CENTER FOR HEALTHCARE INNOVATION AND PATIENT OUTCOMES RESEARCH

Samford University McWhorter School of Pharmacy

# C L I Ps

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## DRUG TREATMENT OF BENZODIAZEPINE DEPENDENCE

Several definitions of substance-abuse disorders are available; however, the International Classification of Diseases, 10th Revision (ICD-10) defines dependence if 3 or more of the following criteria were met in the previous year: "a strong desire or compulsion to take the drug; difficulties in controlling drug use; withdrawal symptoms; evidence of tolerance; neglect of alternative pleasure or interests; and persistent drug use despite harmful consequences". However, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines abuse and dependence based on 11 criteria for substance-use disorders, ranging from mild (in patients meeting 2-3 criteria) to severe (in patients meeting ≥6 criteria). Benzodiazepine dependence presents with doctor shopping; obtaining prescriptions from different pharmacies; and overlapping prescriptions. This issue of *CLIPs* reviews the treatment of benzodiazepine-associated abuse. If you need further information, please contact the Center for Healthcare Innovation and Patient Outcomes Research (CHIPOR) at chipor@samford.edu.

**Soyka M. Treatment of benzodiazepine dependence. N ENgl J Med. 2017;376:1147-1157. DOI:** 10.1056/NEJMra1611832.

### Introduction

- The first benzodiazepine approved for use in the United States was chlordiazepoxide.
- All these agents bind to the GABA type A receptor. The greater the affinity of the GABA receptor, the greater the inhibitory effect of GABA in the central nervous system.
- Benzodiazepines (BDZ) are highly protein-bound agents and are also well-absorbed.
- BDZs are dived into their clinical effects: anxiolytic agents and hypnotic agents.
- These agents are relatively safe for short-term use (2-4 weeks). Dependence typically develops in patients who have been using the agents for > 1 month.
- The most frequent adverse effects associated with BDZ use is drowsiness, lethargy, fatigue, excessive sedation stupor, disturbances of concentration and attention, development of dependence and symptom rebound after discontinuation.

### Prevalence of Benzodiazepine Abuse

- Prescriptions for BDZs have increased dramatically between 1996 and 2013.
- Deaths from overdoses have increased by a factor of 4 (from 0.58 to 3.07 deaths per 100,000 adults). Most of the deaths resulted from a combination of BDZs with other drugs.
- Approximately 46%- 71% of patients using benzodiazepines are also receiving opioid therapy. This combination is associated with an increased respiratory depressant effect of opioids.
- BDZ abuse increases with age. Women use BDZs in the US more than men.

### Clinical presentation

- Sudden BDZ withdrawal has been associated with seizures, delirium and psychosis.
- A unique feature of BDZ abuse is that physical and mental dependence can occur in the absence of tolerance.
- Long-term features of BDZ use are: older patients (>65 years), prescription by a psychiatrist, regular use, use of a high dos, ad concomitant use of psychotropic drugs.

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**Treatment of withdrawal symptoms**

- BDZs should be discontinued gradually over several weeks (e.g., 4-6 weeks or more for patients receiving diazepam >30 mg/day) to prevent seizures and severe withdrawal symptoms.
- Recommendations for tapering include an initial BDZ reduction by 50% every week to reduce the daily dose by between 10%-25% every 2 weeks.
- Most patients benefit from a tapering schedule between 4-6 and 4-8 weeks.
- It is unknown if it is beneficial to switch to a long-acting agent to reduce withdrawal symptoms.
- Although withdrawal is typically done on an outpatient basis, inpatient dose reduction should be considered for patients receiving high doses (e.g., doses ≥ 100 mg of diazepam daily).
- If patients are receiving combination therapy with a BDZ and opioid, the opioid dose should remain constant throughout the taper.
- There is a paucity of information related to which medications can be used for a BDZ taper.
- Treatment for depression and sleep problems include mood stabilizers (e.g., carbamazepine [200 mg twice daily]. In addition, nonbenzodiazepine anxiolytic agents, pregabalin, gabapentin, and beta-blockers can be used.
- Patients with chronic sleep disorder can be treated with trazodone, doxepine, and mirtazapine.

**Prevention of benzodiazepine dependence**

- Discourage use of treatment lasting 2-3 months or more and marked dose increases.
- Encourage interval treatment instead of continuous treatment.
- High risk patients include those who are alcohol and drug dependent, patients who are chronically ill or have chronic sleep disorders, personality disorders, or dysthymia.

**Conclusion**

- Benzodiazepine use is increasing in this country.
- Additional education should be disseminated to prescribers to discourage long term use, and inappropriate use, especially among high-risk patients.
- A gradual tapering of the benzodiazepine dose will reduce symptoms of withdrawal.