Complicated Withdrawal Phenomena During Benzodiazepine Cessation in Older Adults

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The cause of prolonged or recurrent symptoms following the cessation of long-term benzodiazepine use is proposed to be related to downregulation and allosteric decoupling of the $\gamma$-aminobutyric acid/benzodiazepine receptor complex. This case series describes 2 patients with prolonged (>2 weeks) recurrent complications during attempted tapering of benzodiazepine doses after long-term treatment. Excited catatonia developed in a 90-year-old woman, and prolonged delirium developed in a 69-year-old woman. Both patients showed improvement of symptoms after resumption of higher doses of benzodiazepine treatment and recurrence of symptoms when the dose was again lowered. Caution should be exercised regarding the long-term use of benzodiazepines in older adults (aged $\geq$ 65 years). Tapering of benzodiazepines in older patients after long-term treatment may require slow decreases in dose over long periods. Psychotherapeutic interventions, such as brief cognitive therapy with psychoeducation and motivational enhancement, and osteopathic manipulative treatment to decrease paravertebral muscle tension may be beneficial during the tapering process.

Keywords: benzodiazepines, medication cessation, medication withdrawal

Benzodiazepines are identified as potentially inappropriate medications for use in older adults (aged $\geq$ 65 years) in the American Geriatric Society Beers Criteria, with recommendations against prescribing these medications to geriatric patients. Benzodiazepine use has been associated with a variety of adverse outcomes, including falls, fractures, impaired cognition, and dementia. However, benzodiazepines continue to be widely prescribed for older adults. In 2008, approximately 8.7% of US adults aged 65 to 80 years were prescribed benzodiazepines over the course of a year. A 2016 analysis of the percentage of benzodiazepine visits of all outpatient encounters revealed a rate of 6.6% among patients aged 80 years or older. The present article presents unusually difficult problems encountered during attempted tapering of benzodiazepines in 2 older adults.

Reports of Cases

Case 1

Ms A., a thin 90-year-old woman who had been prescribed 1.0 mg of clonazepam twice per day by her primary care physician for about 4 years for anxiety, complained of...
unsteadiness and falling. She was also taking 50 mg of sertraline daily for anxiety and 25 μg of levothyroxine daily for hypothyroidism. It was decided to taper the clonazepam to a dose of 0.5 mg in the morning and 1.0 mg at night.

Five days later, she presented to the emergency department with severe anxiety and tremulousness. She was given 1 mg of lorazepam intramuscularly, which gave her relief. The next day, she presented to the emergency department with more severe symptoms. She was agitated, at times worsening without apparent reason or stimuli. Her heart rate was 76 beats/min and blood pressure, 128/70 mm Hg. She demonstrated intermittent movements of her arms (crossing and uncrossing) and marching-like movements of her legs. She had odd mannerisms, such as touching her chin repetitively and occasional frowning and grimacing. Computed tomography of the head, complete blood cell count, and chemistry analysis results were unremarkable. She was thought to have excited catatonia; with 4 of 12 diagnostic criteria present, she met Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria for a diagnosis of Catatonic Disorder Due to Another Medical Condition (benzodiazepine withdrawal), ICD 10 Code F06.1.8 She was hospitalized and treated with 1 mg of lorazepam intramuscularly as needed to control her symptoms, receiving 4 doses over a period of 12 hours. The catatonia did not fully resolve until the fourth dose. She was discharged with a prescription for 1.0 mg of clonazepam to be taken twice daily.

Subsequent attempts to taper the patient’s clonazepam dose were difficult, and she was only able to tolerate decreases of 0.25 mg at a time, still with considerable discomfort. Even these small decreases in doses resulted in noticeable anxiety and agitation, with periodic recurrence of symptoms of excited catatonia similar to those described above, although not as severe. Attempts to decrease the dose more frequently than monthly also resulted in worsening of these symptoms. Ultimately, Ms A. was able to discontinue clonazepam after 6 months of tapering. She had no recurrence of agitation or excited catatonia.

Case 2
Ms B., a 69-year-old woman with a history of hypothyroidism, hypertension, coronary artery disease, and gastroesophageal reflux disease, was taking 100 μg levothyroxine daily, 200 mg of labetalol twice per day, 25 mg of losartan daily, and 40 mg of pantoprazole daily. She had been taking a variety of benzodiazepines (which she sometimes misused) for anxiety since her teenage years. Most recently, she had been taking 2 mg of lorazepam 3 times per day. During a stressful event (the end of her mother’s life), she “double dosed” the medication, depleting the prescription prematurely. Thus, she experienced withdrawal and was hospitalized. She was initially disoriented, with fluctuations in her level of consciousness, but these symptoms improved with 10 mg of diazepam 3 times per day. Workup revealed unremarkable findings on magnetic resonance imaging, complete blood cell count, blood chemistry analysis, thyroid stimulating hormone level, and urinalysis, and negative findings on hepatitis A, B, and C and HIV screening. At discharge, she was prescribed a 3-week tapering course of diazepam followed by discontinuation of the drug.

Within a few days of the last dose of diazepam, Ms B. had difficulty with concentration and problems with memory that fluctuated during the day and worsened at night. At times, she had difficulty articulating words clearly. She had occasional muscular twitching and jerks. These findings were consistent with a diagnosis of delirium.9 Because her husband did not like the hospital, he cared for her at home for several weeks and reported that she often had trouble with memory and concentration during that time. He finally took her to a psychiatric clinic for evaluation. There, she demonstrated cognitive impairment (oriented to person, place, and year, but not to month or date; unable to perform calculations; unable to draw a clock; recalled 0 of 5 words from a previously learned list of simple words). Her Montreal Cognitive Assessment (MOCA) score was 14/30. The cognitive impairment had not been noted at previous visits to her primary care physician. Her husband insisted that her problems with
cognition had developed with cessation of the diazepam. She was prescribed 1.0 mg of clonazepam twice daily. A week later, her cognition was noticeably improved (MOCA score, 20). Two weeks later, her MOCA score improved to 25, and her husband described her as “almost normal.”

Because of her history of misusing her medication, it was felt that she could not be treated with benzodiazepines long term. Her clonazepam dose was decreased to 1.5 mg daily. Her husband reported that she started getting confused again about 5 days later. At her next visit, the MOCA score had dropped to 20. The dose was increased back to 1.0 mg twice daily, and she began to think more clearly (MOCA score, 24). Subsequently, she underwent tapering of the clonazepam in increments of 0.25 mg per dose over a period of several months. She had some difficulty because of rebound anxiety but was able to tolerate the process. A month after the final dose, her MOCA score was 26.

**Discussion**

Patients with benzodiazepine withdrawal commonly present with anxiety, insomnia, dysphoria, irritability, nausea, vomiting, anorexia, tremor, and, sometimes, seizures. In general, withdrawal symptoms abate within 2 weeks. In the current case series, 2 older adults with prolonged benzodiazepine use (>2 weeks) had recurrent conditions (one excited catatonia, one delirium) following cessation of long-term use of benzodiazepines.

Older adults are especially vulnerable to the effects of benzodiazepines. Usual doses can produce toxic levels. Long-term treatment has been reported to cause impairment in several cognitive domains, with cognitive dysfunction not fully returning to levels that matched benzodiazepine-free controls after cessation of treatment. Benzodiazepines have been associated with the development of dementia, with greater risk at higher cumulative doses. A study of 1796 patients with Alzheimer disease showed that taking a benzodiazepine for 3 to 6 months increased the risk by 32%, and taking a benzodiazepine for more than 6 months increased the risk by 84%. Enlargement of cerebrospinal fluid spaces has also been demonstrated in persons with a history of long-term benzodiazepine abuse.

Catatonia is a rare adverse effect of benzodiazepine withdrawal. Oldham and Desan identified 26 cases (average age, 56 years) of catatonia onset upon alcohol or sedative-hypnotic withdrawal in the literature, all principally with catatonic stupor, with a typical onset of 3 to 7 days after discontinuation and duration of 3 to 10 days. Lebin and Cerimele described a 79-year-old woman who had to continue long-term, low-dose clonazepam treatment because she had recurrent catatonia when attempts were made to discontinue the medication.

Excited catatonia related to benzodiazepine withdrawal, as seen with Ms A., has not been previously described, to our knowledge. Delirium tremens is a well-known complication of withdrawal from sedative hypnotic drugs. However, delirium lasting more than several days in the context of attempted very-slow tapering of benzodiazepine dose, which occurred with Ms B., has not been previously reported, to our knowledge.

A possible mechanism for the complicated withdrawal symptoms described in the present article involves the effects of benzodiazepines on γ-aminobutyric acid (GABA) and GABA receptors. Benzodiazepines affect benzodiazepine receptors, which in turn enhance the effect of GABA by positive allosteric modulation of the GABA<sub>A</sub> receptor. This action results in decreased neuronal excitability and produces a calming effect. However, long-term benzodiazepine exposure results in downregulation and allosteric decoupling of the GABA/benzodiazepine receptor complex. Downregulation of benzodiazepine receptor binding and of GABA receptor function is closely associated with behavioral tolerance to benzodiazepines. After many years of treatment, particularly in older adults, this downregulation could become very difficult to reverse, resulting in prolonged or recurrent withdrawal symptoms. How long it would
take for these receptors to return to their normal state in an older adult is unknown and might explain the occurrence of prolonged or recurrent withdrawal symptoms. Long-term use of benzodiazepines is particularly hazardous in older adults. In light of the risks and adverse effects, tapering and discontinuation should be considered in older adults who do not have unequivocally clear indications to remain taking benzodiazepines. The risk of complicated withdrawal phenomena may be higher in this age group.

There is insufficient evidence to support the use of a particular benzodiazepine for tapering in older adults, but many physicians recommend switching to a long-acting benzodiazepine, such as diazepam or clonazepam, and then gradually decreasing the dose. No clear evidence suggests the optimum rate of tapering, and schedules vary. Paquin et al performed a systematic literature review of 28 studies of older outpatients tapering from long-term benzodiazepine use. Common schedules involved a 25% dose reduction over 1 to 2 weeks until the patients were drug free. A much slower approach is often necessary in older adults who have received long-term benzodiazepine therapy as described in the current cases.

Patients who have been taking benzodiazepines for many years may resist decreasing their benzodiazepine dose, so physicians should exercise care and provide education about tapering and the risks associated with continuing the current dose when proposing tapering. Discontinuation of long-term benzodiazepine use in older adults is feasible. An appropriate pharmacologic strategy that provides adequate coverage of withdrawal symptoms over an adequate amount of time is essential. Psychotherapeutic interventions, such as brief cognitive therapy with psychoeducation and motivational enhancement, may be particularly helpful. Osteopathic manipulative treatment could be a useful adjunct for helping lessen the severity of certain benzodiazepine withdrawal symptoms.

Conclusion

Long-term use of benzodiazepines in older adults may lead to a variety of adverse outcomes, and gradual, long-term tapering and eventual discontinuation of these medications should be considered. Complicated and prolonged withdrawal phenomena may occur in some patients, necessitating slow decreases in dosage over a long period. Further research is needed in this area.

References


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