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Benzodiazepines for Agitation in Patients with Delirium: Selecting the Right Patient, Right Time and Right Indication

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Abstract

Purpose of review: To provide an evidence-based synopsis on the role of benzodiazepines in patients with agitated delirium.

Recent findings: Existing evidence supports the use of benzodiazepines in two specific delirium settings: persistent agitation in patients with terminal delirium and delirium tremens. In the setting of terminal delirium, the goal of care is to maximize comfort, recognizing that patients are unlikely to recover from their delirium. A recent randomized trial suggests that lorazepam in combination with haloperidol as rescue medication was more effective than haloperidol alone for the management of persistent restlessness/agitation in patients with terminal delirium. In patients with refractory agitation, benzodiazepines may be administered as scheduled doses or continuous infusion for palliative sedation. Benzodiazepines also have an established role in management of delirium secondary to alcohol withdrawal. Outside of these two care settings, the role of benzodiazepine remains investigational and clinicians should exercise great caution because of the risks of precipitating or worsening delirium and over-sedation.

Summary: Benzodiazepines are powerful medications associated with considerable risks and benefits. Clinicians may prescribe benzodiazepines skillfully by selecting the right medication at the right dose for the right indication to the right patient at the right time.

Keywords

antipsychotic agents; benzodiazepines; delirium; pharmacologic therapy; palliative care; randomized controlled trial; benzodiazepines; delirium; treatment; neoplasms; palliative care; prognosis

Introduction

Delirium is the most prevalent neurologic complication in patients with advanced illnesses [1–3]. It affects between 11% and 42% of hospitalized patients [4], 80% of patients on

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Conflicts of interest

None

Off-label Use: This manuscript will discuss the off-label use of benzodiazepines and neuroleptics for agitation and delirium

ventilators in intensive care units [5], and up to 90% of patients in palliative care units in the last days of life [6]. Delirium has a negative impact on all aspects of patient care, ranging from symptom assessment, communication, and decision making to patient well-being and caregiver distress [7,8].

Approximately 50%−70% of patients with delirium have hyperactive or mixed subtypes that are characterized by agitation [9], which ranges from restlessness to aggressive violent behavior. In addition to posing a safety risk for patients, caregivers, and healthcare professionals, agitation can be highly distressing to all involved, particularly the 50% of patients with persistent delirium that does not respond to standard treatment with low-dose haloperidol [10–12]. Indeed, agitation is rated consistently as the most distressing manifestation for caregivers [13]. In a study examining agitation in delirium, the mean delirium-related distress level was 3.2 of 4 for patients (with 4 being the most severe), 3.75 of 4 for caregivers, and 3.1 of 4 for nurses [13,14]. Uncontrolled agitated delirium is also one of the most important reasons for prolonged hospital admissions and is the most common indication for palliative sedation [15–18].

The current management of agitation in delirium involves (1) treatment of delirium by identifying and removing any reversible causes, (2) non-pharmacologic measures, and (3) pharmacologic interventions for palliation [19]. The role of benzodiazepines in delirium is particularly controversial, with some clinicians stating that they should never be used while others believing that they may have a role for specific indications. A 2009 Cochrane review examining the use of benzodiazepines for delirium identified only one randomized trial that fit the inclusion criteria, and concluded that there was insufficient evidence to support its use in non-alcohol withdrawal related delirium [20]. However, several important studies have since been published on this topic [21,22]. The aim of this review article is to provide an evidence-based synopsis of the role of benzodiazepines in patients with agitated delirium. Specifically, we will provide an overview of the pharmacological properties of benzodiazepines, and summarize the key randomized controlled trials that examined the use of benzodiazepines for control of agitation and delirium in different care settings.

Pharmacodynamics and Pharmacokinetics

γ-aminobutyric acid (GABA) is the main endogenous inhibitory neurotransmitter in the central nervous system (CNS). Binding of GABA to $GABA_A$ receptors lining the neuronal membranes activate these gated ion channels, resulting in increased chloride conductance and ultimately various CNS inhibitory effects, such as sedation and anxiolysis [23,24]. Currently, benzodiazepines are often prescribed for the indications of anxiety, insomnia due to anxiety or situational stress, premedication for anesthetic procedure, and status epilepticus.

The pharmacokinetic properties of some commonly used benzodiazepines are shown in Table 1. The potency of benzodiazepine is determined by the affinity of drug-receptor binding. For instance, lorazepam and clonazepam have high potency, diazepam has moderate potency, and temazepam has low potency. The onset of action is dependent on its

lipophilicity, with midazolam and lorazepam being the fastest acting and oxazepam being slow acting [25,26].

Among the benzodiazepines, midazolam and lorazepam are considered drugs of choice for management of agitation in delirious patients because of their rapid onset of action, short half-life, and parenteral route availability. Midazolam has a considerably shorter half-life than lorazepam and is thus more often administered with continuous infusion instead of boluses. Moreover, midazolam is metabolized by CYP3A4 and should be used with caution in patients with severe liver failure or those on methadone. In contrast, lorazepam, oxazepam and temazepam are metabolized primarily by conjugation and do not have active metabolites, making them more appropriate for patients with liver dysfunction [23].

Management of agitation in delirious patients under palliative care

To date, only 3 randomized controlled trials have been conducted to examine delirium in the palliative care setting [21,22,27]. Interestingly, all three studies included neuroleptics and benzodiazepines as study interventions. Only one clinical trial specifically examined agitation as the primary outcome [21], while the other two focused on delirium symptoms and severity.

Breitbart et al. completed the first randomized controlled trial, comparing haloperidol (N=11), chlorpromazine (N=13), and lorazepam (N=6) for the first-line management of delirium in human immunodeficiency virus patients [27]. The primary outcome, as assessed by the Delirium Rating Scale, improved with haloperidol ($P<0.001$) and chlorpromazine ($P<0.001$) with no significant between-arm differences ($P=0.44$). The lorazepam arm was stopped prematurely because over-sedation and increased confusion. The adverse effect profile contributed to significant concerns regarding the use of benzodiazepines in patients with delirium. However, this study should be interpreted with caution because of its small sample size and the unique dosing schedule.

More recently, Agar et al. compared low-dose haloperidol, risperidone, and placebo for delirium in patients with mild to moderate delirium. The primary outcome, a composite score based on inappropriate behavior, inappropriate communication, and illusions and hallucinations, was significantly worse in the risperidone (0.48 units higher, $P=0.02$) and haloperidol (0.25 units higher, $P=0.009$) arms than in the placebo arm [22,28]. Midazolam 2.5 mg subcutaneously was used as the rescue medication in all groups and was required less often in the placebo arm. Several design issues complicates its interpretation, including use of a non-validated primary outcome, enrollment of patients with mild delirium, non-exclusion of patients with dementia, and use of low dose oral neuroleptics.

Our research group recently completed a double-blind, randomized controlled trial compared haloperidol 2 mg intravenously (IV) plus either lorazepam 3 mg IV or placebo for a single episode of agitation in delirious patients [21]. The primary outcome, Richmond Agitation Sedation Scale (RASS), decreased significantly within 30 minutes in both arms (lorazepam/haloperidol: −3.62; 95% CI, −4.3, −2.9; placebo/haloperidol: −1.62; 95% CI, −2.21, −1.03), and the effect was maintained at 8 hours (lorazepam/haloperidol: −4.1; 95%

CI, −4.8, −3.4; placebo/haloperidol: −2.27; 95% CI, −2.93, −1.61). Lorazepam/haloperidol was associated with a significantly greater reduction in RASS at 8 h than was placebo (mean difference, −1.85; 95% CI, −2.78, −0.91; P<0.001). Importantly, patients who received lorazepam/haloperidol were perceived to be in greater comfort after study medication administration by both blinded caregivers (84% vs. 37%, P=0.007) and nurses (77% vs. 30%, P=0.005). The rates of adverse events and overall survival did not differ significantly between the two groups. Importantly, all patients had severe delirium in this study and the median survival was only 3 days, highlighting the unique nature of this study population. Because this study only examined a single dose and only enrolled cancer patients from a single center, further studies are needed to confirm its effect.

One key concern regarding the use of lorazepam is the risk of over-sedation, because many patients and families would like to retain the ability to communicate with each other. In the Hui trial, patients were perceived by caregivers and nurses to be much more comfortable in the lorazepam/haloperidol arm who achieved an average RASS between −2 and −3 compared to those in the haloperidol/placebo arm who achieved an average RASS score between 0 and −1 [21]. A subsequent exploratory analysis found that the minimal clinically important difference for RASS was 4 points using 2 anchor based approaches, suggesting that a substantial degree of sedation was required for patients to be perceived to be comfortable in this setting of persistent restlessness in terminal delirium [29].

To summarize, the Breitbart study supported the use of neuroleptics but not benzodiazepine, while the Agar study reached the opposite conclusion, resulting in significant confusion about the management of delirium [21,22]. The Hui trial was the only study that examined agitation as a primary outcome in the palliative care setting and directly compared lorazepam to placebo [21]. It provided strong preliminary evidence to support the clinical benefit of combination of lorazepam and haloperidol as a rescue for refractory agitation in the terminal delirium setting.

In patients who have refractory agitated delirium, palliative sedation may be needed to maximize comfort [15]. Although no randomized controlled trial has been conducted to assess the optimal medication regimen and dosing, multiple cohort studies supported the use of continuous infusion of midazolam or scheduled doses of lorazepam for this indication [30]. Importantly, palliative sedation should be distinguished from the study above which used benzodiazepines as rescue only. A detailed description of palliative sedation is beyond the scope of this review. Multiple clinical practice guidelines provided recommendations on when palliative sedation may be initiated and how benzodiazepines should be administered [31].

Management of delirium outside of palliative care settings

Patients in the critical care setting are at high risk of developing delirium and often require sedation while on mechanical ventilation. Benzodiazepines may be used in this setting to induce sedation. Several non-randomized studies highlighted that benzodiazepines can increase the risk of delirium development in critically ill patients without delirium [32,33]. However, the evidence from randomized trials is less conclusive. Pandharipande et al.

conducted a double-blind, randomized controlled trial to compare lorazepam and dexmedetomidine for sedation during mechanical ventilation [34]. Delirium and agitation were not required at the time of enrollment. The primary outcome was the number of days alive without delirium or coma free days, which was significantly more favorable in the dexmedetomidine group (lorazepam vs. dexmedetomidine: 3 days vs. 7 days, P=0.01). The prevalence of delirium (82% vs. 79%, P=0.65) did not differ between groups, although the prevalence of coma (92% vs. 63%, P<0.001), the proportion of patients with RASS score within 1 point of nurse goal (67% vs. 80%, P=0.04), the proportion of patients over-sedated (33% vs. 15%, P=0.01) and the number of over-sedated study days (2 vs. 1, P=0.01) were better in the dexmedetomidine group. In another double-blind, randomized controlled trial, Riker et al. compared midazolam to dexmedetomidine, and reported no significant difference in the percentage of time within the target RASS range (75% vs.77%, P=0.18) but lower prevalence of delirium during treatment favoring the dexmedetomidine group (77% vs. 54%, P<0.001). Combining data from these two trials, a meta-analysis compared the prevalence of delirium between benzodiazepines and dexmedetomidine and reported that there was no statistically significant difference in this outcome (risk ratio 0.82, 95% 0.61–1.11, P=0.19) [35].

Elderly patients are also at high risk of developing delirium and benzodiazepines are generally not recommended. Only one randomized clinical trial has examined the use of benzodiazepine for delirium in the geriatric setting. Christiansen et al. conducted a crossover trial to compared 3 weeks of alprazolam to 3 weeks of haloperidol for the management of disruptive behavioral episodes in 48 nursing home patients with dementia, delirium, amnesia and other cognitive disorders [36]. The mean age was 83 years and the doses of haloperidol (mean 0.64 mg twice daily orally) and alprazolam (0.5 mg twice daily orally) were low. The primary outcome was number of behavioral episodes, which increased slightly from 6.2 per week at baseline to 7.1 per week in the haloperidol arm and 7.2 per week in the alprazolam arm, although no statistical significance was identified. However, multiple issues with trial design including the heterogeneous inclusion cohort, the sample size, and the dosing significantly complicate interpretation of this study.

In summary, the role of benzodiazepines for management of delirium in critical care and geriatric patient populations remains to be better defined. There is a paucity of studies to inform practice, no placebo controlled trials, and a lack of studies examining agitation/restlessness as a primary outcome in these patients. The handful of randomized controlled trials comparing benzodiazepines and alternative psychotropic agents found similar risk of delirium. More research is thus needed to better define their risks and benefits. In the meantime, clinicians using these medications should proceed with great caution to minimize harm.

Management of delirium tremens

In addition to agitation in the terminal delirium, benzodiazepines have an established role in the management of patients with alcohol withdrawal to prevent and/or treat delirium tremens, seizures and withdrawal symptoms. The efficacy of benzodiazepines have been demonstrated in several systematic reviews [37]. Long-acting benzodiazepines such as

diazepam are typically used, with short-acting agents reserved for patients with impaired hepatic metabolism (e.g. liver failure, elderly).

Optimal medication regimen for management of agitation in patients with delirium

The recent studies by our group and others highlighted the potential use of rescue benzodiazepine for agitation in delirious patients. However, the optimal regimen and dose remains to be determined. One important question relates to efficacy of combination therapy (benzodiazepine plus haloperidol) compared to either agent alone. In a prospective cohort study, Menza et al. compared 14 delirious patients who received intravenous haloperidol and benzodiazepine to 4 patients who received IV haloperidol alone, and reported fewer extrapyramidal symptoms in patients who received the combination [38]. Other neuroleptics such as chlorpromazine may also have a role [28,39]. Further research is needed to identify the optimal strategy.

Our clinical approach to the management of agitation in patients with delirium in the palliative care is to treat any underlying cause, to optimize non-pharmacologic measures, and start neuroleptics for patients with restlessness/agitation. Patients with persistent restlessness/agitation despite scheduled doses of neuroleptics (at least 8 mg/day) may benefit from addition of benzodiazepine. Rotation to a neuroleptic may sometimes be considered. For the few patients who continued to experience refractory agitation, palliative sedation with continuous infusion of benzodiazepine may be considered.

Conclusion

In summary, benzodiazepines are powerful sedatives. Clinicians need to carefully weigh the risks and benefits before prescribing benzodiazepines in patients with delirium and discuss the goals of care with family caregivers and patients (if possible). Appropriate use of benzodiazepines requires clinicians to prescribe the right medications at the right doses for the right indication to the right patient at the right time. In the setting of terminal delirium, the goal of care is to maximize comfort, recognizing that patients are unlikely to recover from their delirium [40]. Lorazepam may be added to haloperidol as rescue for the management of persistent restlessness/agitation in patients with terminal delirium. Patients who present with refractory agitation may require palliative sedation with continuous infusion of benzodiazepine. Benzodiazepines also have an established role in management of delirium secondary alcohol withdrawal. Outside of these two clinical settings, the role of benzodiazepine in delirium remains investigational.

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This double-blind randomized clinical trial is the first study to examine agitation as a primary outcome in patients with terminal delirium. It highlights the potential therapeutic role for lorazepam as an adjunctive agent to haloperidol for control of persistent agitation in this setting.

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This large randomized placebo-controlled trial reported the midazolam rescue without scheduled neuroleptic was more effective than midazolam rescue with schedule neuroleptics for management of delirium symptoms in palliative care patients, highlighting the role of benzodiazepine in this setting

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Bullets

- Clinicians may prescribe benzodiazepines skillfully by selecting the right medication at the right dose for the right indication to the right patient at the right time.
- The literature supports the use of benzodiazepines for persistent agitation in patients with terminal delirium and for patients with delirium tremens.
- A recent randomized controlled trial found that the combination of lorazepam and haloperidol was superior to haloperidol alone in reducing persistent agitation and improving perceived comfort in patients with terminal delirium.
- Among the benzodiazepines, midazolam and lorazepam are preferred for management of agitation in delirious patients because of their rapid onset of action, short half-life, and parenteral route availability.
- Outside of these two defined settings, the benzodiazepines in patients with delirium should be minimized because they may precipitate or worsen delirium symptoms.

Table 1.

Pharmacokinetic Properties of Benzodiazepines [23–26]

Medication	Onset / Peak effect	Elimination Half life	Dose equivalence	Comments
Temazepam	Onset: PO 0.5–2 h Tmax: 1.2–1.6 h	3.5–18.4 h	10 mg	Slow onset Intermediate acting Low potency No active metabolites Preferred in liver disease
Diazepam	Onset: IV 4–5 min Tmax: IV 1 min, IM 1 h, PO 15 min-2.5 h	IV: 33–45 h PO: 44–48 h PR: 45–46 h	5 mg	Fast onset Long acting Low potency Higher risk of abuse
Alprazolam	Onset: PO 1 h Tmax: PO 1–2 h	PO: 11–15 h	0.5 mg	Intermediate onset Intermediate acting High potency Higher risk of abuse
Clonazepam	Onset: PO 20–40 min Tmax: PO 1–4 h	17–60 h	0.25 mg	Fast onset Long acting High potency Partial serotonin agonist
Lorazepam	Onset: IV 2–3 min Tmax: PO 2 h, IM ≤3 h, SL 1 h	IV: 14 h IM: 13–18 h PO: 10 h	1 mg	Fast onset Short acting High potency Higher risk of abuse No active metabolites Preferred in liver disease
Midazolam	Onset: IV 3–5 min, IM 15 min, PO 10–20 min Tmax: IM 0.5–1 h, PO 0.17–2.65 h	3 h	2 mg	Fast onset Ultra short acting Intermediate potency Shortest half life