



EVIDENCE SEARCH RESULTS

Question/subject of request:	The effectiveness of Oxazepam for alcohol detox/withdrawals for people with decompensated livers. I would like to put a case across for the trust to start using oxazepam for patients with decompensated livers.
Date requested:	17/09/2024
Date completed:	24/09/2024
Compiled by:	Roxanne Hart

CITING THIS SEARCH

If you reference this search in any paper, publication or presentation, please let us know.

The citation format is:

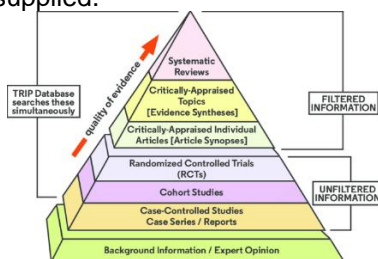
- Hart, R., (2024). *Evidence summary: use of Oxazepam for alcohol detox in people with decompensated liver*. Taunton, UK: Somerset Foundation Trust Knowledge and Library Services.

CONTACT DETAILS

Knowledge & Library Services:	<p>Email: library@somersetft.nhs.uk</p> <p>Telephone: MPH (01823) 342433 or YDH (01935) 384495 / 4697</p> <p>Website: https://somersetft-nhs.libguides.com/home</p> <p>Twitter: @SOMNHS_KLS</p>
Quality Improvement Team:	<p>Email: jessica.pawley@somersetFT.nhs.uk</p> <p>Website: Somerset Collaboration Hub - Home</p>
Primary Care:	<p>Email: LibraryPrimaryCare@somersetft.nhs.uk</p>

Librarian's Comments:

Abstracts are provided where available and relevant. Some articles have full text availability, as indicated by a corresponding link. If you have any problems accessing the links or would like an article which does not have immediate full text access, please contact a member of the library staff who will arrange for the article to be supplied.



The results are presented according to the hierarchy of evidence which is used to rank the relative strength of results obtained from scientific research.

The design of the study and the endpoints measured affect the strength of the evidence.

Evidence hierarchies are often applied in evidence-based practices and are integral to evidence-based medicine.



This work is licensed under a [CC BY NC 4.0 license](https://creativecommons.org/licenses/by-nc/4.0/)

Disclaimer: We will endeavour to use the best, most appropriate and most recent sources available to ensure that the information supplied is accurate, up-to-date and evidence-based. It is the responsibility of the requestor to determine the accuracy, validity and interpretation of the search results. No responsibility can be taken by the library for any action taken on the basis of this information. Read our full disclaimer [here](#).



You will need your [NHS OpenAthens account](#) to access the full text of licenced content. This service is provided to the NHS in England by Health Education England.

Contents (click to jump to each section):

- [Studies which recommend use of Oxazepam for liver disease/cirrhosis/hepatitis](#)
- [Alternative perspective on use of Oxazepam for Severe alcohol withdrawal](#)
- [Physiologically based Pharmacokinetic models](#)
- [Examples of Guidelines from other trusts](#)
- [Guidelines from Health Bodies](#)
- [Point of Care Tools](#)
- [Comparison of safety and effectiveness](#)

There is good consensus from studies that Oxazepam (or Lorazepam) is the preferred agent to use in management of AWS in cases of alcoholic liver disease. This is reflected in both studies [Long et al 2017](#); [Airagnes et al 2019](#), [Mirijello et al 2015](#), [Chand et al 2022](#), consensus guidelines ([ACG](#) & [EASL](#)) and point of care summaries from [BMJ Best Practice](#) and [UpToDate](#). I have also included Guidelines from examples of other NHS trusts who use Oxazepam ([Oxford](#), [Cambridgeshire & Peterborough](#)). I only found one alternative perspective, an opinion piece by an American doctor. [Weintraub 2017](#) asserts that “the widespread preference for the use of lorazepam or oxazepam instead of diazepam for the treatment of alcohol withdrawal in elderly patients and patients with liver disease is unfounded as long as a symptom-based approach is used, and diazepam should be preferred because of the advantages it affords.” I did not encounter a similar perspective elsewhere.

Studies which recommend use of Oxazepam for liver disease/cirrhosis/hepatitis

[Long et al 2017](#) “in the presence of advanced cirrhosis or hepatitis....oxazepam may be a better option in this setting due to the shorter half life and absence of liver metabolites.”

[Airagnes et al 2019](#), Oxazepam should be preferred in patients with reduced liver metabolism, such as in the elderly or in those with advanced liver disease because of their advantageous pharmacokinetics.

[Mirijello et al 2015](#) in patients with reduced liver metabolism, such as in the elderly or in those with advanced liver disease, the use of short-acting agents may be preferred. In these cases, oxazepam and lorazepam represent the drugs of choice.

[Chand et al 2022](#) Lorazepam and oxazepam are preferred agents for the management of AWS in the setting of Alcoholic liver disease

Alternative perspective on use of Oxazepam for Severe alcohol withdrawal

[Weintraub 2017](#)

Comparison of safety and effectiveness

[Qu et al 2024](#), [Bahji et al 2022](#); [Fluyau et al 2023](#) compares 20 non-BZDs and 5 BZDs in 30 RCTs

Fluyau does not specifically discuss decompensated livers but assesses efficacy and safety overall.



The Knowledge & Library Service have a growing archive of completed evidence summaries on [inSPIRE](#) – the organisation’s knowledge, research and evidence repository. You can browse the evidence summaries [here](#).

These results of this search will only be shared in the repository if you have given your permission to do so (we ask this in the evidence search request form).

Thank you.





Comparison of safety and effectiveness

Qu, L., Ma, X. P., Simayi, A., Wang, X. L., & Xu, G. P. (2024). Comparative efficacy of various pharmacologic treatments for alcohol withdrawal syndrome: A systematic review and network meta-analysis. *International Clinical Psychopharmacology*, 39(3), 148–162. For a copy of the full text please email library@somersetft.nhs.uk

This study was to compare multiple classes of medications and medication combinations to find alternatives or additives for patients not applicable to benzodiazepines (BZDs). We performed a network meta-analysis to assess the comparative effect of 11 pharmacologic treatments in patients with alcohol withdrawal syndrome. Forty-one studies were included, comprising a total sample size of 4187 participants. The pooled results from the randomized controlled trials showed that there was no significant difference in the Clinical Institute Withdrawal Assessment-Alcohol, revised (CIWA-Ar) reduction with other medications or medication combinations compared to BZDs. Compared to BZDs, the mean difference in ICU length of stay of anticonvulsants + BZDs was -1.71 days (95% CI = -2.82, -0.59). Efficacy rankings from cohort studies showed that anticonvulsant + BZDs were superior to other treatments in reducing CIWA-Ar scores and reducing the length of stay in the ICU. Synthesis results from randomized controlled trials indicate that there are currently no data suggesting that other medications or medication combinations can fully replace BZDs. However, synthetic results from observational studies have shown that BZDs are effective in the context of adjuvant anticonvulsant therapy, particularly with early use of gabapentin in combination with BZDs in the treatment of alcohol withdrawal syndrome, which represents a promising treatment option.

Fluyau, D., Kailasam, V. K., & Pierre, C. G. (2023). [Beyond benzodiazepines: A meta-analysis and narrative synthesis of the efficacy and safety of alternative options for alcohol withdrawal syndrome management](#). *European Journal of Clinical Pharmacology*, 79(9), 1147–1157.

PURPOSE: To compare the efficacy and safety of non-benzodiazepines (non-BZDs) to benzodiazepines (BZDs) in the treatment of alcohol withdrawal syndrome (AWS). **METHODS:** For relevant literature, Google Scholar, PubMed, Embase, OVID MEDLINE, EBSCO, Cochrane Central Registry of Controlled Trials, Web of Science, and Scopus were searched. Randomized control trials (RCTs) were included, omitted were nonblinded trials, blinded trials that were not randomized, and open-label studies. The Effective Public Health Practice Project Quality Assessment was used to assess the trial's quality. A meta-analysis and a narrative synthesis were carried out. **RESULTS:** Twenty non-BZDs and five BZDs were investigated in thirty RCTs. Meta-analysis favored gabapentin over chlordiazepoxide and lorazepam ($d = 0.563$, p : Twenty non-BZDs and five BZDs were investigated in thirty RCTs. Meta-analysis favored gabapentin over chlordiazepoxide and lorazepam ($d = 0.563$, p **CONCLUSION:** For AWS treatments, non-BZDs are superior to or equally effective as BZDs. Non-BZD adverse events warrant further investigation. Agents that inhibit gated ion channels are promising candidates.

Bahji, A., Bach, P., Danilewitz, M., Crockford, D., El-Guebaly, N., Devoe, D. J., & Saitz, R. (2022). [Comparative efficacy and safety of pharmacotherapies for alcohol withdrawal: A systematic review and network meta-analysis](#). *Addiction*, 117(10), 2591–2601.

BACKGROUND AND AIMS: There have been few head-to-head clinical trials of pharmacotherapies for alcohol withdrawal (AW). We, therefore, aimed to evaluate the comparative performance of pharmacotherapies for AW. **METHODS:** Six databases were searched for randomized clinical trials through November 2021. Trials were included after a blinded review by two independent reviewers. Outcomes included incident seizures, delirium tremens, AW severity scores, adverse events, dropouts, dropouts from adverse events, length of hospital stay, use of additional medications, total benzodiazepine requirements, and death. Effect sizes were pooled using frequentist random-effects network meta-analysis models to generate summary ORs and Cohen's d standardized mean differences (SMDs). **RESULTS:** Across the 149 trials, there were 10 692 participants (76% male, median 43.5 years old). AW severity spanned mild ($n = 32$), moderate ($n = 51$), and severe ($n = 66$).





Fixed-schedule chlormethiazole (OR, 0.16; 95% CI, 0.04-0.65), fixed-schedule diazepam (OR, 0.16; 95% CI, 0.04-0.59), fixed-schedule lorazepam (OR = 0.19; 95% CI, 0.08-0.45), fixed-schedule chlordiazepoxide (OR = 0.21; 95% CI, 0.08-0.53), and divalproex (OR = 0.22; 95% CI, 0.05-0.86) were superior to placebo at reducing incident AW seizures. However, only fixed-schedule diazepam (OR, 0.19; 95% CI, 0.05-0.76) reduced incident delirium tremens. Oxcarbazepine (d = -3.69; 95% CI, -6.21 to -1.17), carbamazepine (d = -2.76; 95% CI, -4.13 to -1.40), fixed-schedule oxazepam (d = -2.55; 95% CI, -4.26 to -0.83), and gamma-hydroxybutyrate (d = -1.80; 95% CI, -3.35 to -0.26) improved endpoint Clinical Institute Withdrawal Assessment for Alcohol-Revised scores over placebo. Promazine and carbamazepine were the only agents significantly associated with greater dropouts because of adverse events. The quality of evidence was downgraded because of the substantial risk of bias, heterogeneity, inconsistency, and imprecision. **CONCLUSIONS:** Although some pharmacotherapeutic modalities, particularly benzodiazepines, appear to be safe and efficacious for reducing some measures of alcohol withdrawal, methodological issues and a high risk of bias prevent a consistent estimate of their comparative performance.

Physiologically based Pharmacokinetic models

Docci, L., Umehara, K., Krähenbühl, S., Fowler, S., & Parrott, N. (2020). Construction and verification of physiologically based pharmacokinetic models for four drugs majorly cleared by glucuronidation: Lorazepam, oxazepam, naloxone, and zidovudine. *The AAPS journal*, 22, 1-14. For a copy of the full text email library@somersetft.nhs.uk

Physiologically based pharmacokinetic (PBPK) modeling is less well established for substrates of UDP-glucuronosyltransferases (UGT) than for cytochrome P450 (CYP) metabolized drugs and more verification of simulations is necessary to increase confidence. To address specific challenges of UGT substrates, we developed PBPK models for four drugs cleared majorly via glucuronidation (lorazepam, oxazepam, naloxone, and zidovudine). In vitro to in vivo scaling of intrinsic clearance generated with co-cultured human hepatocytes was applied for hepatic metabolism and extra-hepatic clearance was extrapolated based on relative expression of UGT isoforms in the liver, kidney, and intestine. Non-metabolic clearance and the contributions of individual UGT isoforms to glucuronidation were based on in vitro and in vivo studies taken from the literature and simulations were verified and evaluated with a broad set of clinical pharmacokinetic data. Model evaluation showed systemic clearance predictions within 1.5-fold for all drugs and all simulated parameters were within 2-fold of observed. However, during the verification step, top-down model fitting was necessary to adjust for under-prediction of zidovudine V_{SS} and renal clearance and over estimation of intestinal first pass for lorazepam, oxazepam, and zidovudine. The impact of UGT2B15 polymorphisms on the pharmacokinetics of oxazepam and lorazepam was simulated and glucuronide metabolites were also simulated for all four drugs. To increase confidence in predicting extra-hepatic clearance, improvement of enzyme phenotyping for UGT substrates and more quantitative tissue expression levels of UGT enzymes are both needed. Prediction of glucuronide disposition is also challenging when active transport processes play a major role.

Alternative perspective on use of Oxazepam for Severe alcohol withdrawal

Weintraub, S. J. (2017). [Diazepam in the treatment of moderate to severe alcohol withdrawal](#). *CNS drugs*, 31(2), 87-95.

In elderly patients and patients with decreased hepatic function, the elimination half-lives of diazepam and desmethyldiazepam are prolonged whereas those of lorazepam and oxazepam are unchanged [12]. On this basis, it is frequently asserted that the risk of prolonged over-sedation with diazepam treatment is unacceptable in these patients and that lorazepam or oxazepam should be used [12]. However, diazepam should be considered the same as any other drug for which dosing is adjusted based on patient-specific alterations in pharmacokinetics [27, 70–72], such as when vancomycin is used in patients with renal impairment. In fact, when an individualized symptom-





based approach is used to dose diazepam intravenously for the treatment of alcohol withdrawal, optimal dosing is facilitated because diazepam is titrated to a rapidly achieved and readily apparent clinical response. Indeed, the authors of a report on diazepam loading commented, “The loading dose method offers a distinct advantage in the treatment of the elderly and patients with impaired liver function, since dosing is adjusted according to individual response, and therefore, the risk of overdosage is avoided

Studies which recommend use of Oxazepam for liver disease/cirrhosis/hepatitis

Chand, P. K., Panda, U., Mahadevan, J., & Murthy, P. (2022). [Management of alcohol withdrawal syndrome in patients with alcoholic liver disease](#). *Journal of Clinical & Experimental Hepatology*, 12(6), 1527–1534.

Alcohol withdrawal syndrome (AWS) is a common condition that is seen in treatment-seeking patients with Alcohol use disorder (AUD) and alcoholic liver disease (ALD). AWS, which typically starts within 4-6 h of the last alcohol use, can range from mild symptoms such as insomnia, tremors, and autonomic hyperactivity to more severe symptoms such as seizures and delirium tremens. Clinical Institute Withdrawal Assessment Scale-Alcohol Revised (CIWA-Ar) is the most commonly used scale to assess AWS in clinical practice. The presence of moderate withdrawal as indicated by a score of more than 8 is an indication for pharmacotherapy. Lorazepam and oxazepam are preferred agents for the management of AWS in the setting of ALD. In severe ALD, benzodiazepines should be used cautiously with monitoring due to the risk of excessive sedation or precipitating hepatic encephalopathy.

Long, D., Long, B., & Koyfman, A. (2017). [The emergency medicine management of severe alcohol withdrawal](#). *The American journal of emergency medicine*, 35(7), 1005-1011.

In the presence of advanced cirrhosis or hepatitis (moderate elevations of AST/ALT (less than 300 IU/ml), AST:ALT ratio >2, elevated serum bilirubin, elevated GGT, moderate leukocytosis (neutrophils), and elevated INR), the duration of lorazepam and diazepam is extended due to hepatic metabolism. Oxazepam may be a better option in this setting due to the shorter half-life and absence of liver metabolites.

Airagnes, G., Ducoutumany, G., Laffy-Beaufils, B., Le Faou, A. L., & Limosin, F. (2019). [Alcohol withdrawal syndrome management: Is there anything new?](#). *La Revue de medecine interne*, 40(6), 373-379.

Oxazepam should be preferred in patients with reduced liver metabolism, such as in the elderly or in those with advanced liver disease because of their advantageous pharmacokinetics

Mirijello, A., D'Angelo, C., Ferrulli, A., Vassallo, G., Antonelli, M., Caputo, F., Leggio, L., Gasbarrini, A., & Addolorato, G. (2015). [Identification and management of alcohol withdrawal syndrome](#). *Drugs*, 75(4), 353–365.

“However, in patients with reduced liver metabolism, such as in the elderly or in those with advanced liver disease, the use of short-acting agents may be preferred in order to prevent excessive sedation and respiratory depression [55]. In these cases, oxazepam and lorazepam represent the drugs of choice due to the absence of oxidative metabolism and active metabolites”

Examples of Guidelines from other trusts:

Oxford Health NHS FT, [Guidelines for the management of alcohol dependence, 2020](#)

Severe liver impairment: “If there is severe liver impairment, the shorter acting benzodiazepines, oxazepam or lorazepam should be considered in order to prevent accumulation, but specialist advice should be sought. Close monitoring and frequent review will be necessary”



This work is licensed under a [CC BY NC 4.0 license](#)



Cambridgeshire & Peterborough, [Alcohol Detoxification \(Inpatient\) Prescribing Guidelines, 2020](#)

The benzodiazepine of choice for uncomplicated withdrawal is chlordiazepoxide. However, its long half-life may lead to accumulation in older patients, or those **with impaired liver function**. In these circumstances a shorter-acting benzodiazepine, such as oxazepam, may be prescribed instead

Guidelines from Health Bodies:

Singal, A. K., Bataller, R., Ahn, J., Kamath, P. S., & Shah, V. H. (2018). [ACG Clinical Guideline: Alcoholic Liver Disease](#). *The American journal of gastroenterology*, 113(2), 175–194

“Short and intermediate-acting benzodiazepines (e.g., lorazepam and oxazepam) are safer for patients with poor liver function.”

European Association for the Study of the Liver. European Association for the Study of the Liver (2018). [EASL Clinical Practice Guidelines: Management of alcohol-related liver disease](#). *Journal of hepatology*, 69(1), 154–181.

“Short and intermediate-acting benzodiazepines (e.g. lorazepam, oxazepam) are safer in elderly patients and those with hepatic dysfunction”

Right Decision Service, Health Improvement Scotland, [Management of Alcohol Withdrawal, 2024](#)

“For patients with known liver impairment, **oxazepam** is the benzodiazepine of choice”

Gov.uk, [UK clinical guidelines for alcohol treatment: core elements of alcohol treatment, 2023](#)

“You can choose benzodiazepines with a shorter half-life, such as oxazepam, for people who potentially metabolise medication more slowly, such as those with extensive liver disease or older patients. “

Point of Care Tools

BMJ Best Practice, [Alcohol-related liver disease](#)

“Shorter-acting benzodiazepines (e.g., oxazepam, lorazepam) are safer in older adults and those with hepatic dysfunction”

UpToDate, [Management of moderate and severe alcohol withdrawal syndromes, 2024](#).

“We prefer [lorazepam](#) (Ativan) or [oxazepam](#) (Serax) for the treatment of patients with advanced cirrhosis or acute alcoholic hepatitis. The shorter half-life of lorazepam and the absence of active metabolites with oxazepam may prevent prolonged effects if oversedation occurs”

FOR OFFICE USE ONLY



This work is licensed under a [CC BY NC 4.0 license](#)



DATABASES AND INFORMATION SOURCES USED

	Pubmed		HMIC	X	BMJ Best Practice
X	Medline		Social Policy and Practice		Cochrane Library
	Emcare		CINAHL		TRIP
X	Embase		PsycINFO	X	Grey Literature
	AMED	X	UpToDate	X	Other

PURPOSE OF SEARCH

	Patient info/health & well being	X	Clinical decision making (inc. patient care)
	Executive Team support		Research/Education/Professional development
	Quality Improvement		Primary Care & Neighbourhoods Directorate support
	KM/Management decision making		Other

USER CATEGORY OF REQUESTOR

	Medical students		Patients/public
	Nursing/midwifery students		Physician Associates
	Junior doctors		Public Health (Somerset CC)
X	Nurses/Midwives		Other
	Allied Health professionals		

HAS PERMISSION TO SHARE THE RESULTS BEEN OBTAINED FROM THE REQUESTOR?

X	YES - share		NO – do not share
---	-------------	--	-------------------

KEY WORDS/SEARCH STRATEGY

LIMITS USED





INCLUDING MESH HEADINGS

decompensated livers
oxazepam
alcohol detox
alcohol withdrawals
liver disease
deranged liver
hepatitis b
hepatitis c
alcoholic hepatitis
kidney metabolism

