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# Can long-term treatment with antidepressant drugs worsen the course of depression?

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### Abstract

**BACKGROUND:** The possibility that antidepressant drugs, while effectively treating depression, may worsen its course has received inadequate attention. **METHOD:** A review of the literature suggesting potential depressogenic effects of long-term treatment with antidepressant drugs was performed. A MEDLINE search was conducted using the keywords tolerance, sensitization, antidepressive agents, and switching. This was supplemented by a manual search of Index Medicus under the heading "antidepressant agents" and a manual search of the literature for articles pointing to paradoxical effects of antidepressants. **RESULTS:** A number of reported clinical findings point to the following possibilities: very unfavorable long-term outcome of major depression treated by pharmacologic means, paradoxical (depression-inducing) effects of antidepressant drugs in some patients with mood and anxiety disturbances, antidepressant-induced switching and cycle acceleration in bipolar disorder, occurrence of tolerance to the effects of antidepressants during long-term treatment, onset of resistance upon rechallenge with the same antidepressant drug in a few patients, and withdrawal syndromes following discontinuation of mood-elevating drugs. These phenomena in susceptible individuals may be explained on the basis of the oppositional model of tolerance. Continued drug treatment may recruit processes that oppose the initial acute effects of a drug and may result in loss of clinical effect. When drug treatment ends, these processes may operate unopposed, at least for some time, and increase vulnerability to relapse. **CONCLUSION:** The possibility that antidepressant drugs may worsen the course of depression needs to be tested, even though its scientific exploration is likely to encounter considerable methodological and ideological difficulties. The clinical implications of this hypothesis in depression are considerable. Antidepressant drugs are crucial in the treatment of major depressive episodes. However, appraisal of paradoxical effects that may occur in susceptible patients during long-term treatment may lead to more effective use of the drugs.

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