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Case Report

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Gabapentin (Neurontin): An Adjunct for Benzodiazepine Withdrawal - A Case Series

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Introduction

Benzodiazepines are among the most commonly prescribed pharmaceuticals in medical practice. A 2009 survey suggested that 5.2% of adults had been prescribed a benzodiazepine[1]. Commonly utilized for the management of anxiety related to panic disorder, generalized anxiety and other related disorders, they have demonstrated efficacy as hypnotics, muscle relaxants and anticonvulsive agents. Benzodiazepines are used in treating conditions related to acute anxiety[2]. All benzodiazepines are classified as Schedule IV under the Controlled Substances Act and have a potential for abuse. While relatively safe in overdose, benzodiazepines can be lethal when combined with other respiratory depressants such as alcohol or opioids[3].

Since 1961 when the first benzodiazepine, chlordiazepoxide, was introduced there has been controversy related to their use over months and years. Use of benzodiazepines over extended periods may result in the development of tolerance and vulnerability to physiologic withdrawal. Abrupt withdrawal is associated with a syndrome that may include anxiety, insomnia, tachycardia and hypertension. Complications of serious withdrawal include grand mal seizures, hallucinations and autonomic hyperactivity[4]. The percentage of individuals who use benzodiazepines increases with age from 2.6% (eighteen to thirty-fiveyears) to 8.7% (sixty-five to eighty years). The elderly are more likely to be prescribed benzodiazepines chronically (31.4%) compared to young adults (14.7%)[1].

When substance abuse is associated with mental health diagnoses, there is increased a risk for misuse of some drugs including benzodiazepines. This often results in a recommendation for a withdrawal of these drugs. Controlled benzodiazepine withdrawal may require weeks or months. The use of a transitional agent that reduces discomfort associated with withdrawal would be helpful in facilitating discontinuation of chronic benzodiazepine use. Within the psychiatric inpatient setting, clinicians will commonly encounter patients with who have misused these agents along with opioids, alcohol, and other sedatives. We reviewed literature for the use of gabapentin in benzodiazepine dependence or withdrawal and were unable to find any data. We describe six cases where use of gabapentin during benzodiazepine withdrawal resulted in a well-tolerated accelerated withdrawal.

Case Series

Case 1

A middle-aged female presented to the emergency department after an intentional clonazepam overdose. She reported ingesting thirty 1 mg tablets intentionally. She reported taking clonazepam 1 mg three times daily (tid) for the previous five months. She was admitted to the inpatient psychiatric program. Gabapentin 300 mg tid was started for anxiety, and clonazepam was tapered from 1 mg tid to 0.25 mg tid on an as-need basis. On day four clonazepam was discontinued. The patient denied withdrawal symptoms and mood rapidly improved. After eight days, she was discharged with diagnoses of depression, generalized anxiety disorder, and benzodiazepine use disorder. This patient denied cravings or significant discomfort during the taper. Clinical Institute Withdrawal Assessment (CIWA), an objective measurement of withdrawal intensity for alcohol or benzodiazepines, was measured daily and

scores were consistently under 6.

Case 2

An elderly woman presented to the emergency room with complaints of overwhelming anxiety despite using clonazepam 2 mg four times daily for the previous several years. She requested additional clonazepam despite awareness of its harmful effects. She was admitted to the inpatient psychiatric unit for further evaluation and stabilization. She endorsed panic attacks, intermittent confusion and subjective memory loss for several months prior. On day one, clonazepam was tapered to 1 mg tid along with initiation of gabapentin 300 mg tid. Over the next two days she became increasingly more anxious as the clonazepam was tapered. Subsequent review revealed that she had been refusing gabapentin. After assurance of administration, clonazepam was rapidly tapered with few complaints of anxiety, insomnia or irritability. No physiological signs of withdrawal were noted. Clonazepam was discontinued on day five. The patient noted markedly reduced anxiety on a regimen of gabapentin 600 mg tid. She was discharged after six days with a diagnosis of depression, panic disorder, and benzodiazepine use disorder.

Case 3

A middle-aged female was brought to the emergency after vandalizing property and displaying hostility towards her boyfriend over the prior three days. Staff learned that she had recently inflicted a superficial laceration to her wrist and took eight 1 mg clonazepam tablets after an argument. The patient denied this was a suicide attempt but rather a misuse of medication to control her anxiety. She had been prescribed clonazepam 1 mg twice daily for the past three years. Over the previous two months, she had been using between 6 and 10 mg daily. She was admitted to the inpatient psychiatric unit. On day one, clonazepam was decreased to 0.5 mg twice daily and gabapentin 300 mg tid was initiated. Over the next two days, clonazepam was further tapered to 0.5 mg at bed time and then discontinued. On day three gabapentin was titrated to 600 mg tid after persistent complaints of anxiety. Throughout the tapering period, there were no symptoms of autonomic arousal noted and subjective anxiety was minimal. CIWA measured between 9 and 4.

Case 4

An elderly female with a history of bipolar disorder and alcohol use disorder presented to the emergency with complaints of worsening depression and a suicide plan. She had discontinued lithium and fluoxetine for five days and one month respectively and had increased her use of benzodiazepines and alcohol over the previous few days. She reported taking clonazepam 0.5 mg tid for anxiety and diazepam 5 mg at bedtime for sleep for the prior six years. She admitted to drinking 80 ounces of beer in the previous week. On first encounter, she was agitated and displayed mood labiality with crying spells. She was started on lurasidone 40 mg and received 0.5 mg clonazepam at bedtime. On day two, gabapentin 300 mg tid was begun and she received 0.5 mg clonazepam at bedtime. On day three, benzodiazepines were discontinued and gabapentin was titrated to 600 mg tid due to complaints of anxiety. CIWA score was 9. The following day lurasidone was increased to 80 mg daily. Throughout the remainder of the hospitalization, she remained free of symptoms of benzodiazepine withdrawal with CIWA scores consistently below 3.

Case 5

A middle-aged female maintained on opiates for pain due to endometriosis had been prescribed Clonazepam for five years. She was brought to the emergency with sudden-onset lethargy, confusion and visual hallucinations. She reported visual hallucinations. Upon presentation blood alcohol level was undetectable and urine toxicology positive for benzodiazepines and opiates. She had been using clonazepam 4 mg daily over the previous six months. Her last reported use was two days prior to admission. Diazepam 5 mg tid and gabapentin 300 mg tid were begun with CIWA monitoring. She tolerated a complete taper of diazepam over the next three days. Within 48 hours, she was free of significant anxiety, hallucinations, or cognitive disturbances. She was discharged with a DSM-5 diagnosis of substance withdrawal delirium. Maximum CIWA score of 6 was recorded during first twenty-four hours.

Case 6

A middle-aged male with a history of multiple psychiatric admissions for depression presented after overdosing on thirteen 0.5 mg alprazolam, thirteen 5 mg oxycodone, and two fentanyl patches. He acknowledged suicidal intent. He admitted to using alprazolam 1 to 1.5 mg at bedtime for the previous six years. With chronic depression he suffered from chronic arthritic back pain. Buprenorphine/naloxone was initiated for management of opioid dependence. Gabapentin 600 mg tid was initiated on day two to assist with pain management. Clonazepam 0.5 mg twice daily was begun on day two and decreased to 0.25 mg twice daily on day three. Clonazepam was discontinued completely on day five. The patient was discharged after seven days with diminished anxiety, improved sleep and pain well controlled. CIWA was not higher than 1.

Table 1: Summary of cases - patient characteristics, observations and management

Case	Age Group	Gender	BZD	BZD dose	Duration on BZD	Gabapentin dose	BZD at discharge	Days required for BZD withdrawal	CIWA range
1	mid-age	F	Clonazepam	1 mg TID	5 months	300mg TID	none	4	0- 6
2	elderly	F	Clonazepam	2 mg QID	years	300rng TID	none	6	
3	mid-age	F	Clonazepam	1 mg BID	years	600mg TID	none	6	9 - 4
4	elderly	F	Clonazepam / Diazepam	0.5 mg TID/5 mg QHS	years	300mg TID	none	4	9 - 0
5	mid-age	F	Clonazepam	4 mg daily	6 months	300mg TID	none	6	6 - 0
6	mid-age	M	Alprazolam	1 - 1.5 mg QHS	years	600mg TID	none	7	1- 0

Summary

Our patients met the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria for Benzodiazepine Use Disorder[4]. Each patient tolerated a withdrawal regimen with minimal signs ordinarily encountered during tapering from these agents. The course of benzodiazepine withdrawal was accelerated when gabapentin was added as adjunctive therapy.

Discussion

Gabapentin has a high affinity for voltage-gated calcium channels, but the exact mechanism of its effects remains unclear[5]. When gabapentin was added to a regimen of structured withdrawal, patients on long-term benzodiazepines tolerated a rapid withdrawal with minimal discomfort or development of physiological changes often encountered in this circumstance. Importantly, patients also denied cravings for benzodiazepines. Recent reports suggest efficacy of gabapentin in the treatment of alcohol dependence[6]. It has been suggested that it may also have efficacy in treating alcohol withdrawal[7]. One limitation in our study is that there is heterogeneity in the patient types and co-administered drugs. However, value in this study lies in the observation of a common effect of ameliorating withdrawal signs and symptoms once gabapentin was initiated. Gabapentin dosing was decided by the severity of pain and anxiety complaints. Even though the patients may have been taking other medications, it was only with gabapentin where the clinicians observed improvement of symptoms classically associated with benzodiazepine withdrawal. It should be noted that follow up information regarding the patients status was not available, and is beyond the scope of this case series. Another limitation in our study is the possibility of other medications contributing to the low CIWA scores. Since CIWA can reflect risk to developing seizures, gabapentin has the property of increasing seizure threshold, and therefore the most likely contributor to the low CIWA scores. While CIWA was helpful in measuring the severity of withdrawal, it was not used as a gauge for gabapentin titration. While the authors had direct contact with the patients described in this paper, a retrospective chart review was used to formulate this study, and is therefore an additional limitation.

Although the development of physiologic dependence is not considered a property, gabapentin is not without its own abuse potential[8]. Reported cases of misuse have included patients with prior histories of substance abuse. There have been some reports suggesting that discontinuing gabapentin may precipitate withdrawal with some similarities to that of benzodiazepine withdrawal[8-10].

Conclusion

Gabapentin may assist in withdrawal signs from chronic benzodiazepines use. We believe that this is the first published data on this topic. A prospective randomized controlled trial with standardized patients could further define the safety and efficacy for use of gabapentin as an adjunct to benzodiazepine withdrawal.

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