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REVIEW

Limited Utility for Benzodiazepines in Chronic Pain Management: A Narrative Review

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ABSTRACT

Introduction: Controversy and uncertainty exist about the use of benzodiazepine receptor agonists (BZRAs) in pain management. This article curates available research to determine the appropriate role of BZRAs in the course of pain management, and how prescribers might address these challenges.

Methods: A narrative review was performed to determine the appropriate role of BZRAs in pain management and to develop practice recommendations. Publications were identified by a search of PubMed, references of retrieved reports, guidelines, and the author's personal files.

Results: BZRAs were found to have analgesic benefit for two pain conditions: burning mouth syndrome and stiff person syndrome. Absence of research, heterogeneity of trials, and small sample sizes precluded drawing conclusions about efficacy of BZRAs for the other 109 pain conditions explored. 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). The utility of BZRAs is limited by loss of efficacy that 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.

Conclusions: BZRAs are often used inappropriately in pain management. Their initiation and duration of use should be limited to a narrow range of conditions. When prescribed for 4 weeks or more, patients should be encouraged to discontinue them through a supported, slow tapering process that may take 12–18 months or longer.

Keywords: Benzodiazepine; Benzodiazepine receptor agonist; Chronic pain; Overdose; Pain management; Tapering; Withdrawal

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Key Summary Points

Benzodiazepine receptor agonists (BZRAs) are frequently prescribed in pain management

Benzodiazepines (BZs) may have an analgesic role in burning mouth syndrome and stiff person syndrome

BZRAs have a narrow role (2–4 weeks) in the management of co-occurring insomnia and anxiety disorders

BZRA deprescribing should be offered to all patients on these agents for more than a month and should proceed by slow tapering that may take a year or more

INTRODUCTION

Chronic pain is quite common, although published estimates vary widely. When "chronic" is not specifically defined, 40% of survey respondents in both developed and developing countries report having that condition [1]. When "persistent pain" is defined as pain present on all or most days in the preceding 3 months, it is reported by one out of five of adults in the USA, half of whom describe it as sometimes unbearable [2]. Decades ago, increased recognition of the importance of pain led to recommendations that inquiry about pain be regarded as the "fifth vital sign". Vital as it is, however, pain is not objective, and, in fact, this concept encouraged opioid overprescribing due to the underlying implied false syllogism that significant pain called for opioid analgesia. Widespread adoption of this simplistic heuristic set into motion a dynamic progression of harms, shaping today's opioid crisis.

Chronic pain management is quite complex and is not equivalent to opioid management. While analgesia lies on the path to success, improved function is the true north and achieving it is a far greater challenge. This includes the need to manage multiple current and limit future potential comorbidities, especially the highly prevalent psychological conditions. Technically, chronic pain is defined as that lasting more than 3–6 months. To affected individuals, however, this means an inability to heal which may result in adverse affective attribution or suffering. This, in turn, may compound existing or generate new medical challenges that need to be addressed if functional gains are to be attained.

Available for 60 years, benzodiazepine receptor agonists (BZRAs) have often been prescribed for such clinical conditions. These compounds work primarily by enhancing the effect of the non-protein amino acid γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter of the central nervous system (CNS) [3], which is active at the orthosteric site on the $GABA_A$ receptor ($GABA_A$ R). BZRAs, on the other hand, are GABAergic primarily as positive allosteric modulators at the benzodiazepine recognition site of $GABA_A$ R to increase chloride conductance amplifying GABA inhibition [3, 4]. A diverse range of substances are $GABA_A$ R agonists, including the barbiturates, carisoprodol, neurosteroids, alcohol, certain anesthetics such as propofol, as well as some compounds found in certain plants like valerian and cannabis [5–7]. The term BZRA, however, is primarily reserved for the benzodiazepines (BZs), defined chemically as the fusion of a benzine and diazepine ring, and the non-benzodiazepines or Z-drugs, so-called as the generic nomenclature of the individual medications includes the letter "z".

To many prescribers BZRAs appear as ready solutions to help those struggling with anxiety and insomnia, and in the short term they are effective, although trouble may ensue later. In the US population, 6–13% receive a BZ prescription in any 1 year [8–11]. In pain management, BZRAs assume a more prominent role being prescribed to 10–33% of persons who are also receiving opioids [12–19]. Of particular concern, use is even greater among those at high risk: the elderly and those who have multiple prescribers, are on at least 200 morphine milligram equivalent (MME) daily opioid doses,

or have greater mental health and substance use problems [14, 18–20].

Harm exposure is clearly increased by such respiratory-depressant polypharmacy. BZ–opioid combinations more than double the likelihood of emergency department and hospital admissions [17]. In addition, there has been a progressive increase in the proportion of opioid-associated accidental deaths in the USA in which BZs have been identified, rising from 13% in 1999 to 31% in 2013 [21]. That proportion is even greater in some locales: 52% in the 11 states reporting to the Centers for Disease Control and Prevention (CDC)'s Enhanced State Opioid Overdose Surveillance program [22] and 80% in North Carolina described in a separate study [23].

BZ involvement in opioid-related negative outcomes is a compelling reason to reconsider public health and clinical approaches. A significant contributing factor is that of inappropriate BZRA prescribing [24]. In response, the US Food and Drug Administration (FDA) requires a boxed warning about co-prescribing on about 400 opioid- and BZRA-containing products [25]. Careful examination of risks, benefits, and utility at the clinical level is now indicated as well. While BZRAs figure prominently in the treatment of anxiety and insomnia, BZs are also employed with analgesic intent, even though safety and efficacy are not well described. In this review, available research is curated and analyzed to determine the appropriate role of BZRAs in the course of pain management, and how prescribers might address their challenges.

METHODS

This is a narrative review and not a systematic review of the literature regarding the clinical use of BZRAs in the context of treating pain. It is based on relevant publications identified through an electronic search of PubMed (inception through February 2020), as well as a manual search of reference lists of identified articles, 26 guidelines, and the author's files. The primary objective was to determine the potential role of BZRAs as analgesics using search terms that combine "benzodiazepines", "non-benzodiazepines", "Z-drugs", and specific drug names along with the names of specific pain conditions. A secondary search was conducted pairing these agents with "anxiety", "sleep", "insomnia", "opioids", and "overdose". Clinical trials, reviews, and meta-analyses were considered if they described involvement of these medications in chronic pain when they compared BZRAs with other medications or placebo. Studies were excluded if they included fewer than 20 study subjects or primarily addressed acute pain, analgoanesthesia, intrathecal administration, or pediatric populations. A total of 9838 citations related to pain, 1735 related to anxiety, and 1096 related to sleep were retrieved. Abstracts and full-text articles of relevant titles were reviewed if available and in English. From these 336 publications were selected to form the core of this review: 189 related to chronic pain, 39 related to anxiety, and 33 related to sleep. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the author.

RESULTS

Benzodiazepine Use for Analgesia

BZs have long been considered for their potential as primary or adjunctive analgesics [26]. While reduction in pain complaints have been observed with their use, it is not clear if this might be due mainly to modulation of affective responses [27, 28]. Preclinical research suggests that direct analgesia might be subserved by functional variants of the $GABA_A$ R subunits α2 and α3 in the dorsal horn of the spinal cord [29, 30]. In 1977 BZs were found to bind peripherally to what was subsequently identified as a distinct receptor, the translocator protein or TSPO, which among other functions appears to be involved in pain generation and sensitivity [31]. TSPO is not only expressed peripherally on mitochondrial membranes but also centrally on microglia [32, 33], which are activated and upregulated in spinal sites to develop and maintain certain pathologic pain conditions [34]. Animal research indicates that

BZs may produce analgesia in part by promoting neurosteroid production through TSPO [35]. Despite such potential, this review identified data on only 29 of 111 pain conditions explored, and of these, the majority had evidence that was judged to be insufficient to provide conclusions about long-term use in chronic pain treatment.

Most studied was the analgesic response to BZs in musculoskeletal symptoms. In recent reviews of primary research investigations, BZs were found ineffective for low back pain and radiculopathy, yet posed significant risks for sedation [36–38]. Research on BZ efficacy for cervical, thoracic, and other spine pain conditions is insufficient. Though data is limited, it appears that BZs are ineffective for pain in rheumatoid arthritis [39, 40]. For pain associated with other rheumatologic or joint pathology including osteoarthritis, no data was identified.

Muscle pain can occur in the absence of muscle tension or result from hypertonia, spasm, and spasticity. With rare exception [41, 42], BZs (primarily diazepam) appear to be no better than placebo for muscular spasms, and other skeletal muscle relaxants are preferred [43–47]. This data, however, is old, not definitive, and generally only addressed spasm and not pain outcomes. Because of that, some experts [27] suggest that BZs remain an option in this context based on clinical experience.

Myofascial pain syndrome is characterized by regional discrete taut muscle bands that on palpation radiate pain along myofascial structures [48]. To date the minimal data available does not support the use of BZs in that condition [49]. Often confused with myofascial pain, fibromyalgia may involve trigger points as well [50] but is defined by tender points [48] and widespread (four-region), centralized (burning, electric) pain [51] due to unbalanced pronociceptive neurophysiology [52]. In a large internet survey (N = 2596) alprazolam, clonazepam, and zolpidem were perceived to be among the most effective medications in fibromyalgia [53]. However, this was not borne out in placebo-controlled investigations of alprazolam [54] or zolpidem [55], and Cochrane reviews were unable to identify research to support clonazepam efficacy [56, 57].

Although there is no research support for use of BZs in the musculoskeletal conditions above, there is demonstrable utility for painful hypertonia associated with stiff person syndrome. In this rare autoimmune disorder with variant clinical expressions (e.g., stiff limb syndrome, paraneoplastic), fluctuating muscle rigidity and spasms are due to continuous activation of muscle motor units [58–60]. Up to half of affected persons have psychological symptoms (data limited) [61, 62], and individuals may be misdiagnosed initially as having a primary anxiety disorder [63, 64]. In stiff person syndrome, BZs are considered to be first-line therapy for muscular spasms and rigidity with good efficacy [58], though treatment-resistance and tachyphylaxis [59, 65] may require other approaches such as other GABAergic drugs, intravenous immunoglobulin administration, and plasmapheresis [58, 65]. Durability of benefit over time from BZs is uncertain, however.

Disabling muscle contractions can be driven by central neurologic processes as well. The dystonias are movement disorders presenting as sustained or repetitive, often painful muscle contractions. While small studies have included BZ therapy, none address analgesic outcomes nor met inclusion criteria for a recent review [66]. A range of medical conditions (e.g., stroke, spinal cord injury, multiple sclerosis) can result in spasticity, which can serve as a pain generator. Like spasms, spasticity is involuntary and uncontrolled, but unlike spasms, it is central in origin and involves repetitive contractions due to hyperexcitability of stretch reflexes [67]. Most research on BZ efficacy involves the use of diazepam, which depresses reactivity of flexor (low dose) and extensor (high dose) reflexes as well as enhances nighttime sedation [67], key to addressing spasticity. Research of oral BZs in spasticity is mixed and insufficient [68–71], however, and when benefit was seen, comparison trials favored other agents for functional and tolerability reasons [68, 72–76]. In a meta-analysis of 23 trials (total N = 2720), diazepam was not recommended for spasticity in multiple sclerosis because of side effects and greater efficacy found with cannabinoids, botulinum

toxin, and transcutaneous electrical stimulation [77]. Note that spasticity trials were not designed to examine pain endpoints so no firm conclusions can be drawn about analgesic efficacy [71].

Managing centralized pain, such as fibromyalgia, is particularly challenging. Reliance on opioids is problematic, since effective analgesic doses may be quite high and pose increased risk for adverse outcomes [78]. Alternatives, especially non-pharmaceutical therapies, are needed and sought after. Of 11 painful neuralgic and neuropathic conditions explored for this review, no data whatsoever was found for BZ use in eight. This was echoed by a Cochrane review which found no evaluable research on the use of clonazepam in neuropathic pain not otherwise specified [79]. From among these conditions, a search revealed only one paper that met inclusion criteria: a placebo-controlled trial in which lorazepam was ineffective for postherpetic neuralgia [80]. In a separate study, BZ use was associated with unsuccessful spinal cord stimulator trials [80]. Pain in multiple sclerosis is seen in at least 40% [81], and is not only related to spasticity for which BZs are discouraged [78] but is also driven by central sensitivity for which no BZ research was identified [72].

Head and facial pain may be nociceptive or centralized in type. There is conflicting data regarding the utility of BZs in chronic daily headache [82–85]. Insufficient evidence precludes drawing conclusions about their use in temporomandibular disorders (TMDs) [86] and trigeminal neuralgia [87, 88]. On the other hand, numerous high-quality trials, systematic reviews, and meta-analyses support use of oral and topical clonazepam with as little as 3 weeks of therapy in burning mouth syndrome, a centralized pain condition seen in perimenopausal women who have xerostomia, dysgeusia, allodynia, and spontaneous burning pain in the oral cavity in the absence of an identified cause [89–91]. Results did not correlate with underlying psychopathology [92], and at least a 50% reduction in symptoms was maintained in 70% of patients for at least 6 months after 1 month's therapy while one-third experienced side effects that were transient and mild [93, 94]. In comparison trials, amitriptyline [95] and acupuncture [96] had similar efficacy, and low-level laser therapy was found to be superior [97].

BZs are poorly researched in chronic abdominal-pelvic pain. Many of these conditions involve central sensitivity [98, 99], as is the case for irritable bowel syndrome (IBS) which was the only abdominal disorder for which research on BZs was found among the 18 explored in this review. Considering their widespread use, it is surprising there are so few IBS trials involving BZs which are generally combined with anticholinergics. In short-term studies, symptomatic improvement can be seen, though it remains unclear if analgesic benefit might actually be indirectly derived from anxiolysis [100–104]. Long-term use in this chronic condition, however, has not been well studied and is discouraged [105]. Medical problems of the pelvis can be painful and due to peripheral and/or central mechanisms [98, 99, 106]. Limited information was identified for only two of nine painful conditions involving the pelvis and nearby structures researched here. Pelvic floor dysfunction is multifactorial, and data is limited and mixed with respect to BZ efficacy [107, 108]. In a single small study ($N = 22$), alprazolam did not improve symptoms of premenstrual syndrome [109].

Benzodiazepine Receptor Agonist Use for Non-Analgesic Reasons

BZRAs (BZs and Z-drugs) are frequently used for non-pain indications within pain management. A bidirectional relationship between pain and both anxiety and insomnia is well established in research with prevalence among persons with pain exceeding 50% [110, 111]. It is no surprise, then, that BZRAs are often considered.

BZs are indicated first-line for only a few conditions: alcohol withdrawal [112], status epilepticus [113], anesthesia for amnestic effect [114], and crisis anxiety without psychotic features [115]. For insomnia, cognitive behavioral therapy for insomnia (CBT-I) is first-line [116] with durable treatment effects lasting up to 18 months [117]. FDA-approved BZs (estazolam, flurazepam, quazepam, triazolam) and Z-drugs

(zolpidem, zaleplon, eszopiclone) can be otherwise considered for short-term use (2–4 weeks) [118, 119]. Though not first-line, BZs also have a limited role in certain intractable treatment-resistant seizure disorders (clobazam, clonazepam) [120].

Their role in anxiety is limited as well. Although short-term use in crisis anxiety is established [115], they are often prescribed inappropriately [121, 122], such as for ordinary anxiety that comes with normal life experiences when self-management strategies or brief therapy would suffice. BZs are either ineffective or contraindicated for anxiety associated with depression [123, 124], alcohol addiction following withdrawal [125], post-traumatic stress disorder [126, 127], and obsessive–compulsive disorder [127]. They can be considered when criteria for an anxiety disorder are met: anxiety lasting 6 months or more, functionally limiting, and disproportionate to the actual threat [128]. As effective as BZs [129], CBT is preferred as this avoids medication side effects and because sustained improvement has been observed for half of those treated on follow-up 8–14 years later [130]. However, since access to and benefit from CBT may be delayed, BZs can be prescribed as a bridge for 2–4 weeks for those who are functionally impaired. As BZs may interfere with efficacy of psychological therapies [131], discontinuation should proceed as soon as is feasible.

DISCUSSION

The purpose of this review is to define the boundaries of appropriate BZRA use in medical pain management. Efficacy in selected pain and non-pain conditions is outlined in Tables 1 and 2, respectively. Unfortunately, BZRAs are often prescribed to those who are already at risk for poor outcomes [24]. Long-term (more than 4 weeks) efficacy and safety of BZRAs has not been demonstrated [124, 132]. There are three aspects to consider: (1) efficacy, (2) tolerability, and (3) physiologic dependence.

Sufficient evidence to support the use of BZs for analgesic purposes was found for only two of 111 pain conditions explored here: burning mouth syndrome and stiff person syndrome. Burning mouth syndrome is successfully treated with a short course of clonazepam (3–4 weeks), but durability of BZ efficacy in stiff person syndrome is unknown. When alternatives are inadequate, BZRAs used short-term (2–4 weeks) may benefit co-occurring insomnia and anxiety disorders. It is not unusual, however, for improvements to diminish over time [133–136], though this may be difficult to distinguish from worsening of the underlying conditions. Loss of efficacy may become apparent only upon cessation of the medication, which has also been observed in a clonazepam discontinuation study in seizure disorders [137]. Many clinicians may not recognize declining benefit because discontinuation prompts near-term increased symptoms and because this was not identified in earlier studies, perhaps because studied cohorts were too small or observed for too short a period of time [138].

BZRAs may have side effects that may or may not be evident [139–141]. Although true addiction is unlikely [142] other side effects are frequent and sometimes severe [133, 139]. Excess mortality overall [143], suicide [144], and accidental overdose fatalities [22] are associated with use. Some reactions with documented associations may be miscast as unrelated, such as akathisia, depersonalization, and even pain itself. Decrements in psychomotor and cognitive functions may occur gradually and be attributed to other causes or aging [145, 146]. Causation has not been confirmed, but correlation with dementia [147] and cancer [148, 149] has been identified. As with efficacy, BZRA involvement in symptom expression or functional declines may become apparent only upon deprescribing. Ashton, for example, found that anxiety and agoraphobia that developed during BZ use improved upon discontinuation [140]. It remains to be determined, though, whether or not there may be benzodiazepine-induced hyperanxiogenesis analogous to opioid-induced hyperalgesia.

Perhaps of greatest concern is the development of physiologic dependence which develops in 20–100% of those on BZs even at normal doses for more than a month [150–154]. Withdrawal symptoms may occur during medication

Table 1 Benzodiazepine analgesic efficacy in selected pain conditions

Pain condition	Treatment outcomes
Burning mouth syndrome	Effective
Stiff person syndrome	Effective
Multiple sclerosis	Effective—other treatments favored
Dystonia	Evidence insufficient
Neck pain	Evidence insufficient
Low back pain	Ineffective
Sciatica (radiculopathy)	Ineffective
Rheumatoid arthritis	Ineffective
Fibromyalgia	Small studies: probably ineffective
Irritable bowel syndrome	Short-term benefit, long term not recommended
Postherpetic neuralgia	One small study: lorazepam ineffective
Trigeminal neuralgia	Evidence insufficient
Temporomandibular dysfunction	Evidence insufficient
Pelvic floor dysfunction	Evidence mixed
Chronic daily tension-type headache	Evidence mixed

Table 2 Benzodiazepine or Z-drug efficacy in selected non-pain conditions

Non-pain condition	Treatment outcomes
Procedural amnestic/analgoanesthesia	Effective 1st line for one-time use
Status epilepticus	Effective 1st line for one-time use
Anxiety: Crisis without psychosis	Effective 1st line for one-time use
Anxiety: Mild–moderate	Not indicated
Anxiety: Anxiety disorder	Effective 2nd line for short-term use (2–4 weeks)
Anxiety: Associated with depression	Not indicated
Anxiety: Associated with PTSD	Contraindicated
Anxiety: Associated with OCD	Ineffective
Anxiety: Associated with substance use disorder	Effective 1st line for BZRA, alcohol withdrawal Otherwise contraindicated
Insomnia	Effective 2nd line for short-term use (2–4 weeks)
Selected intractable seizures	Effective 2nd line for adjunctive use

Table 3 Benzodiazepine receptor agonists: best practice recommendations

1. Limit initiation to clear indications
2. Limit duration of use to 2–4 weeks
3. For those on BZRAs long term do not
(1) Assume symptoms indicate a need to increase the dose
(2) Assume difficulties mean addiction—this is rare
4. Offer deprescribing to all who are using BZRAs > 4 weeks
5. For those who decline the offer, continue to monitor for and manage adverse reactions
6. For those who accept the offer
(1) First: educate, plan, establish support
(2) Initiate CBT prior to tapering
(3) Consider substituting with a long-acting BZRA prior to tapering
(4) Taper slowly anticipating it may take 12–18 months or longer
(5) Tapering amounts and intervals are best patient-directed
(6) Avoid up-dosing BZRAs or as-needed doses
7. Regard discontinuation symptoms seriously even if sounding peculiar
8. Regard patient reports seriously—they are the experts on their own experience
9. Support patients with ongoing symptoms that may continue months or years

use (interdose or tolerance withdrawal) [139], after as little as 2–6 weeks of exposure [155], and be quite severe [133–135, 139]. Symptom expression while tapering may be attributed to relapse or rebound of the underlying condition [156]. Their dramatic and widely fluctuating nature [139] may prompt consideration of alternative diagnoses, such as somatic symptom disorder [128]. While the latter may technically be applied to conditions with defined pathophysiologic explanations, in practice assigning this diagnosis and other related terms (e.g., functional, catastrophizing) is pejorative, casts doubt on symptom validity, and implies patient self-culpability [98]. In addition, this may impart a sense of therapeutic nihilism, limiting prescriber motivation to work towards solutions. These are bone fide symptoms that are neurophysiologically based and possibly due to oxidative stress described in a hypothesis by LaCorte [157]. Protracted, sometimes severe symptoms are seen in an estimated 10–15% of patients [139], and because they may persist indefinitely, the term "benzodiazepine injury syndrome" may be a more accurate descriptor than "withdrawal", as the latter implies ultimate resolution.

Patients are probably not benefited by avoiding or delaying discontinuation [158]. Abrupt cessation is dangerous, and slow tapering over 12–18 months is recommended along with careful planning and support. Success is improved with the use of CBT, (substituted) long-acting BZRAs, and perhaps adjunctive medications. A description of this process is beyond the scope of this paper and is detailed in the Ashton Manual [139] and elsewhere [159].

CONCLUSIONS

Medical providers are challenged as to how to address the complexities of pain. A multimodal, multidisciplinary approach is indicated, and

non-pharmacologic options are often preferred, though medications may be necessary. Far less is known about the role of benzodiazepine receptor agonists (benzodiazepines and the related Z-drugs) than other agents like opioids in pain management. Evidence supports a very limited role for their use in co-occurring anxiety disorders and insomnia. This review identified demonstrated analgesic value for two painful conditions: burning mouth syndrome and stiff person syndrome. For the other 109 conditions examined, evidence was either absent or insufficient to draw any conclusions about the long-term efficacy necessary in addressing the chronic nature of the pain. A number of best practice recommendations can be made (Table 3) to include offering discontinuation to patients on these medications for over a month by means of a slow tapering process that may take 12–18 months or more to complete. Unusual and persistent symptoms during and/or after tapering (benzodiazepine injury syndrome) are valid and are not to be minimized or discounted. Affected individuals need ongoing support and therapeutic effort.

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