-Lorenzi JR, Nayak DV: Prophylactic lithium carbonate with and without imipramine for bipolar I patients. *Arch Gen Psychiatry* 1981; 38:902–907
- Kane JM, Quitkin FM, Rifkin A, Ramos-Lorenzi JR, Saraf K, Howard A, Klein DF: Prophylactic lithium with and without imipramine for bipolar I patients: A double-blind study. *Psychopharmacol Bull* 1981; 17:144–145

22. Wehr TA, Sack DA, Rosenthal NE, Cowdry RW: Rapid cycling affective disorder: Contributing factors and treatment responses in 51 patients. *Am J Psychiatry* 1988; 145:179–184
23. Winokur G, Clayton P, Reich T: *Manic Depressive Illness*. St. Louis, CV Mosby: 1969
24. Kupfer DJ., Carpenter LL, Frank E: Possible role of antidepressants in precipitating mania and hypomania in recurrent depression. *Am J Psychiatry* 1988; 145:804–808
25. Horowitz GI, Liebowitz MR: Antidepressant-induced rapid cycling: Six case reports. *J Clin Psychopharmacol* 1993; 13:52–56
26. Simpson HB, Hurowitz,GI, Liebowitz MR: General principles in the pharmacotherapy of antidepressant-induced rapid cycling: A case series. *J Clin Psychopharmacology* 1997; 17:460–466
27. Angst J, Dittrich A, Grof P: Course of endogenous affective psychoses and its modification by prophylactic administration of imipramine and lithium. *Int Pharmacopsychiat* 1969; 2:1–11
28. Tondo L, Laddomada P, Serra G, Minnai G, Kukopulos A: Rapid cyclers and antidepressants. *Int Pharmacopsychiat* 1981; 16:119–123
29. Akiskal HS, Mallya G: Criteria for the “soft” bipolar spectrum: Treatment implications. *Psychopharmacol Bull* 1987; 23:68–73
30. Altshuler L, Kiriakos L, Calcagno J, Goodman R, Gitlin M, Frye M, Mintz J: The impact of antidepressant discontinuation versus antidepressant continuation on 1-year risk for relapse of bipolar depression: A retrospective chart review. *J Clin Psychiatry* 2001; 62:612–616

