

# Benzodiazepines for Generalized Anxiety Disorder

## **Q.** What are benzodiazepines?

**A.** Benzodiazepines are a class of psychoactive drugs with anxiolytic, anticonvulsant, muscle relaxant, and sedative effects (Sieghart, 1994). First discovered in the 1950s, benzodiazepines are now used for a wide range of indications, such as anxiety, insomnia, muscle relaxation, and epilepsy.

## **Q.** What are the potential mechanisms of action underlying benzodiazepines?

**A.** Benzodiazepines exert their effects via modulation of the gamma-amino butyric acid<sub>A</sub> (GABA<sub>A</sub>) receptor. In the central nervous system (CNS), activity is regulated by the balance between excitatory and inhibitory activity. GABA, an inhibitory neurotransmitter, is the most common neurotransmitter in the CNS. Increasing the efficiency of GABA leads to greater inhibition; where excitatory activity is excessive, this inhibitory action may result in clinically desirable effects including anxiolytic and sedative effects (Nutt & Malizia, 2001). Found in high concentrations in the cortex and limbic system, GABA suppresses CNS activity in a relatively nonspecific fashion (Griffin III, Kaye, Bueno, & Kaye, 2013). Benzodiazepines exert their effects via modulation of the GABA<sub>A</sub> receptor. Benzodiazepine receptors are modulatory sites on GABA<sub>A</sub> receptors, and benzodiazepines lower the concentration of GABA required to open the channel of the GABA<sub>A</sub> receptor, thereby facilitating inhibitory GABA activity (Sieghart, 1994).

## **Q.** Are benzodiazepines recommended as a front-line treatment for generalized anxiety disorder (GAD) in the Military Health System (MHS)?

**A.** There is no Department of Veterans Affairs (VA)/Department of Defense (DoD) clinical practice guideline (CPG) for the treatment of GAD.

*The MHS relies on the VA/DoD CPGs to inform best clinical practices. However, in the absence of an official VA/DoD recommendation, clinicians should look to CPGs published by other recognized organizations, and may rely on knowledge of the literature and clinical judgement.*

## **Q.** Do other organizations with CPGs for the treatment of GAD recommend benzodiazepines as a front-line treatment?

**A.** **No.** CPGs published by other organizations do not recommend the use of benzodiazepines as a front-line treatment for GAD.

- The United Kingdom's National Institute for Health and Care Excellence (NICE) states not to offer a benzodiazepine for the treatment of GAD except as a short-term measure during crises (NICE, 2011).
- The Canadian Psychiatric Association recommends benzodiazepines as a second-line treatment, after inadequate response to two first-line agents, or at any time agitation or anxiety is severe (Canadian Psychiatric Association, 2006).

## **Q.** Do other authoritative reviews recommend benzodiazepines as a front-line treatment for GAD?

**A.** **No.** Other authoritative reviews have not substantiated the use of benzodiazepines as a front-line treatment for GAD.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: No reports on GAD were identified.
- Cochrane: No systematic reviews on benzodiazepines for GAD were identified.

**Q. Is there any recent research on benzodiazepines as a treatment for GAD?**

**A.** Benzodiazepines have been shown to be efficacious in the short-term treatment of GAD in systematic reviews (Bandelow et al., 2015; Baldwin, Woods, Lawson, & Taylor, 2011; Mitte, Noack, Steil, & Hautzinger, 2005). However, benzodiazepine treatment is associated with a number of side effects, such as fatigue, dizziness, impaired driving skills, and impaired cognitive function, and long-term treatment may result in dependency (Bandelow, Michaelis, & Wedekind, 2017). In recent years, there has been a shift from prescribing benzodiazepines for GAD (Uhlenhuth, Balter, Ban, & Yang, 1999) to prescribing antidepressants, such as selective serotonin reuptake inhibitors (Baldwin, Allgulander, Bandelow, Ferre, & Pallanti, 2012). Recent research has focused on the comparative efficacy of benzodiazepines and other treatments, with mixed findings (Bandelow et al., 2015; Gomez et al., 2018; Offidani, Guidi, Tomba, & Fava, 2013). Methodological differences in systematic reviews, such as variation in the inclusion criteria, make it difficult to compare findings across reviews.

**Q. What conclusions can be drawn about the use of benzodiazepines as a treatment for GAD in the MHS?**

**A.** Based on an established evidence base, benzodiazepines have proven efficacy for the short-term treatment of GAD. More head-to-head trials are needed to determine the comparative effectiveness of benzodiazepines and antidepressants. However, due in large part to their abuse potential and increased risk of respiratory depression, especially when used in combination with other CNS depressants, benzodiazepines are not recommended as a front-line treatment for GAD. Short-term use of benzodiazepines may be considered in specific circumstances, such as times of crises or severe anxiety. It is important to note that benzodiazepines are not recommended for long-term treatment, due to the potential for dependence. Additionally, benzodiazepines do not treat depression, which is commonly comorbid with GAD (Gorman, 2003).

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