Limited Utility of Benzodiazepines in Chronic Pain Management

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Abstract

Purpose: Benzodiazepine receptor agonists (BZRAs) are agents, such as benzodiazepines and Z-drugs, which interact with the $GABA_A$ receptor to enhance the effect of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter of the central nervous system. Controversy and uncertainty exist about the appropriate role of BZRAs for analgesic and non-analgesic purposes in pain management.

Aim: To review available research that examines the appropriate role of BZRAs in the course of pain management, and how prescribers might address these challenges.

Methods: Publications were identified by a search of PubMed, references of retrieved reports, published guidelines, and personal files. A total of 12,699 citations were retrieved of which 189 related to chronic pain, 39 related to anxiety, and 33 related to sleep and BZRAs were selected for this narrative review.

Findings:
1. BZRAs have clear analgesic benefit for 2 chronic pain conditions: burning mouth syndrome (clonazepam) and stiff person syndrome (diazepam, clonazepam).
2. BZRAs were found to be ineffective in 5 chronic pain conditions.
3. For 2 pain conditions (irritable bowel syndrome and multiple sclerosis) BZRA use is discouraged for long-term use.
4. Data supports the use of BZRAs to treat co-occurring insomnia and anxiety disorders but only when alternatives are inadequate and only for short periods of time (2–4 weeks).
5. Absence of research, heterogeneity of trials, and small sample sizes precluded drawing conclusions about efficacy of BZRAs for the other 102 pain conditions explored.
6. The utility of BZRAs is limited by loss of efficacy which may be seen with continued use and adverse reactions including physiologic dependence which develops in 20–100% of those who take these agents for more than a month.

Limitations: a systematic review and meta-analysis was not performed. Use of BZRAs in acute pain conditions was not examined.

Conclusions:
1. BZRAs are often inappropriately used in pain management.
2. Analgesic efficacy has been demonstrated only in burning mouth syndrome and stiff person syndrome.
3. BZRAs have a short-term (2-4 weeks) role in insomnia and anxiety disorders which often co-occur with pain.
4. When prescribed for four (4) weeks or more, physiologic dependence often results and patients should be encouraged to discontinue them through a supported, slow tapering process that may take 12-18 months or longer.

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Open access. Evidence table available.

Results

Benzodiazepine Analgesic Efficacy in Selected Pain Conditions

Pain Condition	Treatment Outcome
Burning Mouth Syndrome	Effective
Stiff Person Syndrome	Effective
Pelvic Floor Dysfunction	Evidence mixed
Chronic Daily Tension-Type Headache	Evidence mixed
Multiple Sclerosis	Evidence insufficient for long-term use
Irritable Bowel Syndrome	Evidence insufficient for long-term use
Dystonia	Evidence insufficient
Neck Pain	Evidence insufficient
Trigeminal neuralgia	Evidence insufficient
Temporomandibular Dysfunction	Evidence insufficient
Fibromyalgia	Probably ineffective
Low Back Pain	Ineffective
Sciatica (radiculopathy)	Ineffective
Rheumatoid arthritis	Ineffective
Post-Herpetic Neuralgia	Lorazepam ineffective

BZRA Efficacy in Selected Non-Pain Conditions

Non-Pain Condition	Treatment Outcomes
Procedural amnestic / analgoanesthesia	Effective 1st line for acute use
Status epilepticus	Effective 1st line for acute use
Anxiety: Crisis without psychosis	Effective 1st line for acute use
Anxiety: Mild-Moderate	Not indicated
Anxiety: Anxiety Disorder	Effective 2nd line short-term (2-4 weeks)
Anxiety associated with depression	Worse outcomes with long-term use
Anxiety associated with PTSD	Contraindicated
Anxiety ssociated with OCD	Ineffective
Substance Use Disorder	Effective 1st line for alcohol withdrawal Otherwise contraindicated
Insomnia	Effective 2nd line short-term (2-4 weeks)
Selected intractable seizures	Effective 2nd line for adjunctive use

Clinical Practice Recommendations Benzodiazepine Receptor Agonists In Pain Management

1. Limit BZRA initiation to clear indications
   a. Burning Mouth Syndrome (1st line)
   b. Stiff Person Syndrome (1st line)
   c. Anxiety Disorders (2nd line)
   d. Insomnia (2nd line)
2. Limit BZRA duration of use to 2-4 weeks whenever possible
3. For those taking BZRAs long-term do not assume
   a. Symptoms indicate need to increase BZRA dose
   b. Difficulties indicate addiction is present - this is rare
4. Offer BZRA deprescribing to all using BZRAs > 4 weeks
5. For those declining the offer to deprescribe BZRAs
   a. Monitor for the development of adverse reactions
   b. Use motivational interviewing to encourage deprescribing
6. For those who agree to deprescribing BZRAs
   a. First educate, plan, and establish support
   b. Then initiate Cognitive Behavioral Therapy if available
   c. Consider substituting with a long-acting BZRA before tapering
   d. Initiate tapering with a dosage reduction of no more than 5%
   e. Subsequent reduction amounts and intervals are best patient-led
   f. Take discontinuation symptoms seriously, even when "peculiar"
   g. Avoid up-dosing BZRAs or using as needed dosages
   h. Taper slowly - it may take 12-18 months or longer
7. Listen and respond to patients
8. Share decision-making while using motivational interviewing
9. Support patients with symptoms that may continue months or years