Do benzodiazepines have a role in the management of pain?

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Despite the widespread prescription of benzodiazepines in patients with pain there is very little evidence of their effectiveness. In addition, their combined use with opioids can result in significant adverse effects and their long-term use has been associated with an increase in mortality.

A recent Australian study of patients prescribed long-term opioids for chronic noncancer pain found that 33% of patients reported taking benzodiazepines in the previous month and 17% reported daily benzodiazepine use.[1] Despite this, there is limited evidence for any long-term benefit in using benzodiazepines for the treatment of pain, and their combined use with opioids is associated with significant risks including increased cognitive and psychomotor impairment, respiratory depression, sedation and overdose.[1]

Benzodiazepine chemical structure and method of action

Benzodiazepines are a class of compounds made up of a core structure consisting of a benzene ring fused to a seven-membered diazepine ring. Side chain substituent groups in varying positions determine their individual properties such as onset of action, potency, metabolism, metabolite activity and subsequent elimination half-life.[2]

This class of medications exert their effect primarily through allosteric modulation of the GABA-A receptor. This results in potentiation of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the central nervous system, resulting in anxiolytic, hypnotic, sedative, muscle relaxant and anticonvulsant effects.

Studies in rats have also demonstrated that intrathecal administration of midazolam has analgesic effects and these can be reversed by selective opioid receptor antagonists such as naloxone.[3,4] In addition, an in vitro study of the benzodiazepine agonists diazepam, chlordiazepoxide (not licensed in Australia) and midazolam showed they can bind to and activate human [kappa]-opioid receptors and midazolam can also modestly activate [delta]-opioid receptors.[5] However, it is important to note that these studies acknowledge benzodiazepines

Key points

- **There is very limited evidence for the clinical efficacy of benzodiazepines in the treatment of patients with pain.**
- **The current pattern of benzodiazepine prescribing in Australia most likely represents a high level of overuse given the relatively few indications for long-term benzodiazepine therapy.**
- **The use of benzodiazepines can cause dependence and long-term use has been associated with increased mortality while their potential for misuse and abuse is well documented.**
- **Concurrent use of benzodiazepines and opioids is associated with significant risks such as increased cognitive and psychomotor impairment, respiratory depression, sedation and overdose.**
- **National guidelines (from the RACGP) recommend that a pain specialist is involved in the care of patients with chronic pain who take multiple psychoactive medications including benzodiazepines.**
- **Initiation of benzodiazepines in the management of chronic pain should be limited to a pain specialist experienced in their use.**

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Table. Comparative information for commonly used benzodiazepines[9-16]

Drug name	Length of action	Mean half-life of parent drug and active metabolites*	Comparative oral potency†	Licensed indications in Australia
Midazolam	Very short	• 3 h (range, 1.4 to 6.4 h) for IV dosing • Increased in congestive heart failure, renal and hepatic impairment	(No oral formulation in Austraia)	Sedation, premedication, induction of anaesthesia
Alprazolam‡	Short	• 11 h (range, 6 to 27 h) • 16 h in the elderly • 20 h in hepatic impairment • 22 h in obesity	0.5 mg (range, 0.25 to 0.5 mg)	Anxiety and panic disorders
Oxazepam	Short	• 8 h (range, 3 to 20 h)	15 mg (range, 10 to 40 mg)	Anxiety disorders, short-term relief of anxiety symptoms, acute alcohol withdrawal
Temazepam‡	Short	• 10 h (range, 3 to 19 h)	10 mg	Adjunctive therapy in short-term treatment of insomnia
Lorazepam	Medium	• 12 to 14 h (range, 10 to 20 h) • Increased in renal impairment	0.5 mg (range, 0.5 to 1 mg)§	Anxiety disorders, short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms, premedication
Clobazam	Long	• Parent compound: – 17 h in young men – 31 h in young women – 48 h in elderly men – 49 h in elderly women • N-desmethylclobazam (active metabolite): – 48 to 72 h for young men and women – 72 to 120 h in elderly men and women • Prolonged once steady state is reached	10 mg	Acute anxiety and associated sleep disturbances in adults, treatment of epilepsy in adults and children (4 years and older)
Clonazepam	Long	18 to 50 h	0.5 mg (range, 0.25 to 4 mg)‖	Epilepsy in both adults and children (oral), status epilepticus (IV)
Diazepam‡	Long	• Parent compound, 20 to 50 h • Further prolonged in the elderly (approx 1 h for each year of age beginning with a half-life of 20 h at 20 years of age) and with hepatic and renal impairment • Half lives of active metabolites can be in excess of one week (e.g. nordiazepam, 194 h; range, 67 to 533 h)	5 mg	Anxiety disorders, short-term relief of anxiety symptoms, acute alcohol withdrawal, adjunct for muscle spasm/spasticity, status epilepticus, spasms of tetanus, premedication
Flunitrazepam‡	Long	• Parent compound, 16 to 35 h • 7-Aminoflunitrazepam (active metabolite), 10 to 16 h • N-desmethylflunitrazepam (active metabolite), 23 to 33 h	0.5 mg	Severe cases of insomnia
Nitrazepam	Long	• 27 h (range, 16 to 48 h) • Prolonged in the elderly	5 mg (range, 2.5 to 20 mg)	Short-term management of insomnia

* Half-life ranges from those given across all references.
† Due to interpatient variability, differing receptor binding characteristics and drug half-lives, these figures should only be used as a guide.
‡ Rapid onset (<1 hour) after oral administration.
§ Lorazepam may be relatively more potent at higher doses.
‖ Particular care should be taken when adjusting clonazepam dosing due to the wide variation in reported equivalences.

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have only weak opioid agonistic properties, require high local concentrations and the mechanism of opioid receptor interaction is most likely complex, involving both direct and indirect effects.[3-5]

Benzodiazepines and pain management

Acute anxiety and pain

Benzodiazepines are effective in the treatment of patients with acute anxiety, exerting an effect within minutes to hours depending on the agent and route of administration.[6] The anticipatory anxiety a patient experiences when undergoing a painful treatment procedure has been shown to contribute to the perceived unpleasantness of the pain.[7]

In mild cases of acute procedural anxiety, providing the patient with accurate information about the procedure and its associated risks is often sufficient to reduce their level of anxiety to a tolerable level. For patients with moderate to severe preprocedural anxiety, psychotherapy or pharmacological interventions may be required; in which case benzodiazepines are the drug class of choice.[8] Comparative information on commonly used benzodiazepines is provided in the Table.[9-16]

Chronic pain

Benzodiazepines have a higher rate of use in patients with chronic pain compared with the general population.[1] There is very little evidence that benzodiazepines are useful in the management of chronic pain, and their use is associated with tolerance, dependence and abuse.[9,10,17] A review from 1994 listed only three specific conditions where some evidence of efficacy was noted: chronic tension headache, trigeminal neuralgia and temporomandibular joint dysfunction.[9] However, evidence was scant and therefore the use of benzodiazepines in these conditions should only be considered when established therapies have failed.[1,17]

Patients with chronic pain have increased rates of anxiety compared with patients without chronic pain.[17] Chronic pain has also been linked to depression, frustration and sleep disturbance, which are thought to worsen the emotional pain experience. Higher pain estimates have been reported in patients suffering from chronic pain who have coexisting anxiety and/or depression compared with those without anxiety/depression.[17] Benzodiazepines are no longer recommended as first-line therapy for anxiety or insomnia due to the risk of dependence, abuse and tolerance associated with their long-term use.[6,9,17,18] When pharmacological interventions are required, the use of benzodiazepines has been superseded with the emergence of evidence supporting the use of alternative agents such as selective serotonin reuptake inhibitors (SSRIs)[19,20] and serotonin and noradrenaline reuptake inhibitors (SNRIs).[21,22]

Combined use of benzodiazepines and opioids is associated with significant adverse effects including increased sedation, respiratory depression, falls, psychomotor and cognitive impairment and risk of overdose.[1,23] Very few studies have investigated the effects of benzodiazepine use on the long-term outcomes in patients with chronic pain. One study of 1220 patients with chronic pain prescribed long-term opioids found that past or current benzodiazepine use was associated with reduced pain self-efficacy (i.e. reduced confidence in ability to cope with pain and complete activities such as household tasks, socialising and work).[1] In addition, no difference in the duration of opioid prescriptions (i.e. continuous opioid use) was noted between patients taking a benzodiazepine and those not taking them.[1] Patients taking benzodiazepines in this study also generally reported higher use of emergency services such as emergency department presentations, poorer health outcomes and an increased history of accidental overdose (reported in approximately 25% of patients taking a benzodiazepine daily compared with in 10% of those who had never used a benzodiazepine).[1] The authors concluded that patients with chronic noncancer pain who were prescribed long-term opioids and who were taking benzodiazepines on a daily basis represented a particularly high-risk group and that the high usage rates were inconsistent with clinical guidelines for the management of such pain, which do not advocate long-term prescription of benzodiazepines.[1]

Although diazepam is registered for adjunct use in muscle spasm and spasticity, the Royal Australian College of General Practitioners (RACGP) evidence-based guidelines on the use of benzodiazepines in primary care state 'benzodiazepines have little place in the management of chronic musculoskeletal pain', acknowledging there was a lack of evidence for clinical efficacy.[23] These guidelines recommended benzodiazepines should only be used with specialist consultation and on an individualised basis for patients with muscle disorders or multiple sclerosis.[23]

Adverse effects and risks of benzodiazepine use

Tranquillisers/sleeping tablets (including benzodiazepines) were reported to be the second most commonly misused class of medication in the Australian 2013 National Drug Strategy Household Survey after analgesics/pain killers.[10,24] In Victoria, benzodiazepines co-contributed to 68% of all overdose deaths involving pharmaceutical opioids between 2009 and 2014.[25]

Benzodiazepines commonly cause drowsiness, memory loss, ataxia, oversedation, visual disturbances and dependence.[11] Diversion, misuse and morbidity and mortality related to withdrawal and overdose is also a significant concern. In elderly patients, benzodiazepines have been associated with dementia, falls and cognitive decline that may not be fully reversible.[11,18] Increased mortality has been associated with long-term benzodiazepine use.[18] In patients in whom misuse or abuse is of concern, the advice of an addiction medicine specialist should be sought.

Benzodiazepine use in primary care

Close to 7 million prescriptions for benzodiazepines are recorded in Australia each year.[23] Given the relatively few indications for long-term benzodiazepine therapy, the current pattern of prescribing most likely represents a high level of overuse.[18]

Benzodiazepine use exceeding one month, especially at higher doses, is likely to result in the development of dependence and patients

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may then experience withdrawal symptoms if the drug is stopped abruptly.[9,18] These symptoms are highly variable but may include insomnia, anxiety, palpitations, irritability, myoclonic jerks, photophobia and seizures (which can be life-threatening if not treated appropriately).[9,11,18] The degree of withdrawal can be affected by drug-related factors such as the half-life of the agent, daily dose, duration of treatment and the rate of tapering as well as patient factors such as personality features and neurochemical variations.[26]

Gradual benzodiazepine dose reduction over several months may be needed, with weaning over at least 10 weeks shown to be successful in achieving long-term abstinence in several primary care studies.[9,18] For patients taking high doses of benzodiazepines or using benzodiazepines with short half-lives, changing to an equivalent dose of diazepam is suggested before initiating a dose reduction regimen to allow a gradual taper of blood concentrations.[10,23] For patients with severe benzodiazepine withdrawal, management in a specialist or hospital facility is recommended.[10]

The future

Although current evidence acknowledges that the available benzodiazepines lack any significant clinical analgesic activity in humans, compromised functioning of GABA receptors contributes to the difficulty in controlling chronic pain states. Experiments in mice with genetically engineered resistance to the dose-limiting sedative effects of benzodiazepines showed a reduction in heightened sensitivity to pain when the mice were exposed to high concentrations of these compounds.[27] The ongoing development of novel selective GABA subgroup receptor agonists has the potential to change the future management of patients with complex pain conditions.

Conclusion

Despite the widespread prescription of benzodiazepines in patients with pain there is very little evidence of their effectiveness in the management of pain and their associated adverse effects are well documented. Concurrent use of benzodiazepines and opioids increases the risk of psychomotor impairment and fatal and nonfatal overdose. The RACGP recommends that, where available, a pain specialist be involved in the care of patients with chronic pain who take multiple psychoactive medications including benzodiazepines.[23] Initiation of benzodiazepines as an adjunct in the management of chronic pain resistant to standard treatment should also be limited to pain specialists experienced in their use. **PMT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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