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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: In the central nervous system (CNS), activity is regulated by the balance between excitatory and inhibitory activity. Gamma-amino butyric acid (GABA) is an inhibitory neurotransmitter that is found in high concentrations in the cortex and limbic system (Griffin III et al., 2013). When there is excessive excitatory activity in the CNS, increasing the efficiency of GABA leads to greater inhibition and may result in clinically desirable effects, including anxiolytic and sedative effects (Nutt et al., 2002). Benzodiazepines exert their effects via modulation of the gamma-amino butyric acidA (GABAA) receptor. Benzodiazepine receptors are modulatory sites on GABAA receptors and benzodiazepines lower the concentration of GABA required to open the channel of the GABAA receptor, thereby facilitating inhibitory GABA activity (Sieghart, 1994).

Q: Are benzodiazepines recommended as a treatment for GAD in the Military Health System (MHS)?

A: There is no VA/DOD clinical practice guideline (CPG) on the treatment of GAD.

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

Q: Do other authoritative reviews recommend benzodiazepines as a treatment for GAD?

A: Yes. CPGs and authoritative reviews published by other organizations recommend the use of benzodiazepines under certain circumstances for GAD.

Other recognized organizations publish CPGs or conduct systematic reviews and evidence syntheses on psychological health topics using grading systems similar to the VA/DOD CPGs. These include the American Psychiatric Association, American Psychological Association, and the United Kingdom's National Institute for Health and Care Excellence. Additionally, Cochrane is an international network that conducts high-quality reviews of healthcare interventions.

- United Kingdom's National Institute for Health and Care Excellence (NICE): In primary or secondary care, benzodiazepines should only be offered on a short-term basis for patients in crisis (NICE, 2011).

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

A: Historically, benzodiazepines have been shown to be efficacious in the short-term treatment of GAD in systematic reviews (Bandelow et al., 2015; Baldwin et al., 2011). However, benzodiazepine treatment is

associated with the risk of tolerance and dependence, as well as multiple side effects, including fatigue, dizziness, impaired driving skills, and impaired cognitive function (Bandelow et al., 2015). Consequently, there has been a shift from prescribing benzodiazepines for GAD (Uhlenhuth et al., 1999) to prescribing antidepressants, such as selective serotonin reuptake inhibitors (SSRIs; Baldwin et al., 2011). Recent research has focused on the comparative efficacy of benzodiazepines and other pharmacological treatments and has examined when benzodiazepines may be most effectively used in treatment. Chen et al. (2019) performed a network meta-analysis comparing different pharmacotherapies to psychological interventions and self-help interventions. Benzodiazepines were an effective treatment for GAD when compared with placebo, though the effect size compared to placebo was larger for longer-acting classes of medication, including norepinephrine-dopamine reuptake inhibitors (NDRIs), SSRIs, and serotonin-norepinephrine reuptake inhibitors (SNRIs). In their meta-analysis, Gomez et al. (2018) compared the efficacy of classes of drugs – benzodiazepines, SSRIs, and SNRIs – and found that benzodiazepines had the highest effect size. A systematic review and meta-analysis performed by Gale et al. (2019) examined the influence of covariates on benzodiazepine effectiveness and found that higher baseline anxiety and a shorter study duration was associated with greater effectiveness.

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, particularly as an adjunct when treatment is initiated or in more exigent circumstances. More head-to-head trials are emerging and confirming that benzodiazepines are effective in reducing anxiety symptoms in the short-term but may not be the most effective in the long-term. Due to the questionable long-term effectiveness of benzodiazepines and their potential risks and side effects, they are not recommended as a first-line treatment for GAD but may be considered for specific treatment purposes, including treatment-resistant anxiety.

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