

Alprazolam-Induced Panic Disorder

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The Food and Drug Administration indication of alprazolam for the treatment of panic disorder tacitly suggests that it does not induce panic attacks. This suggestion is amplified by the history of alprazolam as the first medication approved for panic disorder.¹ Moreover, alprazolam acutely decreases anxiety symptoms, including panic, and is widely used for this indication.² Although dependence, withdrawal, and rebound anxiety from alprazolam have been noted, alprazolam has not previously been reported to cause frank panic attacks. We observed a patient with panic attacks induced by alprazolam, presumably a severe rebound effect.

Case Report

A 77-year-old, married, 110-pound woman was hospitalized in response to her complaints of feeling as if she were dying from heart attacks. Attacks of this sort began 1 month earlier, occurring two to three times a day. She denied having such attacks before this time. During these attacks she had a sense of impending death and had intense and racing heart beat, chest pain, flushing, choking sensations, and shakiness. The patient described herself as anxious all her life, but more so for the past 2 years in reaction to her husband's "Parkinson's disease and dementia" and his associated abusive and aggressive behavior. The patient was extremely concerned about having these attacks and said that it caused major changes in her behavior and daily life.

Specifically, until 3 months earlier, she had enjoyed shopping and other activities outside the house. She said she is now too anxious and fatigued to shop, and she stays at home more. She claimed to have lost 35 pounds during the past 6 months.

Likewise, 6 months before her admission she began taking alprazolam, initially at a dosage of 0.5 mg twice daily, which was increased to four times a

day 1 month ago. This increase in medication happened just before panic attacks started. She admitted that the panic attacks never began less than 2 hours after an alprazolam dose. She told of brief trials of sertraline, bupropion, buspirone, and venlafaxine, each quickly discontinued because of headaches and stomach problems. All medications were prescribed by primary care physicians. Other medical history was noncontributory, and there was no alcohol or substance abuse.

When examined, she was hypervigilant, fidgety, easily agitated, and intensely concerned. She responded to questions, elaborated, and interacted actively without hesitation, speaking with normal rate and rhythm and to the point. There was no sadness or apathy. The Mini Mental State Examination (MMSE) score was 30/30. Alprazolam was stopped and lorazepam started at 1 mg four times daily with a gradual linear 20-day taper scheduled. Bisoprolol 2.5 mg twice a day was prescribed to diminish somatic anxiety symptoms.³ Buspirone 5 mg twice a day was given on the third hospital day. When the patient complained of insomnia and shaking from buspirone, it was replaced by citalopram 10 mg/d. Although she had no elevation in temperature, respiratory rate, pulse, or blood pressure, and she had no tremors, piloerection, or other objective signs of withdrawal, the patient frequently demanded to receive more alprazolam or lorazepam. After several replies that these would not be provided, she left the hospital against medical advice. A follow-up appointment at a mental health center was made.

Discussion

This patient did not experience panic attacks until she had taken alprazolam for 5 months, and the attacks began only after an increase in dose. This finding suggests that the duration of action of alprazolam is too brief to prevent rebound anxiety with dose administration four times daily.

The clinical deterioration that follows prolonged benzodiazepine use consists of several phenomena. Relapse is reemergence of the pretreatment anxiety symptoms. Rebound is the expression

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of new time-limited symptoms that were not present before treatment and depend on the pharmacokinetics of the drug. Somatic and psychological anxiety symptoms that exceed pretreatment levels of severity are likely to be rebound phenomena.⁴ The development of early morning awakening after taking a short-acting benzodiazepine agent (eg, triazolam) at bedtime for 2 weeks is an example of rebound. Essentially, rebound goes beyond tolerance into the early phase of a withdrawal syndrome that develops between doses. Some speculate that rebound is not the early phase of withdrawal but a homeostatic response that differs from it, analogous to tardive dyskinesia from neuroleptics.⁵ Finally, the longstanding adverse cognitive side effects of benzodiazepines are liable to change the vocational and social roles of the patient. These adverse effects include impairments of memory, learning, and performance as well as disinhibition. Agitation, depersonalization, and perceptual distortion can occur during withdrawal from alprazolam.⁶ Short-acting benzodiazepines, such as alprazolam, might be associated with more intense rebound anxiety or withdrawal symptoms, so that psychological dependence, because it is reinforced by these phenomena, might occur more often.⁷

Although there were no physical signs of withdrawal, psychological dependence apparently contributed to the patient's abandonment of her treatment plan. Successful treatment of benzodiazepine dependence can require regular efforts for many months to treat psychological withdrawal symptoms. Clinical experience suggests that once older patients have taken benzodiazepines for more than a few months, they can become psychologically as well as physically dependent on them. Although physical dependence is associated with a clear-cut discontinuation syndrome in elderly as well as in younger patients, psychological dependence can be more intense in elderly patients. In psychological dependence, elderly patients are reluctant to discontinue a benzodiazepine even if continued therapeutic efficacy is uncertain.⁸ For this patient, we see this hospitalization as an initial phase of treatment for a chronic condition.

Rebound effects are more distinct and severe when medication effects vary rapidly with time, as with benzodiazepines that have a short half-life. Abrupt discontinuation of steady doses of a benzodiazepine results in a sequence of withdrawal symptoms. The earliest phase is dominated by somatic

anxiety symptoms, including agitation, irritability, restlessness, hypervigilance, jumpiness, and insomnia. It tends to begin within 1 to 4 days of discontinuation, depending on the half-life of the particular drug. With the short half-life of alprazolam, these early-phase withdrawal symptoms eventually begin to surface between regular doses, ie, as rebound.

Concern regarding benzodiazepine use in elderly patients focuses on the potentials for cognitive impairment and for exacerbation of age-associated or dementia-related decline in mental function. Acute treatment with benzodiazepines can impair anterograde memory and concentration, although the degree of impairment varies widely among elderly patients.⁹⁻¹⁴ Generally, elderly long-term users of benzodiazepines are less likely to report cognitive decline than are new users or short-term users.¹⁵ Elderly patients eliminate alprazolam more slowly than young patients and usually do not develop tolerance as rapidly or to the same extent.¹⁶ In view of the advanced age and relatively small body mass of our patient, this dose she took is probably equivalent to 1 mg four times a day or more for a nonelderly adult.¹⁷ Moreover, in view of her repeated demands for additional doses, she might have taken higher doses of alprazolam before admission than she admitted.

Panic attacks are discrete periods of intense fear and discomfort. Diagnostic and Statistical Manual of Mental Disorders – IV (DSM IV) criteria of panic disorder include that these attacks be recurrent and unexpected.¹⁸ At least one attack must be followed by 1 month or more of persistent worry about additional attacks or their implications and a major change in behavior related to the attacks. Our patient met these criteria. The requirements for somatic anxiety symptoms in panic attacks were met by the patient's report of a sense of dying from heart attack, impending death and racing heart, chest pain, flushing, choking, and shakiness. Accordingly, our patient met all DSM IV criteria for panic disorder except the causative alprazolam rebound effects.

Alprazolam might be the most extensively studied of all benzodiazepines in panic disorder. The first cross-national collaborative panic study found that alprazolam was more effective than placebo in an 8-week trial.² Alprazolam was more effective than placebo in 8-week trials in two subsequent studies.^{19,20} Abrupt discontinuation of alprazolam

after 8 weeks of treatment was followed by a 27% incidence of withdrawal panic attacks and a 35% incidence of withdrawal syndrome, which contrasts with no incidence of such effects in patients who had received placebo.²¹ These findings provide a precedent for our present observation. The present case serves to illustrate the potential severity of alprazolam rebound and how its long-term use can exacerbate the symptoms for which it was originally administered.

It may be worthwhile to use benzodiazepines to treat anxiety disorders in a manner that avoids rebound effects and chronic neuropsychological impairment, such as by daily administration for less than 2 weeks or administration less frequently than daily of a short-acting agent. The regimen might be best in conjunction with an antianxiety drug that does not have tolerance or rebound effects, eg, a serotonergic agent such as citalopram or buspirone.

A literature review found many drugs and chemicals that appear to induce or exacerbate panic attacks or panic disorder. Selective serotonin reuptake inhibitors (SSRIs), neuroleptics, isoproterenol, cocaine, pentagastrin, lactate, yohimbine, and carbon dioxide can induce panic attacks.²²⁻³⁰ Oral and depot contraceptives can induce panic disorder.^{31,32} Flumazenil provocation of panic attacks³³ and methyldioxymethamphetamine (MDMA) (Ecstasy) precipitation of panic disorder³⁴ have been reported. The present case is the first report of alprazolam-induced panic disorder; we do not believe it to be rare, but rather simply unrecognized as a medication effect.

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