Three Case Reports of Acute Paroxysmal Excitement Associated With Alprazolam Treatment

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Three patients receiving alprazolam developed, within days after beginning treatment, acute excitatory states with features more suggestive of mania than of disinhibition syndrome. The authors suggest a neurochemical link between mania and disinhibitory states.

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It frequently has been reported that monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants are associated with an increased rate of manic episodes in patients with bipolar affective disorder (1, 2) and in some patients with major depressive disorder (3). Much has been written about the development during treatment with benzodiazepines of disinhibition syndromes or paradoxical rage reactions (4–6) that seem to resemble the idiosyncratic intoxication sometimes seen with the use of alcohol and barbiturates (7). However, we have been unable to find any reports on the development of mania or disinhibitory states associated with the use of alprazolam as an anxiolytic, antidepressant, or antipanic agent. In this paper, we report on three such cases in which the use of alprazolam seemed to be linked to the development of an acute excitatory state. These cases differ in presentation and course from those seen with other benzodiazepines or antidepressants.

CASE REPORTS

Case 1. Ms. A, a 32-year-old artist, had an 8-year history of recurrent bipolar disorder. She had been maintained on lithium therapy (average serum levels=0.8–1.0 meq/liter) during this time, with no major manic episodes but with occasional mild depressive episodes.

During a period of stress following a job transition, Ms. A demonstrated symptoms of anxiety during the working day. A short-term trial of oral alprazolam, 0.5 mg t.i.d. as needed, was initiated. Within 72 hours, Ms. A reported the onset of substantial insomnia, racing thoughts, increased energy, and associated manic symptoms. She reported, reluctantly, that the alprazolam made her feel as if she were taking amphetamines. Her blood lithium level was 0.9 meq/liter at this time.

On discontinuation of the alprazolam, her symptoms persisted for an additional 2–3 days. Thioridazine, 100–150 mg h.s., was prescribed to help her sleep during the interval. Ms. A became euthymic and the thioridazine was stopped. One year later she had had no manic or depressive episodes.

Case 2. Mr. B, a 34-year-old man, had a 5-year history of generalized anxiety without agoraphobia that occasionally was punctuated by periods of panic attacks. The patient, a college graduate, was steadily employed and demonstrated good premorbid social functioning. He had no history of alcohol or drug abuse, nor was there a family history of affective disorders. His only previous psychiatric treatment had been for difficulties adjusting to an out-of-town college environment.

Mr. B now presented with increasingly severe panic attacks, occurring especially on public transportation and in novel social situations. His treatment began with a regimen of oral alprazolam, 0.25 mg t.i.d., which was ineffective in controlling his panic; the dose was increased after 1 week to 0.5 mg t.i.d. This dose also was ineffective in remitting the panic attacks and Mr. B now complained too of initial insomnia and perseverative thoughts. Because it was otherwise well tolerated, the alprazolam was increased to 1 mg t.i.d. Within 4 days of this increase in dose, the patient became irritable and reported impulsivity in interpersonal situations. He noted that he now experienced the perseverative thoughts as racing and occasionally as paranoid, but he demonstrated good reality testing. His sleep was markedly diminished but his appetite remained satisfactory.

At this juncture the alprazolam was discontinued, and treatment with oral perphenazine, 4 mg b.i.d. and h.s., was initiated. Within 72 hours, Mr. B's psychomotor agitation subsided.

Case 3. Ms. C, a 32-year-old woman, had a long history of panic attacks associated with heights. She had no personal or family history of affective disorders or of drug or alcohol abuse.

Ms. C was referred for treatment after her panic attacks increased when, following a promotion at work, she was forced to take an elevator to her new office. These attacks were characterized by depersonalization, palpitations, and other somatic anxiety symptoms. Initially she did not demonstrate affective symptoms or report a disturbance in mood state. She began treatment with oral alprazolam, 0.5 mg

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b.i.d. After 48 hours, she reported racing thoughts, insomnia, and interpersonal conflicts with her boss, co-workers, and boyfriend, with whom she had never previously had altercations. On discontinuation of the alprazolam, Ms. C noted complete remission within 48 hours of her irritable mood, agitation, and insomnia.

DISCUSSION

The well-established anxiolytic effects of alprazolam (8) relate to its benzodiazepine structure and γ-aminobutyric acid (GABA) potentiation. The chemical structure of alprazolam is unique among the benzodiazepines because of its triazolo ring moiety. This makes it a structural analogue of tricyclic antidepressants as well, which may, in part, explain its efficacy as an antidepressant (9) as well as an anxiolytic. Given that alprazolam appears to be a chemical structural bridge between the benzodiazepines and the dibenzazepines, it would appear logical that its action would be a bridge also between antidepressant and anxiolytic effects.

One can speculate that this action may occur through some form of feedback loop that involves GABA-ergic neurons with receptors not usually affected by other benzodiazepines, or at least having a lesser affinity for benzodiazepines other than alprazolam. This is feasible when one takes into account that the GABA-ergic neurons innervate both the median raphe nucleus and the locus ceruleus, sites of serotonin and norepinephrine release.

The invocation of a different mode of action than that used by tricyclics or other anxiolytics seems necessary to explain the atypical presentation and treatment course seen in our three patients, as well as the spectrum of symptoms exhibited by these patients, which could be features of disinhibitory side effects, a toxic state, or the hypomania or mania of an affective disorder.

Paradoxical excitatory states or disinhibition syndromes previously described in the literature (4–6) are characterized by anger, verbal hostility, and assaultiveness; it has been suggested that these states occur most often in patients with a history of poor impulse control or previous aggressive and destructive behavior (6). This is in contrast to mania, which may have these symptoms but which also has the vegetative symptoms of decreased appetite, increased energy or activity, and classically racing thoughts.

None of our patients was known to have suppressed rage or aggression or a history of poor impulse control during long treatment. Although they did demonstrate some irritability and developed impulsivity with agitation, both of which suggest a disinhibition state, our patients were most discomforted by the emergence of symptoms most often noted in manic states, such as insomnia, racing thoughts, and the subjective feelings of increased energy that are not found in disinhibition.

The time course of symptom progression in all three patients more nearly approximates that of a disinhibitory state or a toxic state. Latency to onset of mania associated with use of MAOIs and tricyclic antidepressants is reported to be between 18 and 20 days (10), which supports the involvement of neuroreceptor adaptation in behavioral changes. However, when alprazolam was used in larger doses than recommended to achieve anxiolytic effects, two out of three patients had a latency to onset of a few days. This finding implies that alprazolam has a more direct effect than one exerted through amine reuptake blockage increasing amine concentration at supersensitive receptor sites—a process that requires weeks to achieve.

In addition, the rapid resolution of the manic-like behavior in patient 3 achieved by discontinuing the alprazolam is more reminiscent of toxic organic states that resolve quickly with the decrease or discontinuation of the offending agent. Indeed, patients 1 and 2 did not require the longer time course needed to achieve a euthymic state as in the "switch" process that can occur during antidepressant treatment. In this case, the antidepressant-associated mood change generally is more prolonged, requiring treatment with neuroleptics and/or lithium carbonate (10).

Clearly, more investigation into the neurochemistry involved in these mood and behavior disorders needs to be done to elucidate further the relationship between mood states and disinhibitory behavior changes. We think that our patients' symptoms which are similar to both mood and behavior disorders, the duality of action of alprazolam observed in other studies, and the unusual chemical structure of alprazolam all imply a neurochemical link between mania and disinhibitory states.

These three cases should serve to warn physicians that alprazolam may unexpectedly induce an acute paroxysmal excitatory state. As with two of our patients, this excitatory state may occur in individuals without a history or symptoms suggestive of an affective disorder. Furthermore, our patients did not have conflicts over impulse control or aggressive states, as is frequently seen in patients who develop disinhibition syndromes. Our patients' diverse premorbid states do not suggest any characteristics that define a group of patients at risk for this reaction; however, we think one should exercise increased caution in monitoring patients taking alprazolam who have a previous history of mania. If reduction in dose or discontinuance of the drug does not cause the symptoms to remit, the use of neuroleptics may be indicated.

REFERENCES

1. Murphy DL: The behavioral toxicity of monoamine oxidase-inhibiting antidepressants. Adv Pharmacol Chemother 14:71–105, 1979
2. Kukopulos A, Reginaldi D, Laddonada P, et al: Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatry 13:156–167, 1980
3. Bunney WE Jr, Goodwin FK, Murphy DL, et al: The "switch process" in manic-depressive illness, II: relationship to catecholamines, REM sleep, and drugs. Arch Gen Psychiatry 27:304–309, 1972

4. Gardos G, DiMascio A, Salzman C, et al: Differential actions of chlordiazepoxide and oxazepam on hostility. Arch Gen Psychiatry 18:757–760, 1968
5. Hall RCW, Zisook S: Paradoxical reactions to benzodiazepines. Br J Clin Pharmacol 11:995–1045, 1981
6. Gardos G: Disinhibition of behavior of antianxiety drugs. Psychosomatics 21:1025–1026, 1980
7. Barraclough BM: Barbiturate prescribing: psychiatrists' views. Br Med J 2:928–929, 1976
8. Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam, and placebo in clinically anxious patients. J Clin Psychiatry 42:347–351, 1981
9. Feighner JP, Aden GC, Fabre LF, et al: Comparison of alprazolam, imipramine, and placebo in the treatment of depression. JAMA 249:3057–3064, 1983
10. Pickar D, Cowdry RW, Zis AP, et al: Mania and hypomania during antidepressant pharmacotherapy: clinical and research implications, in Neurobiology of Mood Disorders. Edited by Post RM, Ballenger JC. Baltimore, Williams & Wilkins, 1984