Research

Antidepressants and Mania: To Stop or Not to Stop?

Danny Allen, Rob Horvath and David Nutt
Psychopharmacology Unit, University of Bristol, School of Medical Sciences,
University Walk, Bristol BS8 I TD, UK

Abstract

The clinical problem of whether to stop antidepressants when patients develop mania is looked at in the light of existing practice and advice both in the UK and in the USA. It is concluded that practice is based more on an empirical than a scientific basis, The literature on the subject is reviewed with especial reference to the questions of whether antidepressants actually cause mania, whether they interfere with the treatment of mania, whether discontinuing them stops mania and whether withdrawal of antidepressants causes mania. Finally a case notes study conducted by one of the authors is summarized and recommendations for further research are made.

Keywords - Antidepressants, mania.

Introducton

A common clinical problem is that of depressed patients who develop mania during treatment with antidepressant therapy. Standard practice in the United States is to stop the antidepressant, although in the United Kingdom it is not uncommon practice for the dose of antidepressant merely to be reduced or an antipsychotic treatment to be added. This approach seems to be taken in order to minimize the risk of a severe depressive swing that may be hard to treat and with the attendant danger of suicide. Strangely, when one examines the evidence for and against these treatment options there appear to be very few facts on which to base a clinical decision

What guidance is there? We looked at 15 standard psychiatric texts to see what advice they had on whether to stop antidepressants when mania or hypomania supervenes. Only two (Dunn, 1984; Talbott et al., 1988) made any mention of the subject. Both suggested that a sensible strategy in the first instance would be to reduce the antidepressant but neither book offered any references to support this advice.

In deciding whether or not to stop antidepressants several key questions need to be answered. Firstly: do antidepressants cause or precipitate mania? If they do then there would be some reasons for stopping or reducing them. Secondly: do antidepressants interfere with the treatment of mania? If they do then there may similarly be reasons for stopping or reducing them once an episode of mania occurs.

If, on the other hand, discontinuing antidepressants does not stop mania then the rationale for stopping or reducing antidepressants is somewhat limited. Furthermore, if withdrawing antidepressants can actually precipitate mania then this course of action may be positively counterproductive, particularly if a severe depressive underswing later develops. The rest of this paper examines the evidence regarding these questions.

Do Antidepressants cause mania?

The evidence for:

This question has recently been reviewed by Wehr and Goodwin (1987), who concluded that the balance of the available evidence supported the view that some patients switch to mania and others experience rapid cycling when they are treated with antidepressants. The main problem with most of the studies they quoted is that they were not placebo-controlled. The one exception is the doubleblind prospective study of Prien et al. (1973). Subjects were given lithium, imipramine or placebo. Between five and 24 months, 33 per cent of patients on placebo, 67 per cent on imipramine and 12 per cent on lithium developed mania. The differences were not significant but because of the small samples there was a risk of a type I1 error occurring; furthermore the incidence of hypomania was not stated. This latter omission occurs again in Prien et al.'s (1984) study comparing patients treated with imipramine and lithium and imipramine alone. The incidence of mania in the latter group was higher but not significantly so.

There are other problems with many of the studies. For instance, as Wehr and Goodwin (1987) point out, generally there is not random allocation of patients as those most likely to switch into mania have been excluded from the studies and what is being looked at is maintenance therapy. In one study (Prien et al., 1973) only patients who could be stabilized on imipramine during an acute treatment phase entered the study which may well have excluded those most likely to swing into mania.

Certain factors may increase the likelihood of swings into mania. Quitkin et al. (1981) note that a history of proneness to mania may be predictive of a manic response to tricyclic antidepressants. Extending Prien et aZ.'s (1973) study, Jann et al.(1982) noted that low serum lithium levels makes the switch to mania with tricyclic antidepressants more likely, suggesting that this substance provides some protection against iatrogenic switches as well as natural ones. Nasrallah et al. (1982) found that younger patients, those with an earlier onset of their illness, those with a higher incidence of hospitalization and those with a positive family history of psychiatric illness were all more likely to switch. A number of studies make the point that bipolar patients are more prone to swings than are unipolar subjects; this is well reviewed in Bunney's paper (1 978). In bipolar patients there is some evidence that tricyclic antidepressants may also cause rapid cycling between mania and depression (Wehr and Goodwin, 1979).

Zis et al. (1979) in a study of the effects on 3-methoxy-4-hydroxy-phenylglycol (MHPG) excretion during treatment with tricyclic antidepressants found that within

the group developing mania or hypomania on tricyclics there was a highly significant correlation between pre-treatment 24-h urinary MHPG and the latency of onset of the manic episode; that is, patients with the lowest MHPG excretion were the first to switch. The researchers believe that these findings were consistent with the postulated noradrenergic involvement in the switch process from depression into mania and with the alteration in sensitivity which it is hypothesized occurs in the noradrenergic receptors. They argue that the administration of biogenic amine re-uptake inhibitors (tricyclics) increases noradrenaline at the synaptic cleft and that this coupled with the receptor receptor supersensitivity may account for the short latency and longer duration of episodes in bipolar patients with low MHPG excretion (that is, those with the most 'bipolar' pattern).

The evidence against:

A number of papers suggest that, in fact, there is no evidence for a treatment-induced switch. Angst (1985) in a retrospective case note study of patients admitted to Zurich hospitals between 1920 and 1982 (a period which covers the pre- and post-antidepressant eras) noted that there was an overall increase in the number of admissions for both mania and depression, leading to clinicians seeing more switches between one and the other. However, he noted that bipolarity correlated positively with readmissions and switches, and therefore studies, such as that of Lewis and Winokur (1982) which selected readmissions, probably over-represented 'switchers'. This study compared a group of patients on no medication with a group taking antidepressants. The vast majority of those who switched were bipolar and there was no significant difference between the two groups. Unfortunately, this was a small study that excluded patients who had had antidepressant-induced mania in the past.

Solomon et al. (1990) who performed a retrospective case note study concluded that there was insiifficient evidence to implicate antidepressants as the cause of switching. They noted that individual patients switched both with and without antidepressants and that there were some problems in validating diagnoses when the information on which the original diagnoses had been based was examined. The main confounding variable was coexisting substance misuse.

More recently Peet (in press) has looked at the rate of switch into mania for patients on specific serotonin reuptake inhibitors and concludes that it is no greater than placebo in bipolar patients and less than 1 per cent for unipolar patients and he makes the point that it is impossible to tell how many patients classified as unipolar depressives are, in fact, having the first episode of a bipolar illness.

Do Antidepressants interfere with the treatment of mania?

We could find no evidence from the literature to prove that this is the case, and it appears not to have been specifically studied. There is an early open Japanese study that actually found high dose imipramine to be effective in the treatment of mania (Akimoto et al., 1961).

Does discontinuing antidepressants stop mania?

Murphy et al. (1975), referring to six bipolar patients in a larger study, noted that half of them developed mania whilst on phenelzine but that stopping the drug did not

reduce manic behaviour, whereas treatment with lithium and phenothiazines did. A similar observation was made on clomipramine-induced mania by van Scheyen and van Kammen (1979) in that stopping antidepressants did not seem to abort the mania, which still needed antipsychotic treatment.

Withdrawal of antidepressants may result in a deepening of depression and the inherent risk of suicide associated with the early phase of the illness (Guze and Robins, 1970). In addition antidepressants have a clear role in prophylaxis in unipolar depression (Prien et al., 1984).

Does withdrawal of antidepressants cause mania?

There is evidence that withdrawal of antidepressants can, in itself, precipitate mania. Mirin et al. (198 1) looked at seven patients who developed mania between two and seven days after stopping antidepressants. They postulated that as tricyclic withdrawal is accompanied by changes in the turnover rate of individual neurotransmitters, as well as shifts in the equilibrium between various transmitters, these events may be accompanied by alterations in mood. Their study is small and did not include controls. Kupfer et al. (1988) in a prospective study of 230 patients with recurrent depression found that only six patients developed mania or hypomania. In three of these this occurred within two weeks of stopping the antidepressant (imipramine) and in one it occurred when the antidepressant had been tailed down prior to stopping.

How big is the problem?

The impetus for us to review this field came from a number of patients of ours who became manic while being withdrawn from antidepressants. Most had been severely depressed for many years despite a variety of antidepressant treatments and several relapsed into extreme depressions with multiple suicide attempts following cessation of antidepressant mania

There are no published data on what proportion of admissions for mania are secondary to the withdrawal of antidepressants. One of the authors (RH) has conducted a case note survey of 59 consecutive admissions to Barrow Hospital, Bristol, with a diagnosis of mania and found that 17 per cent were currently on antidepressants.

Discussion

The answer to the question posed in the title, "*To Stop or Not to Stop?*", is unfortunately not available at present. There appear to be no studies which have directly assessed in a prospective fashion relative outcomes of matched patient groups that continued or stopped antidepressants. It would appear that the American practice of stopping antidepressants may be a reflection of a therapeutic tradition that is bolstered by the fear of litigation. We suggest that this issue is of sufficient clinical importance to warrant a proper investigation.

References

Akimoto, H., Nakakuki, M., Honda, Y., Takahashi, Y., Toyoda, J., Sasaki, K. and Machiyama, Y. (1961). Clinical evaluation of the effect of central stimulants, MAO inhibitors, and imipramine in the treatment ofaffective disorders. Proceedings of the Third World Congress of Psychiatry, 2, 958-963.

Angst, J. (1985). Switch from depression to mania-a record study over decades between 1920 and 1982. Psychopathology, 18, 140-154.

Bunney, W. E. Jr. (1978). In: Psychopharmacology: A Generation of Progress, Lipton, M. A., DiMascio, A.and Killiam, K. F. (Eds) Raven Press, New York, pp. 1249-1259.

Dunn, C. G. (1984). Textbook of Contemporary Psychiatry. Collamore Press, D. C. Heath & Co, Lexington, Mass.

Guze, S. B. and Robins, E. (1970). Suicide and primary affective disorders. British Journal of Psychiatry, 117, 437-438.

Jann, M. W., Bitar, A. H. and Rao, A. (1982). Lithium prophylaxis of tricyclic antidepressant-induced mania in bipolar patients. American Journal of Psychiatry, 139 5, 683-684.

Kupfer, D. J., Carpenter, L. L. and Frank, E. (1988). Possible role of antidepressants in precipitating mania and hypomania in recurrent depression. American Journal of Psychiatry, 145 7, 804-808.

Lewis, J. L. and Winokur, G. (1982). The induction of mania. Archives of General Psychiatry, 39,303-306.

Mirin, S. M., Schatzberg, A. F. and Creasey, D. E. (1982). Hypomania and mania after withdrawal of tricyclic antidepressants. American Journal of Psychiatry, 138, 1 87-89.

Murphy, D. L., Brand, E., Baker, M., Van Kammen, D. and Gordon, E. (1975). In: Neuropsychophamacology, Boissier, J. R., Hippius, H. and Pichot, P. (Eds) Elsevier, New York, pp. 788-799.

Nasrallah, H. A., Lyskowski, J. and Schroeder, D. (1982). TCA-induced mania: differences between switchers and non-switchers. Biological Psychiatry, 17, 2, 271-274.

Peet, M. Induction of mania with specific serotonin reuptake inhibitors and tricyclic antidepressants. BritishJournal of Psychiatry.

Prien, R. F., Klett, C. J. and Caffey, E. M. Jr. (1973). Lithium carbonate and imipramine in prevention of affective episodes-a comparison in recurrent affective episodes. Archives of General Psychiatry, 29, 420-425.

Prien, R. F., Kupfer, D. J., Mansky, P. A., Small, J.G., Tuason, V. B., Voss, C. B. and Johnson, W. E. (1984). Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Archives ofGeneral Psychiatry, 41, 1097-1104.

Quitkin, F. M., Kane, J., Rifkin, A., Ramos-Lorenzi, J. R. and Nayak, D. V. (1981). Prophylactic lithium carbonate with and without imipramine for Bipolar- I patients. Archives of General Psychiatry, 38, 902-907.

Solomon, R. L., Rich, C. L. and Darko, D. F. (1990). Antidepressant treatment and the occurrence of mania in bipolar patients admitted for depression. Journal of Affective Disorders, 18, 253-257.

Talbott, J. A., Hales, R. E. and Yudofsky, S. C. (1988). Textbook of Psychiatry. American Psychiatric Press Inc.

van Scheyen, J. D. and van Kammen, D. P. (1979). Clomipramine-induced mania in unipolar depression. Archives of General Psychiatry, 36, 560-565.

Wehr, T. A. and Goodwin, F. K. (1979). Rapid cycling in manic-depressives induced by tricyclic antidepressants. Archives of General Psychiatry, 36, 555-559.

Wehr, T. A. and Goodwin, F. K. (1987). Can antidepressants cause mania and worsen the course of affective illness? American Journal of Psychiatry, 144 11, 1403-1411.

Zis, A. P., Cowdry, R. W., Wehr, T. A., Muscettola, G. and Goodwin, F. K. (1979). Tricyclic induced mania and MHPG excretion. Psychiatry Research, 1, 93-99.

Appendix: Textbooks Consulted

Batchelor, I. R. C. (1969). Henderson and Gillespie's Textbook of Psychiatry. Oxford University Press, Oxford.

Gelder, M., Gath, D. and Mayou, R. (1989). Oxford Textbook of Psychiatry. Oxford University Press, Oxford.

Dunn, C. G. (1984). Textbook of Contemporary Psychiatry. Collamore Press, D. C. Heath & Co, Lexington, Mass.

Goldberg, D., Benjamin, S. and Creed F. (1987). Psychiatry in Medical Practice. Routledge, London.

Goidman, H. H. (1984). Review of General Psychiatry. Lange Medical Publications, Los Altos.

Hill, P., Murray, R. and Thorley, A. (1986). Essentials of Postgraduate Psychiatry. Grune and Stratton, London.

Kaplan, H. I. and Sandok, B. J. (1981). Modern Synopsis of Comprehensive Textbook of Psychiatry ZV. Williams and Wilkins, Baltimore.

Kendall, R. E. and Zealley, A. K. (1988). Companion to Psychiatric Studies. Churchill Livingstone, Edinburgh.

Nicholi, A. M. (1988). The New Harvard Guide to Psychiatry. Belknap Press, Cambridge, Mass.

Rose, N. (1988). Essential Psychiatry. Blackwell Scientific, Oxford.

Sim, M. (1981). Guide to Psychiatry. Churchill Livingstone, Edinburgh.

Slater, E. and Roth, M. (1977). Clinical Psychiatry. Balliere Tindall, London.

Stafford-Clark, D., Bridges, P. and Black, D. (1990). Psychiatry for Students. Unwin Hyman, London.

Talbott, J. A., Hales, R. E. and Yudofsky, S. C. (1988). Textbook of Psychiatry. American Psychiatric Press Inc.

Trimble, M. R. (1988). Biological Psychiatry. John Wiley and Sons, Chichester.