## Adinazolam-Induced Mania

SIR: Two recent reports (1, 2) described the appearance of manic symptoms in three bipolar depressed patients during treatment with alprazolam, a triazolobenzodiazepine which may possess antidepressant properties. Adinazolam, another triazolobenzodiazepine, is currently being investigated specifically as an antidepressant (3). We recently observed a manic switch during adinazolam therapy, which suggests that it has side effects similar to those of alprazolam.

Ms. A, a 29-year-old woman, had a 3-year history of bipolar disorder, including hospitalizations for three manic episodes and one depressive episode. The patient was readmitted to the University Hospital in Liège, Belgium, with a *DSM-III* diagnosis of major depressive episode with melancholia that had lasted 2 weeks. Her score on the 24-item Hamilton Rating Scale for Depression was 42. After a drug-free period of 2 weeks, the patient gave informed consent to participate in a double-blind study comparing adinazolam, amitriptyline, and diazepam. The code, broken following discontinuation of the study due to the appearance of side effects, revealed that the patient had been receiving adinazolam. According to the protocol, the dose of adinazolam was progressively increased until a plateau level was reached on day 9. The patient received 10 mg on day 1, 30 mg on day 2, 40 mg on day 4, and 60 mg from days 4 to 8. On day 8, all depressive symptoms had disappeared and were progressively replaced by manic symptoms. On day 11, the patient fulfilled all *DSM-III* criteria for a definite manic episode, with irritability, increased activity and speech, flight of ideas, inflated self-esteem, and decreased need for sleep. Over the next 24-hour period, the adinazolam was tapered to 20 mg and then stopped while the patient was being treated with moderate doses of neuroleptic medication (clothiapine, 80 mg/day) for 2 days and lithium carbonate, 750 mg/day. On day 15, the patient was again normothymic. From day 19, depressive symptoms began to reappear; her Hamilton score of 9 increased to 20 3 weeks later. At that time, treatment with amitriptyline was begun.

The evolution of affective symptoms in this patient suggests that adinazolam may have induced the manic symptoms. Alprazolam has previously been reported to induce manic shifts in bipolar patients (1, 2). Adinazolam, pharma-

cologically very close to alprazolam, may be responsible for the same side effects. Of course, one cannot rule out a spontaneous evolution of affective symptoms in a bipolar patient, even if the manic symptoms disappeared very rapidly with the discontinuation of adinazolam.

This induction of manic shifts may support actual antidepressant properties of adinazolam. Indeed, manic shifts have been described during treatment with all the classic antidepressants, such as tricyclic drugs and monoamine oxidase inhibitors (MAOIs) (4). Latency to onset of mania associated with use of MAOIs and tricyclic antidepressants is reported to be between 18 and 20 days (4). This latency was somewhat shorter in our patient (11 days); however, two manic shifts have been reported in a patient within 3 days of beginning alprazolam therapy (2). On the pharmacological level, triazolobenzodiazepines, unlike classic benzodiazepines, share one property with tricyclic antidepressants: inhibition of reserpine-induced up-regulation of β-adrenergic receptors in the mammalian brain (5). Finally, this case report suggests the need for careful monitoring when one is treating bipolar patients with a triazolobenzodiazepine such as adinazolam.

REFERENCES

1. Arana GW, Pearlman C, Shader RI: Alprazolam-induced mania: two clinical cases. Am J Psychiatry 142:368–369, 1985
2. Strahan A, Rosenthal J, Kaswan M, et al: Three case reports of acute paroxysmal excitement associated with alprazolam treatment. Am J Psychiatry 142:859–861, 1985
3. Pyke RE, Cohn JB, Feighner JP, et al: Open-label studies of adinazolam in severe depression. Psychopharamcol Bull 19:96–98, 1983
4. Pickar D, Cowdry RW, Zis AP, et al: Mania and hypomania during antidepressant pharmacotherapy: clinical and research implications, in Neurobiology and Mood Disorders. Edited by Post RM, Ballenger JC. Baltimore, Williams & Wilkins, 1984
5. Sethy VH, Hodges DH Jr: Role of beta-adrenergic receptors in the antidepressant activity of alprazolam. Res Commun Chem Pathol Pharmacol 36:329–332, 1982

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## A Cybernetic Theory of How Psychotropic Drugs Work

SIR: In "Overview: Toward a Dysregulation Hypothesis of Depression" (September 1985 issue), Larry J. Siever, M.D., and Kenneth L. Davis, M.D., helped our understanding of pathophysiology and pharmacological treatment by applying cybernetic thinking to the neuron receptor level.

John Davis and I (1), in 1969, suggested on clinical grounds that psychotropic drugs normalize a deranged cybernetic system because these agents have so little effect on normal affect and behavior. This discussion has been updated and amplified (2).

The catecholamine theory postulated that mood is directly proportional to the level of synaptic norepinephrine. This was dubious on two counts. First, such synaptic effects were immediate whereas antidepressant effects were delayed. Second, when antidepressants were given regularly to normal subjects, synaptic norepinephrine levels were increased, yet there was no heightening of mood. If anything, there was sedation. We suggested that the effects of psychotropic drugs could best be understood in terms of a normalizing effect on a deranged thermostat rather than by the synaptic rheostat analogy.

Antipsychotic drugs are effective for both excited and retarded acute schizophrenias. Lithium is effective for both bipolar mania and depression. This is difficult to reconcile with a rheostat model. However, if a drug repaired a cybernetic circuit defect it would restore the system to normal regardless of the direction of the activation derangement.

Tricyclic antidepressants, on the other hand, do not quite fit this model because they are effective for depression but ineffective for mania. However, some treated subjects with bipolar depression develop a shortened cycle length that is incompatible with a simple rheostat shift but that could occur if cybernetic repair was incomplete.

There are other clinical similarities between affective disorders and deranged cybernetic circuits. For instance, defects in amplification or timing can convert a stabilizing negative feedback loop into a positive feedback loop. This results in sharp, maintained accelerations or decelerations of activation level, as may be the case with mania and retarded depression. Further, decreases in the sensitivity of a receptor element in the detector can result in continued oscillations (hunting) of the activation level, thus resembling cyclothymia.

The simplest cybernetic circuit has at least three components: a detector that compares the level of the variable being controlled with the set point, a transmission line, and an effector system. Therefore, at least three receptor sites are necessary. Further, it is likely that there are separate receptors with regard to both the direction of the change in level and the speed of change.

It is not plain whether any of the neuronal receptor sites, referred to by Drs. Siever and Davis, can be equated with any of these functional sites.

The next step may be a functional circuit analysis that can determine the nature of receptor functions. Unfortunately, studies of normal animals are not likely to find circuit defects analogous to human illness. Inbreeding animals prone to emotionality or separation anxiety may produce a suitable model, both for physiological analysis and therapeutic trials.

REFERENCES

1. Klein DF, Davis JM: Diagnosis and Drug Treatment of Psychiatric Disorders. Baltimore, Williams & Wilkins, 1969
2. Klein DF, Gittelman R, Quitkin F, et al: Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children. Baltimore, Williams & Wilkins, 1980

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## Drs. Siever and Davis Reply

SIR: We appreciate Dr. Klein's comments and agree with his arguments that a cybernetic rather than a rheostat model better accommodates the observed clinical effects of psychotropic medications. His observations have contributed greatly to our understanding of the mechanism of action of antidepressant drugs. As he and Dr. John Davis noted, one important implication of these observations is that it is likely to be the regulatory mechanisms rather than the absolute activity of relevant neurotransmitter systems that are disturbed in the affective disorders.