



EVIDENCE SEARCH RESULTS

Question/subject of request:	What is a good dose range of Chlordiazepoxide for symptom triggered alcohol withdrawals in acute hospital? I would like to know what are the average dosing ranges when using a symptom triggered alcohol withdrawal tool.
Date requested:	17 th September 2024
Date completed:	
Compiled by:	Cate Newell – Knowledge & Library Services Manager

CITING THIS SEARCH

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

The citation format is:

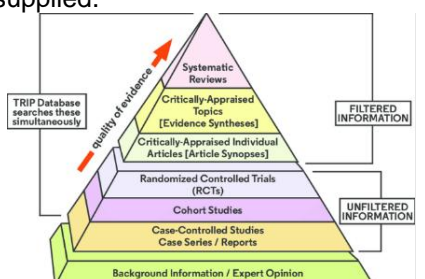
- Surname, Initial., (Year). *Evidence summary: <insert title of evidence search>*, Taunton, UK: Somerset Foundation Trust Knowledge and Library Services.

CONTACT DETAILS

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Quality Improvement Team:	<p>Email: jessica.pawley@somersetFT.nhs.uk Website: Somerset Collaboration Hub - Home</p>
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Librarian's Comments:

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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.



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Contents (click to jump to each section):

- [BNF](#)
- [NICE Guidelines](#)
- [BMJ Best Practice](#)
- [UpToDate](#)
- [Journal articles](#)

Summary of search results:

From [BNF \(British National Formulary\)](#):

Treatment of alcohol in moderate dependence:

10–30 mg 4 times a day, dose to be gradually reduced over 5–7 days, consult local protocols for titration regimens (Adults)

Treatment of alcohol withdrawal in severe dependence

10–50 mg 4 times a day and 10–40 mg as required for the first 2 days, dose to be gradually reduced over 7–10 days, consult local protocols for titration regimens; maximum 250 mg per day (Adults)

From [NICE Guidelines](#):

Follow a symptom-triggered regimen for drug treatment for people in acute alcohol withdrawal who are:

- In hospital
- In other settings where 24 hour assessment and monitoring are available.

From [BMJ Best Practice](#):

Choose a drug and dose regimen based on the indication, severity of symptoms, and patient factors (e.g., presence of hepatic impairment, delirium, or dementia; ability to tolerate oral medication; inpatient vs. outpatient). Follow local protocols.

In the UK, a fixed-dose regimen is generally preferred for any patient being managed on a general inpatient ward. A symptom-triggered regimen may put these patients at risk of being under-treated if the regimen is not followed closely. It requires more regular observation and may only be practical in environments that have the facilities for close monitoring, such as the emergency department or intensive care.

Use a symptom-triggered regimen if the patient is in hospital and can be monitored closely or in settings where 24-hour assessment and monitoring are available (e.g., the emergency department or intensive care).

Patients with mild to moderate alcohol withdrawal symptoms (CIWA-Ar < 10 or GMAWS < 2) can generally be managed with supportive care only

From [UpToDate](#):

A symptom-triggered approach is recommended for most patients to treat alcohol withdrawal when pharmacotherapy is indicated. It involves providing medication only when a patient has symptoms.





To use this approach, a regular systematic assessment should be made of the patient's status using a validated instrument, such as the Clinical Institute Withdrawal Assessment for Alcohol–Revised (CIWA–Ar), a measure of withdrawal severity ([table 5](#)) [48], or some equivalent assessment, such as the Severity of Ethanol Withdrawal Scale (SEWS) [49] or Brief Alcohol Withdrawal Scale (BAWS) [50,51]..... Once severe symptoms are controlled, hourly reassessment of such patients is reasonable. By contrast, an interval of four to six hours is reasonable for stable patients with mild symptoms receiving oral benzodiazepines.

When the score is elevated (any score of 8 or greater on the CIWA–Ar or 6 or greater on the SEWS), additional medication is given. For acute withdrawal, we give [chlordiazepoxide](#) 25 to 100 mg orally ([oxazepam](#) 10 to 30 mg orally in patients with severe liver disease).

I've included a few [journal articles](#) which may be relevant or further reading. This includes a conference abstract on AAW in Yeovil District Hospital, dated 2 years ago, for historical knowledge ([Germesheid 2022](#)).

I hope this is helpful. Please do let us know if you need any further information.



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.

BNF (British National Formulary)

[Chlordiazepoxide hydrochloride](#) | [Drugs](#) | [BNF](#) | [NICE](#)

Accessed: 30th September 2024.

NICE Guidelines

[Overview](#) | [Alcohol-use disorders: diagnosis and management of physical complications](#) | [Guidance](#) | [NICE](#)

Accessed: 30th September 2024

BMJ Best Practice

[Alcohol withdrawal - Treatment algorithm](#) | [BMJ Best Practice](#)

Accessed: 30th September 2024.

NHS OpenAthens login may be required to access full-text.

UpToDate



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<https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes>

Accessed: 30th September 2024

NHS OpenAthens login may be required to access full-text.

Journal articles

1. [Comparative efficacy of various pharmacologic treatments for alcohol withdrawal syndrome: a systematic review and network meta-analysis](#)

Authors: Qu, Li;Xue-Ping Ma;Simayi, Alimujiang;Xiao-Li Wang and Gui-Ping Xu

Publication Date: 2024

Journal: International Clinical Psychopharmacology 39(3), pp. 148–162

Abstract: 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.

Access or request full text: <https://libkey.io/10.1097/YIC.0000000000000526>

2. [Beyond benzodiazepines: a meta-analysis and narrative synthesis of the efficacy and safety of alternative options for alcohol withdrawal syndrome management.](#)

Authors: Fluyau, D.;Kailasam, V. K. and Pierre, C. G.

Publication Date: 2023

Journal: European Journal of Clinical Pharmacology 79(9), pp. 1147–1157

Abstract: Purpose: To compare the efficacy and safety of non-benzodiazepines (non-BZDs) to benzodiazepines (BZDs) in the treatment of alcohol withdrawal syndrome (AWS).

Access or request full text: <https://libkey.io/10.1007/s00228-023-03523-2>



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3. [Assessment of Treatment Patterns in Patients with Alcohol Withdrawal Syndrome during Hospitalisation and Post-discharge: A Retrospective Cohort Study](#)

Authors: Shah, Nilesh;Karia, Sagar;Gowda, Mahesh;Gupta, Gorav;Dey, Snehanshu;Phani, Prasant Mulakaluri;Sidana, Aninda and Pangaonkar, Shailesh

Publication Date: 2023

Journal: Journal of Clinical and Diagnostic Research 17(09), pp. 1

Abstract: Introduction: Alcohol dependence is an increasing and pervasive problem. Alcohol Withdrawal Syndrome (AWS) is a cluster of symptoms that occur in alcohol-dependent individuals after cessation or reduction of alcohol consumption. However, studies on the clinicoepidemiological profile of patients with AWS and treatment patterns in India are scarce. Aim: To assess the treatment patterns during hospitalisation and after discharge in Indian patients with AWS. Materials and Methods: A retrospective observational study was conducted using data from 1000 patients with AWS who were admitted to nine addiction centres across India. Data from medical charts from the previous five years were collected over six months, from January to June 2022. The study included patients of either sex, aged ≥ 18 years at the time of data collection, who had been hospitalised for AWS symptoms and had ≥ 3 months of documented follow-ups. The primary endpoints of the study were the most commonly used medications and their dose titrations in the treatment of AWS, as well as the duration of treatment in the hospital and post-discharge. Key secondary endpoints included the socio-demographic profile of patients, common comorbidities, common signs and symptoms, the association between prescription patterns of Benzodiazepines (BZDs) and liver enzyme levels, and the average duration of hospital stay. Continuous variables were summarised as mean and Standard Deviation (SD), while categorical variables were summarised as frequency and percentages. Levels of serum Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), γ -Glutamyl Transferase (GGT), and bilirubin were recorded from the source data, if available, and the association with the use of chlordiazepoxide and lorazepam was analysed using the Chi-square test. Results: The mean \pm SD age of the 1000 enrolled patients was 41.4 \pm 9.6 years, with the majority (n=997; 99.7%) being males. BZDs were the mainstay pharmacotherapy, with lorazepam (n=686; 68.6%) and chlordiazepoxide (n=482; 48.2%) being the two most commonly prescribed BZDs during hospitalisation. During post-discharge treatment, 57.0% (n/N=74/130) of patients received lorazepam, while 52.0% (n/N=67/130) received chlordiazepoxide. Frequently used drug regimens during hospitalisation included fixed doses of chlordiazepoxide {25 mg twice a day (BID:143/482; 29.7%), 20 mg thrice a day (TID:103/482; 21.4%), or 25mg TID (87/482; 18.0%)}, or lorazepam {2 mg TID (188/686; 27.4%), 2 mg BID (183/686; 26.7%), or 2 mg once a day (OD;175/686; 25.5%)}. Commonly observed signs and symptoms included tremors (n=567; 56.7%), irritability (n=539; 53.9%), and agitation (n=500; 50.0%). Depression (n=182; 18.2%) and anxiety (n=136; 13.6%) were the most commonly reported co-morbidities. Among the patients, only 13.4% (86/641) had an AST/ALT ratio >2 , and 12.9% (44/340) had AST and GGT levels $>2\times$ Upper Limit of Normal (ULN). There was no significant difference in these patients between those receiving and not receiving chlordiazepoxide ($p>0.05$). The mean \pm SD duration of hospitalisation was 23.1 \pm 18.97 days, while the mean \pm SD duration of treatment during hospitalisation and post-discharge was 22.3 \pm 16.36 days and 71.6 \pm 52.3 days, respectively. Conclusion: The two most commonly prescribed drugs during hospitalisation and post-discharge were the BZDs, lorazepam and chlordiazepoxide. Fixed-dose regimens of chlordiazepoxide at 25 mg BID or TID, or 20 mg TID, and lorazepam at 2 mg TID, BID, or OD were frequently used during hospitalisation.

Access or request full text: <https://libkey.io/10.7860/JCDR/2023/65720.18469>



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4. [Comparative efficacy and safety of pharmacotherapies for alcohol withdrawal: a systematic review and network meta-analysis](#)

Authors: Bahji, Anees;Bach, Paxton;Danilewitz, Marlon;Crockford, David;el-Guebaly, Nady;Devoe, Daniel J. and Saitz, Richard

Publication Date: 2022

Journal: Addiction 117(10), pp. 2591–2601

Abstract: 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 γ -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.

Access or request full text: <https://libkey.io/10.1111/add.15853>

5. [Clinical management of the alcohol withdrawal syndrome](#)

Authors: Day, Ed and Daly, Chris

Publication Date: 2022

Journal: Addiction (Abingdon, England) 117(3), pp. 804–814

Abstract: Up to half of individuals with a history of long-term, heavy alcohol consumption will experience the alcohol withdrawal syndrome (AWS) when consumption is significantly decreased or stopped. In its most severe form, AWS can be life-threatening. Medically assisted withdrawal (MAW) often forms the first part of a treatment pathway. This clinical review discusses key elements of the clinical management of MAW, necessary adjustments for pregnancy and older adults, likely outcome of an episode of MAW, factors that might prevent completion of the MAW process and ways of overcoming barriers to ongoing treatment of alcohol use disorder. The review also discusses the use of benzodiazepines in MAW. Although



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there is clear evidence for their use, benzodiazepines have been associated with abuse liability, blunting of cognition, interactions with depressant drugs, craving, delirium, dementia and disrupted sleep patterns. Because glutamatergic activation and glutamate receptor upregulation contribute to alcohol withdrawal, anti-glutamatergic strategies for MAW and other potential treatment innovations are also considered. (© 2021 The Authors. Addiction published by John Wiley & Sons Ltd on behalf of Society for the Study of Addiction.)

Access or request full text: <https://libkey.io/10.1111/add.15647>

6. [Harmful Outcomes in Patients Admitted to Yeovil District Hospital in Acute Alcohol Withdrawal](#)

Item Type: Conference Proceeding

Authors: Germscheid, E. and Sherwin, T.

Publication Date: 2022

Publication Details: BJPsych Open. Conference: Royal College of Psychiatrists International Congress, RCPsych 2022. Edinburgh United Kingdom. 8(Supplement 1) (pp S154-S155); Cambridge University Press,

Abstract: Aims. Our aim was to assess what proportion of patients in Acute Alcohol Withdrawal (AAW) experience harm during their admission to hospital. Our hypothesis was that patients who came to harm were likely to have had sub-optimal withdrawal management. Therefore, we also aimed to identify any underlying issues in the way AAW is currently managed which may be contributing to harmful outcomes. Methods. Inclusion criteria for the audit was inpatients at Yeovil District Hospital over a three-month period from May to July 2021, clinically coded under the heading 'alcohol abuse', with a minimum two-day admission. Data were gathered from the patients' medical notes. An outcome was determined as harmful if firstly, it occurred during the withdrawal period, and secondly it was clinically feasible that it had occurred at least in part, as a result of poor AAW management. Notes from 15 patients were qualitatively reviewed, guided by NICE recommendations, to assess both adherence to, and suitability of YDH AAW policy. Results. Alcohol abuse was identified at the time of medical clerking in all 15 patients. Audit-C scores were completed in 7 patients. All 15 patients had CIWA scoring initiated within 1 hour of clerking, and chlordiazepoxide prescribed as a STAT dose and then a fixed PRN dose according to whether CIWA score was above 10 or not. 10 patients had their CIWA scores monitored for at least 24 hours. 3 out of 15 inpatients had harmful outcomes, including falls, intracerebral haemorrhage, fractured neck of femur, and cardiac arrest. Conclusion. Overall, adherence to YDH guidelines was good. Despite this, a high proportion of patients admitted under our care were harmed as a result of inadequate management of alcohol withdrawal. Where issues were identified, these were arguably linked to problems with the YDH AAW policy itself. Unclear guidance over how long to monitor CIWA scores, limitation of chlordiazepoxide doses to 10 mg for even the highest CIWA scores, and omission of Audit-C score in the current hospital guidelines, are suggested as contributors to harm in the three patients identified. Going forward, it will be important to review and make appropriate changes to the YDH policy in these areas according to NICE recommendations, to protect our patients from further harm. These results may well have wider implications in terms of adjustment to AAW policy at other hospitals across the UK.

Access or request full text: <https://libkey.io/10.1192/bjo.2022.439>



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7. [Implementation of a Symptom-Triggered Protocol for Severe Alcohol Withdrawal Treatment in a Medical Step-down Unit](#)

Authors: Huang, Paul W. and Bhalla, Rohit

Publication Date: 2021

Journal: Journal of Clinical Outcomes Management 28(3), pp. 134–138

Abstract: Objective: This single-center, quasi-experimental study of adult patients admitted or transferred to a medical step-down unit with alcohol withdrawal diagnoses sought to determine if symptom-triggered therapy (STT) is more effective than combined fixed-scheduled (FS) and STT in severe alcohol withdrawal. Methods: In the preintervention group (72 episodes), patients were treated with FS and STT based on physician preference. In the postintervention group (69 episodes), providers were required to utilize only the STT protocol. Results: Implementation of the intervention was associated with a significant reduction in average (per patient) cumulative benzodiazepine dose, from 250 mg to 96 mg ($P < .001$) and a decrease in average length of stay from 8.0 days to 5.1 days ($P < .001$). Secondary safety measures included a reduction in the proportion of patients who experienced delirium tremens from 47.5% to 22.5% ($P < .001$), and a reduction in intubation rates from 13.8% to 1.3% ($P = .003$). Conclusion: The STT protocol proved to be more effective and safer in treating severe alcohol withdrawal patients than usual care employing STT with FS. We believe the successful implementation of a STT protocol in high-acuity patients requires frequent monitoring to assess withdrawal severity combined with appropriate and timely dosing of benzodiazepines.

Access or request full text: <https://libkey.io/10.12788/jcom.0048>

8. [Symptom-Triggered Therapy for Alcohol Withdrawal Syndrome: a Systematic Review and Meta-analysis of Randomized Controlled Trials](#)

Authors: Holleck, Jürgen L.; Merchant, Naseema and Gunderson, Craig G.

Publication Date: 2019

Journal: JGIM: Journal of General Internal Medicine 34(6), pp. 1018–1024

Abstract: Background: Benzodiazepines are the standard medication class for treating alcohol withdrawal. Guidelines recommend dosing based on objectively measured symptoms (symptom-triggered therapy) rather than fixed dose regimens. However, the superiority of symptom-triggered therapy has been questioned, and concerns have been raised about its inappropriate use and safety. We aimed to assess whether symptom-triggered therapy is superior to fixed dose schedules in terms of mortality, delirium, seizures, total benzodiazepine dose, and duration of therapy. Methods: A systematic literature search using Medline, Embase, and the Cochrane Registry through February 2018 was conducted for randomized controlled trials of patients with alcohol withdrawal syndrome comparing fixed dose benzodiazepine schedules to symptom-triggered therapy. Risk of bias was assessed using the Cochrane Risk of Bias Tool. Outcomes were pooled using random effects meta-analysis. Heterogeneity was estimated using the I² statistic. Strength of evidence was assessed using methods outlined by the Agency for Healthcare Research and Quality. Results: Six studies involving 664 patients were included. There were no deaths and only one seizure in each group. Four studies reported delirium, which occurred in 4 out of 164 patients randomized to symptom-triggered therapy compared to 6 out of 164 randomized to fixed dose therapy (odds ratio, 0.64 95% CI, 0.17–2.47). Three studies reported duration of therapy, which was 60.4 h less with symptom-triggered therapy (95% CI, 39.7–81.1 h; $p < 0.001$). Six studies reported total benzodiazepine



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dosage, which was 10.5 mg in lorazepam-equivalent dosing less with symptom-triggered therapy (95% CI, 7.1–13.9 mg; $p = 0.011$). Discussion: Moderate strength evidence suggests that symptom-triggered therapy improved duration of therapy and total benzodiazepine dose in specialized detoxification settings of low-risk patients but the applicability of this evidence in general hospital settings is low. There was insufficient evidence for any conclusions about symptom-triggered therapy for the major outcomes of mortality, seizure, and delirium in any setting. PROSPERO Registration: CRD42017073426

Access or request full text: <https://libkey.io/10.1007/s11606-019-04899-7>

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DATABASES AND INFORMATION SOURCES USED					
	Pubmed		HMIC	X	BMJ Best Practice
	Medline		Social Policy and Practice		Cochrane Library
	Emcare		CINAHL		TRIP
X	Embase		PsycINFO		Grey Literature
	AMED	X	UpToDate	X	Other – NICE, BNF

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
X	KM/Management decision making		Other

USER CATEGORY OF REQUESTOR			
	Medical students		Patients/public
X	Nursing/midwifery students		Physician Associates
	Junior doctors		Public Health (Somerset CC)
	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 INCLUDING MESH HEADINGS	LIMITS USED
Chlordiazepoxide Chlordiazepoxide /DT Alcohol withdrawal Symptom triggered therap* Dose* or dosage*	

