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Tinnitus associated with benzodiazepine withdrawal syndrome: A case report and literature review

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Abstract

In light of the ongoing opioid crisis, many have encouraged the medical community as well as local and national US government agencies to reconsider the prevalent use of benzodiazepines. As prescribers continue to weigh the risks and benefits of ongoing benzodiazepine use, care must be taken when the decision is made to taper and discontinue these medications in patients who have been maintained on them chronically. We present a case of an adult patient maintained on a benzodiazepine for several years who developed tinnitus during a gradual dose taper. This patient developed tinnitus within 7 weeks of gradual reduction of the patient's clonazepam dose to 50% of the original dose in an outpatient clinic. The persistence of these symptoms prevented further dose reductions. Upon review of the available literature, several other cases were identified describing development of tinnitus upon discontinuation or tapering of a benzodiazepine. In weighing the risks and benefits of chronic benzodiazepine therapy, tinnitus must be considered as a rare but debilitating and long-term risk of benzodiazepine withdrawal. Providers must be prepared to individualize benzodiazepine tapers and be vigilant about emergence of withdrawal symptoms to prevent undue stress in patients.

Keywords: benzodiazepine, tinnitus, withdrawal, clonazepam, taper

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Background

Benzodiazepines, such as clonazepam, diazepam, and lorazepam, are approved by the Food and Drug Administration (FDA) to treat several conditions, including anxiety disorders, epilepsy, and alcohol withdrawal.[1-4] According to data from the Medical Expenditure Panel Survey and the Centers for Disease Control and Prevention, benzodiazepine prescriptions have increased in both number of adults receiving prescriptions (from 8.1 to 13.5 million) and total quantity dispensed (from 1.1 to 3.6 kg lorazepam equivalents per 100 000 adults) from 1996 to 2013.[5] Additionally, an FDA-mandated black box warning was added to all prescription benzodiazepine and opioid drug labels in August 2016 due to risk of fatality from overdose.[6] Both the risk for addiction with benzodiazepines and the increased risk for mortality when used concomitantly with opioids have driven recent scrutiny of prescribing patterns.[7,8] As prescribers weigh the risks and benefits of ongoing benzodiazepine use, care must be taken when deciding to taper and discontinue these medications after long-term use. Tapering is required due to risks of rebound anxiety, seizures, and other withdrawal symptoms associated with abrupt discontinuation. We present a case of an adult patient maintained on clonazepam for 14 years who developed tinnitus, a lesser known but documented complication of benzodiazepine withdrawal, during a gradual dose taper.

Case Report

This is a case of a 40-year-old white male who presented to the Behavioral Health Services Pharmacy Clinic for

TABLE: Benzodiazepine taper course used in this study

Visit No.	Time Since Taper Initiation, wk	Clonazepam Total Daily Dose, mg	GAD-7 Score at Visit	Goal Clonazepam Total Daily Dose by Next Visit, mg	Tinnitus Status
1	0	2	0, No anxiety	1	None
2	5	1.5[a]	0, No anxiety	1	None
3	7	1	GAD not administered	1	Initial report
4	9	1	18, Severe anxiety	1	Continued
5	11	1.5	12, Moderate anxiety	1.5	Decreased severity
6	15	1.5	0, No anxiety	1.5	Decreased severity
7	23	1.5	7, Mild anxiety	1.5	Decreased severity

GAD = generalized anxiety disorder.

[a]Patient did not have access to clonazepam for 2 days, then resumed at 1.5 mg total daily dose.

initiation of a benzodiazepine taper. His anxiety had been well controlled for 14 years on venlafaxine XR 150 mg by mouth once daily and clonazepam 1 mg by mouth twice daily, and these were the only medications he was currently taking. The past medical history was significant for hyperlipidemia and spondylolysis of the lumbar region. His most recent labs (complete blood count, lipid panel, comprehensive metabolic panel) had been completed 3 months prior and were within normal limits with the exception of slight elevations in his total cholesterol, triglycerides, and low-density lipoproteins. He reported his anxiety was well controlled and expressed interest in tapering off of both venlafaxine and clonazepam. Considering the potential risks associated with long-term benzodiazepine use, a slow taper was initiated (Table). To minimize complications of withdrawal, a venlafaxine taper was not simultaneously initiated.

At week 5 of the taper, he had completed the reduction to 0.75 mg by mouth twice daily (a 25% dose reduction) but had not further decreased to 0.5 mg twice daily for an unknown reason (see the Table). He reported feeling unwell following a 2-day lapse in clonazepam before obtaining a refill and resuming 1.5 mg by mouth once daily at which time his symptoms improved back to baseline. As he was still interested in tapering, he was instructed to decrease his clonazepam dose to 1 mg in 2 divided doses daily (a 50% reduction from his initial starting dose).

At week 7, he returned and reported decreasing his dose to 1 mg daily in the morning despite the recommendation of splitting the total daily dose into twice daily dosing. For the first time in the taper, he also reported trouble concentrating, tinnitus, and difficulty sleeping secondary to the tinnitus. Due to these withdrawal symptoms, the patient was instructed to maintain his current daily dose but take 0.5 mg in the morning and 0.5 mg at bedtime to allow for more consistent levels throughout the day.

He presented to the clinic at week 9 endorsing continued tinnitus and worsened anxiety. As a result, clonazepam was maintained at the current dose. The patient returned at week 11 and reported an episode of tachycardia with a heart rate of 130 beats/min, after which he self-increased his total daily dose of clonazepam back to 1.5 mg (0.5 mg in the morning and 1 mg at night). He stated that his symptoms of worsened anxiety and tinnitus had not resolved but had been ameliorated since increasing his dose. The tinnitus was no longer interfering with his sleep. Due to the intensity of these symptoms experienced at the 1 mg total daily dose, the current 1.5 mg daily dose was continued, and the plan was to reevaluate in 1 month.

At visits occurring at weeks 15 and 23 of the taper, the patient's tinnitus had improved in overall severity, but the impact it had on his sleep varied. He planned to follow up in about 3 months for symptom reevaluation and reassessment of the taper plan. During a primary care visit, the patient was offered an ear, nose, and throat consult and declined. At the time of this report, the patient remains at the total daily dose of 1.5 mg clonazepam (a 25% reduction from initial dose). He continues to report tinnitus that interferes with his sleep at times.

Discussion

When benzodiazepine use is discontinued, it is necessary to taper the dose slowly to minimize withdrawal symptoms, which may include rebound anxiety and seizures.[8] Recommendations regarding optimal tapering methods include slowly decreasing the dose over 3 to 6 months, allowing for flexibility in the taper schedule, and considering a switch to a long-acting benzodiazepine prior to tapering.[9,10] More specifically, recommendations exist to decrease the dose initially by 25% every 2 weeks until a 50% dose reduction has been completed, followed by maintaining the dose for 1 to 2 months and then resuming

the taper by reducing the dose by 25% every 2 weeks.[9] Alternatively, a dose reduction of 10% to 25% every 4 weeks has been recommended.[9] Tinnitus is infrequently reported as a symptom of benzodiazepine withdrawal. The PubMed database was searched using the terms *benzodiazepine* and *tinnitus*. Relevant articles' references were also reviewed. The search yielded 4 articles.[11-14]

In an outpatient study by Schweizer et al,[11] 63 patients on daily benzodiazepines for at least 12 months underwent a taper with a 25% dose reduction per week. Withdrawal severity was measured using a 34-item physician withdrawal checklist.[15] Nine of the 63 patients reported tinnitus as a withdrawal symptom. Seven of 25 patients tapering off of long half-life agents (diazepam and clorazepate) experienced tinnitus compared to only 2 out of 38 patients tapering off of short half-life agents (lorazepam and alprazolam; $P < .01$). This finding is unexpected as it is often recommended to convert patients on short-acting benzodiazepines to long-acting agents to minimize withdrawal symptoms during the taper.[9] However, these findings may be influenced by other factors, such as longer durations of benzodiazepine treatment in the long-acting benzodiazepine group as compared to those on short-acting agents.

Ashton[12] presented the effects of benzodiazepine tapering in 12 patients taking benzodiazepines for time periods ranging from 3 to 22 years. All patients taking benzodiazepines other than diazepam were switched to an equivalent dose of diazepam for the final taper; the conversion used was 10 mg diazepam for every 1 mg lorazepam. Total daily diazepam doses were reduced by approximately 25% to 50% per day and administered 2 to 3 times daily. Initial doses were not reported. Tapering was generally completed within 2 weeks, and withdrawal symptoms were monitored with a 55-symptom checklist that was developed based on the author's past clinical experience. Symptoms were rated on a scale of 0 (none) to 3 (severe). Patients were assessed at baseline and followed at weekly or biweekly intervals for up to 6 months. Prior to starting the taper, 7 patients were experiencing tinnitus at baseline and 1 patient was on a benzodiazepine for treatment of tinnitus. Following taper initiation, there was an initial increase from 7 to 9 patients reporting tinnitus at the 2-week mark. Both the number of patients experiencing tinnitus as well as the severity of tinnitus decreased as time went on. Although the rapid taper schedule in this observational study differs from that of this case, this study demonstrates a potential link between benzodiazepine withdrawal and development of tinnitus. It must be noted, however, that a majority of subjects were experiencing tinnitus at baseline.

In a study by Busto et al,[13] 40 patients on long-term benzodiazepine therapy were transitioned to either placebo or the diazepam dose equivalent of their original benzodiazepine dose. Those in the diazepam group received gradual dose reductions over 8 weeks. Patients receiving placebo reported more symptoms and a higher severity of symptoms—including tinnitus—than those who received diazepam. Two patients experienced tinnitus for 6 to 8 months after benzodiazepine discontinuation.

In a subsequent publication, Busto et al[14] described 3 cases of tinnitus development after benzodiazepine withdrawal. The first 2 of these cases were observed within the study discussed previously. The first, a 57-year-old male taking diazepam 25 to 30 mg daily for 3 years, began experiencing tinnitus without hearing loss when his dose reduction reached 5 mg total daily dose during a 2-month taper. At a 6-month follow-up, he still reported tinnitus. Due to this unique adverse effect, a double-blind, controlled, 1-subject study was conducted in which, after 7 days, this patient was given either diazepam or placebo in increasing doses weekly. Tinnitus severity was self-reported daily as either "no change," "better," or "worse." Results showed an inverse relationship between the total plasma diazepam concentration and the severity of the tinnitus. The patient reported worse tinnitus when receiving placebo. It must be noted, however, that the likelihood of the patient detecting which he was receiving—placebo or diazepam—is high and may have affected results. In the second case, a 34-year-old male taking 10 mg diazepam daily for 8 years developed tinnitus 4 days after stopping diazepam. By 6 months, both frequency and duration of tinnitus were decreased, and symptoms resolved by 1 year. The final case described a 49-year-old male taking diazepam as needed for anxiety (between 5 and 20 mg daily) for 12 years who experienced tinnitus after diazepam discontinuation. He reported that tinnitus would resolve 15 minutes after diazepam administration but would return in about 4 hours. He never completely discontinued use due to this adverse event.

Pathophysiology of tinnitus is not well characterized and is thought to have multiple potential causes,[16-19] including medications, traumatizing sound, elevated cortisol levels, decreased neuronal inhibition via gamma aminobutyric acid (GABA), Ménière disease, and sensory deprivation following hearing loss. Changes in GABA neurotransmission have been associated with development of tinnitus due to the observation that the administration of benzodiazepines, which act as positive allosteric modulators of GABA receptors, can result in decreased tinnitus symptoms.[16,17] According to the Academy of Otolaryngology–Head and Neck Surgery clinical practice guideline for tinnitus, recommended treatments to manage tinnitus that persists beyond 6 months include sound therapy, cognitive behavioral therapy, and self-help books.[20]

Risk factors for tinnitus include ear infections, hearing loss, impacted cerumen, migraine, multiple sclerosis, epilepsy, head or neck injury, temporomandibular joint disorder, hypertension, rheumatoid arthritis, diabetes, hypothyroidism, anxiety, depression, and ototoxic medications.[16] The patient in this case report experienced chronic anxiety, which was well controlled on venlafaxine extended-release and clonazepam. He developed tinnitus after a 50% dose reduction of his clonazepam dose. The patient denied any hearing loss, changes to usual lifestyle, or medication changes during the taper. He self-reported good medication adherence. However, it was discovered that at least 2 days were missed between visits 1 and 2, which may be a risk factor for development of tinnitus as reported in the first case by Busto et al.[13]

Conclusion

Considering recent concerns regarding use of concomitant opioids and benzodiazepines and overuse of chronic benzodiazepines, providers must be aware of risks of benzodiazepine withdrawal beyond rebound anxiety and seizure precipitation. In weighing the risks and benefits of continued benzodiazepine treatment, tinnitus must be considered as a rare but debilitating and long-term risk of benzodiazepine withdrawal. Although the onset of tinnitus during benzodiazepine taper is documented in the literature, the scarcity of its documentation along with limitations in those reports do not provide enough evidence to make specific recommendations regarding the prevention of benzodiazepine withdrawal–induced tinnitus. Providers must be prepared to individualize benzodiazepine tapers and be vigilant about emergence of withdrawal symptoms to prevent undue stress to patients. In patients who develop persistent tinnitus, sound therapy and cognitive behavioral therapy may be recommended.[20]

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