

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Gabapentin, Phenobarbital, Diazepam, and Lorazepam for the Treatment of Alcohol Withdrawal: Clinical Effectiveness and Guidelines

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Research Questions

1. What is the clinical effectiveness of gabapentin, phenobarbital, diazepam, and lorazepam for the management of individuals with alcohol withdrawal?
2. What are the evidence-based guidelines regarding the management of individuals with alcohol withdrawal in the emergency department?
3. What are the evidence-based guidelines regarding the provision of addiction services to vulnerable populations with alcohol withdrawal during the coronavirus pandemic?

Key Findings

Two systematic reviews and eleven non-randomized studies were identified regarding the clinical effectiveness of gabapentin, phenobarbital, diazepam, and lorazepam for the management of individuals with alcohol withdrawal. Four evidence-based guidelines were identified regarding the management of individuals with alcohol withdrawal in the emergency department. No relevant evidence-based guidelines were identified regarding the provision of addiction services to vulnerable populations with alcohol withdrawal during the coronavirus pandemic.

Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were the use of gabapentin, phenobarbital, diazepam, and lorazepam for addiction services, and COVID-19. No filters were applied to limit the retrieval by study type for question #1. For questions #2 and #3, a guidelines filter was applied. The search was also limited to English language documents published between January 1, 2015 and June 2, 2020.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Populations	Q1: Individuals with alcohol withdrawal Q2: Individuals presenting to the emergency department with alcohol withdrawal Q3: Vulnerable populations with alcohol withdrawal (e.g., those in need of supported self-isolation)
Interventions	Q1: Gabapentin; phenobarbital; diazepam; lorazepam Q2: Any intervention for managing alcohol withdrawal (e.g., pharmacologic treatments, non-pharmacologic treatments) Q3: Addiction services for managing alcohol withdrawal
Comparators	Q1: Any combination of gabapentin, phenobarbital, diazepam, or lorazepam Q2-Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g.: <ul style="list-style-type: none"> • symptom severity

Study Designs	<ul style="list-style-type: none"> • intensive care admissions • withdrawal seizures • mortality • safety [e.g., rates of adverse events]) <p>Q2-Q3: Recommendations regarding best practices (e.g.:</p> <ul style="list-style-type: none"> • Treatment protocols and advice for drug selection • Recommended safeguards • Guidance relating to how medications should be dispensed and monitored, • Discharge and admission protocols [e.g., using the Prediction of Alcohol Withdrawal Severity Scale] • Guidance relating to how isolation practices can be implemented)
	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Two systematic reviews^{1,2} and eleven non-randomized studies³⁻¹³ were identified regarding the clinical effectiveness of gabapentin, phenobarbital, diazepam, and lorazepam for the management of individuals with alcohol withdrawal. Four evidence-based guidelines¹⁴⁻¹⁷ were identified regarding the management of individuals with alcohol withdrawal in the emergency department. No relevant health technology assessments or randomized controlled trials were identified.

References of potential interest that did not meet the inclusion criteria are provided in the appendix.

Overall Summary of Findings

Two systematic reviews^{1,2} and eleven non-randomized studies³⁻¹³ were identified regarding the clinical effectiveness of gabapentin, phenobarbital, diazepam, and lorazepam for the management of individuals with alcohol withdrawal.

Two systematic reviews^{1,2} and seven non-randomized studies⁷⁻¹³ compared barbiturates to benzodiazepines for the treatment of alcohol withdrawal syndrome (AWS). The authors of one systematic review¹ and four non-randomized studies⁸⁻¹¹ found that patients treated with phenobarbital with or without concomitant benzodiazepine therapy experienced similar rates of intensive care unit (ICU) admission,^{1,9-11} median ICU length of stay,⁸ and hospital length of stay^{1,10} as patients treated with benzodiazepines alone. The second systematic review² found that barbiturates alone or in combination with benzodiazepines are as effective as benzodiazepines, with similar tolerability and safety profiles in an acute care setting. Patients treated with a combination of benzodiazepines and phenobarbital also had a similar improvement in severity of alcohol withdrawal and duration of withdrawal symptoms as patients treated with benzodiazepines alone.¹³ However, Tidwell et al.¹² found that patients treated with phenobarbital had significantly shorter ICU and hospital stays compared to patients treated with benzodiazepines. Similarly, Ibarra et al.⁷ found that significantly more patients in the lorazepam and phenobarbital treatment group were discharged within a three-day period compared to patients in the lorazepam control group.

The authors of one non-randomized study³ compared frontloading lorazepam to diazepam in patients with AWS. There was no significant difference among the groups in the mean

change in severity of alcohol withdrawal following treatment.³ Patients frontloaded with lorazepam had a significantly increased incidence of delirium in the intensive care unit.³

The authors of three non-randomized studies⁴⁻⁶ compared combination gabapentin and benzodiazepine therapy with benzodiazepines alone for the treatment of AWS. The authors of two of these non-randomized studies^{4,6} found similar outcomes between groups in terms of decrease in severity of alcohol withdrawal symptoms,⁴ duration of alcohol withdrawal protocol,⁶ and length of hospital stay.⁶ However, Levine et al.⁵ found that patients in the gabapentin treatment group had significantly lower levels of alcohol withdrawal symptoms on day three of hospitalization and shorter lengths of hospital stay compared to patients in the control group.

Four evidence-based guidelines¹⁴⁻¹⁷ were identified regarding the management of individuals with alcohol withdrawal in the emergency department. The guideline by Butt et al.¹⁴ recommends that older adults with symptoms of alcohol withdrawal should receive 24-hour care in intensive treatment or hospital settings if they are in poor general health, acutely suicidal, have dementia, are medically unstable, or need constant one-on-one monitoring.¹⁴ Older adults should be treated with a short-acting benzodiazepine such as lorazepam.¹⁴ The British Columbia Centre on Substance Abuse recommends that the Prediction of Alcohol Withdrawal Severity Scale be used to assess the risk of complications of alcohol withdrawal, and patients at high risk be treated with benzodiazepines in an inpatient setting.¹⁵ The National Institute for Health and Care Excellence recommends that patients with acute alcohol withdrawal in a hospital setting be treated with a benzodiazepine, carbamazepine, or clomethiazole and follow a symptom-triggered regimen.¹⁶ Guidelines from the Veteran Affairs and the Department of Defense recommend symptom-triggered therapy with benzodiazepines for the treatment of moderate to severe alcohol withdrawal.¹⁷ Carbamazepine, gabapentin, or valproic acid can be appropriate alternatives for managing mild to moderate alcohol withdrawal in patients for whom the risks associated with the use of benzodiazepines outweigh the benefits.¹⁷

No relevant evidence-based guidelines were found regarding the provision of addiction services to vulnerable populations with alcohol withdrawal during the coronavirus pandemic; therefore, no summary can be provided.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-Analyses

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Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

Lorazepam versus Diazepam

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Benzodiazepines versus Gabapentin

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Benzodiazepines versus Phenobarbital

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Guidelines and Recommendations

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See: Recommendations #15 and #16, page 146
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See: Recommendations #4-8, page 13; Section 5: Withdrawal Management, page 43
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<https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf>
See: Section VI: Recommendations, Recommendations #29-32, page 28

Appendix — Further Information

Previous CADTH Reports

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Systematic Reviews and Meta-Analyses

Comparator Not Specified

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Non-Randomized Studies

Alternative Population

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Alternative Outcomes

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Clinical Practice Guidelines – Unclear Methodology

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