Naltrexone: A safe and effective standard of care in treating alcohol use disorder

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Background
Harmful alcohol consumption is a common presentation in primary care. Naltrexone is a safe and effective treatment for alcohol use disorder (AUD) that remains underused because of prescriber unfamiliarity, inconsistencies in guidelines, stigma and historical safety considerations.

Objective
This article reviews recent key research to assist naltrexone prescribing, including prescribing for patients with liver disease.

Discussion
Naltrexone is prescribed for fewer than 3% of patients with AUD in Australia, including patients with alcohol-related liver disease who access tertiary care and for whom treatment can be lifesaving. Evidence indicates that naltrexone is safe for patients with severe alcohol-associated cirrhosis. Naltrexone's safety in patients with severe acute hepatitis or acute-on-chronic liver failure remains unknown; however, naltrexone's ability to reduce alcohol consumption may outweigh any risks. Prescribers can align treatment with the patient's goal: naltrexone can be initiated with or without prior alcohol withdrawal, and targeted (non-daily) dosing is suitable for some patients.

HARMFUL ALCOHOL CONSUMPTION is a common and undertreated presentation in general practice. Twenty-two per cent of Australian adults report a pattern of alcohol consumption that is hazardous to health,[1] and approximately 2.1 million Australian adults (9.7%) meet *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for alcohol use disorder (AUD) in the previous 12 months.[2] Alcohol consumption is the fifth highest contributor to disease burden in Australia,[3] so treatment to reduce alcohol consumption benefits patients and public health. Most Australian general practitioners (GPs) routinely ask about alcohol consumption,[4] and most patients with AUD want their GP to offer pharmacotherapy.[5] Despite this, pharmacotherapy is prescribed to only approximately 3% of patients with AUD in Australia.[6] The situation is similar when patients with alcohol-related liver disease access tertiary care,[7] for whom treatment can be lifesaving.[8–11]

How does naltrexone work?

It is recognised that alcohol consumption is a learned behaviour that is reinforced by the release of endogenous endorphins.[12] Naltrexone reduces alcohol consumption by blocking endogenous opioid peptide ligands (ie molecules released by alcohol consumption) at μ-opioid receptors, which attenuates alcohol's euphoric effects.[13]

In the 1980s, evidence emerged indicating that administering opioid antagonists to alcohol-preferring rats that continued to drink alcohol resulted in gradual reductions in alcohol consumption.[12] This effect was demonstrated in patients with AUD: the patients also reported that alcohol was less pleasurable, and cravings gradually reduced.[12]

Alcohol consumption can also be negatively reinforced.[13] Over time, heavy alcohol consumption activates κ-opioid receptors, which contributes to dysphoria and craving for alcohol to relieve the negative emotional states.[13] Naltrexone's ability to block binding at the κ-opioid receptor reduces the dysphoria, and the cravings diminish.[13]

Naltrexone pharmacotherapy

Naltrexone is a remarkably long-acting opiate receptor antagonist with high μ- and κ-opioid receptor affinity.[14–17] Naltrexone is distinctive in that its clinical effects in research samples correspond with duration of occupancy at the synapse rather than circulating plasma concentration.[15] A 50 mg dose achieved a greater than 90% μ-opioid receptor blockade and 82% κ-opioid receptor blockade after approximately 49 hours in healthy subjects.[14–17] Although the plasma half-life is 4–12 hours, naltrexone is likely to block opioid receptors considerably longer and may have implications for patients who will soon need opiate medication.[15]

How to prescribe: Daily and targeted dosing and the Sinclair Method

Naltrexone is a Pharmaceutical Benefits Scheme (PBS) streamlined authority item for individuals who are alcohol dependent. Alcohol dependence is the International Classification of Diseases 11th Revision term and is comparable to moderate-to-severe AUD in the DSM-5. Recent changes to the PBS criteria expand the use of naltrexone to include the goal of reduced alcohol consumption.[18] Thus, patients do not need to be abstinent to take naltrexone. PBS subsidy requires a 'comprehensive treatment program with the goal of maintaining abstinence/controlled consumption'.[18] Regular GP review meets this requirement;[19] however, when needed and available, GPs should also encourage patients to engage with peer groups, community-based alcohol and other drug counselling or psychological therapy. A motivational interviewing approach when discussing patients' patterns of drinking and maintaining factors for drinking will assist to match these therapies with patient need and stage of readiness to change. Not all patients will need these additional therapies, and not engaging with these additional therapies should not be a barrier to naltrexone treatment.

Daily dosing is the usual regimen.[20] Patients may initiate dosing at 25 mg (half tablet) daily with meals for up to 3 consecutive days to limit nausea and other side effects before increasing to 50 mg daily.[20] If initiated during a period of abstinence, patients should be advised to continue taking naltrexone if they lapse.[20]

Targeted dosing involves taking 50 mg 'as needed' in anticipation of 'high-risk-to-drink situations', strong cravings or an intention to drink moderately.[21] A popular targeted dosing approach, the Sinclair Method, has four main components: prior withdrawal is not required, patients are not instructed to abstain, patients take naltrexone when alcohol consumption is expected, and treatment continues indefinitely.[12]

For all approaches, it is recommended to arrange follow-up 1 week after initiation to discuss the patient's experience of naltrexone, side effects and adherence. Thereafter, monthly review is recommended, and repeat liver enzymes at 1 month and every third month thereafter to screen for alcohol-related liver disease.[20] Treatment duration should reflect each patient's unique considerations including side effects, risk of relapse and social circumstances.[20] Many patients will report reduced cravings and alcohol consumption within 3 weeks of commencing naltrexone and will report further reductions in craving and alcohol consumption over the next several months (even abstinence) if they continue to take naltrexone.[12] Managing patient expectations regarding the immediacy of results and rate of reduction of alcohol consumption is important. Naltrexone does not cause withdrawal when discontinued and can be discontinued without tapering.[22]

Managing side effects

Naltrexone is generally well tolerated.[20] A common side effect is nausea,[23] which is typically mild and resolves a few days after initiation.[20] If side effects arise, the dose can be reduced to 25 mg/day, and once side effects have resolved, the dose can be increased to 50 mg/day.[20] Collaborative decision making and regular follow-up improve adherence.[24]

Contraindications and precautions

Naltrexone is contraindicated for patients taking opioids or those who have been dependent on opioids and stopped them within the past week.[20]

Naltrexone cannot be routinely recommended during pregnancy or lactation because of the lack of well-controlled safety studies.[20,25] There is no evidence linking naltrexone for AUD during pregnancy with increased frequency of malformation or other harmful effects to the human foetus; however, in women treated for opioid use disorder, some evidence links naltrexone exposure during pregnancy with ectopic pregnancies and urogenital birth defects.[23] Animal studies indicate an increased risk of foetal damage, so naltrexone is classed as Category B3.[20,25] However, given alcohol's teratogenic effects, naltrexone may be safer than continued alcohol consumption in some pregnant or breastfeeding individuals,[20] particularly when psychosocial treatments have not been successful or are not accepted.[25] If naltrexone is considered, guidelines recommend consultation with the patient about the risks and benefits.[20]

No requirement for withdrawal or abstinence with naltrexone

Withdrawal is not required to initiate naltrexone, and abstinence prior to initiating naltrexone has not been shown to improve outcomes.[20] Naltrexone's hypothesised mechanism of action (μ-opioid receptor blockade and consequent dampening of alcohol's pleasurable effects) suggests that patients who consume alcohol while taking naltrexone learn that alcohol consumption is less rewarding.[12] Setting a goal for reduction of alcohol use can be consistent with both a harm-reduction framework and a person-centred approach.[20]

Many people with AUD prefer a gradual reduction of alcohol consumption over abrupt withdrawal.[26] Gradual reduction also eliminates the need for inpatient withdrawal management, which is expensive and disruptive to patients' lives and contributes to stigma. Withdrawal also dramatically increases brain glutamate, which is neurotoxic, and when withdrawal is recurrent is associated with lowering of the seizure threshold, more severe future withdrawal, increased likelihood of relapse, and cognitive decline.[26] In contrast, gradual reduction allows smaller homeostatic adjustments of glutamate and GABA, which is less neurotoxic. Gradual reduction also provides opportunities to experience incremental success and regain a sense of control over drinking while practising the strategies learned during psychological therapy.[26] Patients do not become unwell if they consume alcohol while taking naltrexone, and naltrexone has no effect on physiological withdrawal from alcohol. Treatment in the community may not be appropriate for some patients (eg patients consuming alcohol with seizure history, where reduction of alcohol consumption may precipitate a seizure).[20]

Benefits of naltrexone in practice

A meta-analysis in 2023 examined naltrexone's efficacy in preventing a return to heavy alcohol consumption for ≥12 weeks versus placebo. It defined heavy alcohol consumption as ≥4 drinks per day for women and ≥5 drinks per day for men. In people with moderate-to-severe AUD, the number needed to treat (NNT) to prevent a return to heavy

alcohol consumption was 11.[23] Relevant to appraising the magnitude of these effects, it is important to highlight that these NNTs relate solely to pharmacological effects and underestimate overall treatment effects.[27] Overall treatment effects (ie pharmacological plus placebo/contextual effects) are determined by comparing pharmacological treatment with no treatment. These are the choices available to GPs (ie treat or do nothing). Regarding mild-to-moderate AUD, targeted dosing (2–5 times/week) has been associated with fewer drinking days and less heavy drinking at 3-month follow-up.[21]

Prescribing for patients with liver disease, including decompensated cirrhosis

Preliminary studies in the 1980s of patients without AUD reported transient transaminase elevations in some patients when taking 300 mg/day of naltrexone but not at 200 mg or less per day.[28] This led to an abundance of concern about possible hepatotoxic effects.[28] What has since been shown is that naltrexone is safe and appropriate to prescribe for most patients with liver disease.[7–11,29,30]

Pharmacotherapy can be lifesaving for patients with alcohol-related liver disease (ALD), including decompensated ALD and alcohol-associated hepatitis, because abstinence improves prognosis and extends survival for these patients.[8–11] This is critical, as most patients with ALD continue to consume alcohol,[8,9,29] and prognosis is poor even for early/compensated ALD.[8] One study showed that abstinence improved survival (84% abstinent vs 65% non-abstinent) at 24 months and led to fewer decompensations (36% abstinent vs 58% non-abstinent) in patients with biopsy-proven alcohol-associated hepatitis.[9] Another study found that naltrexone improved survival for patients with alcohol-associated cirrhosis, with longer duration of naltrexone treatment associated with greater survival.[10] Furthermore, naltrexone therapy was found to lower the risk of hepatic decompensation by 64%, improve survival by 51% and increase the likelihood of abstinence by 42% in a sample of patients with AUD and either ALD or unspecified cirrhosis when compared with patients who were not treated with naltrexone.[11] Similarly, a large retrospective cohort study found that patients with AUD and alcohol-associated cirrhosis who took naltrexone had a lower incidence of hepatic decompensation than untreated patients even if naltrexone was initiated after diagnosis of cirrhosis.[29] That study also reported that patients with AUD who took naltrexone were less likely to develop cirrhosis than patients not treated with naltrexone.[29]

The largest study investigating the safety of naltrexone for patients with compensated and decompensated alcohol-associated cirrhosis found no evidence of naltrexone-induced liver injury, and naltrexone was not associated with new decompensation or death.[30] At the end of the study, only 2% of patients had elevated transaminases, and a likely alternative cause was found for 77% of these cases.[30]

We are unaware of evidence relating to the safety of naltrexone for patients with severe acute hepatitis or acute-on-chronic liver failure. The benefits of naltrexone in reducing alcohol consumption likely outweigh any possible risk of hepatotoxicity,[31] and consideration should be included as part of informed decision making.

Vulnerable and isolated groups

It is well recognised that Aboriginal and Torres Strait Islander peoples and those in rural and remote communities have increased barriers to accessing AUD treatment.[32] The need to travel long distances to access care, wariness of services, shame and stigmatisation are all likely to contribute to low prescribing of AUD pharmacotherapies.[33] Naltrexone represents a viable treatment option for these communities, as it can be initiated immediately, requires little infrastructure and is very portable and relatively inexpensive.

Conclusion

The rate of prescribing of alcohol pharmacotherapy, in particular naltrexone, is too low to effectively treat and manage patients with AUD in Australia. GPs play a vital part in the provision of care to people with AUD and should feel empowered to offer this evidence-based treatment as the standard of care.

Key points

- There is no need for withdrawal from alcohol prior to initiating naltrexone.
- Patients do not need to be abstinent from alcohol to take naltrexone.
- Naltrexone may be particularly effective for gradual reduction in alcohol use.
- Naltrexone can be taken daily or 'as needed' (targeted dosing).
- Naltrexone is not hepatotoxic.

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Competing interests: None.

Funding: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

AI declaration: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript.

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References

1. O'Brien H, Callinan S, Livingston M, Doyle JS, Dietze PM. Population patterns in Alcohol Use Disorders Identification Test (AUDIT) scores in the Australian population; 2007–2016. Aust N Z J Public Health 2020;44(6):462–67. doi: 10.1111/1753-6405.13043.

2. Mewton L, Slade T, McBride O, Grove R, Teesson M. An evaluation of the proposed DSM-5 alcohol use disorder criteria using Australian national data. Addiction 2011;106(5):941–50. doi: 10.1111/j.1360-0443.2010.03340.x.
3. Australian Institute of Health and Welfare (AIHW). Australian Burden of Disease Study 2018: Interactive data on risk factor burden. AIHW, 2021. Available at www.aihw.gov.au/reports/burden-of-disease/abds-2018-interactive-data-risk-factors/contents/about [Accessed 19 February 2025].
4. Miller ER, Ramsey IJ, Tran LT, et al. How Australian general practitioners engage in discussions about alcohol with their patients: A cross-sectional study. BMJ Open 2016;6(12):e013921. doi: 10.1136/bmjopen-2016-013921.
5. Stewart SH, Connors GJ. Interest in pharmacotherapy and primary care alcoholism treatment among medically hospitalized, alcohol dependent patients. J Addict Dis 2007;26(2):63–69. doi: 10.1300/J069v26n02_08.
6. Quintrell E, Page A, Wyrwoll C, et al. Alcohol pharmacotherapy dispensing trends in Australia between 2006 and 2023. Alcohol Alcohol 2024;59(5):agae063. doi: 10.1093/alcalc/agae063.
7. Rogal S, Youk A, Zhang H, et al. Impact of alcohol use disorder treatment on clinical outcomes among patients with cirrhosis. Hepatology 2020;71(6):2080–92. doi: 10.1002/hep.31042.
8. Lackner C, Spindelboeck W, Haybaeck J, et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. J Hepatol 2017;66(3):610–18. doi: 10.1016/j.jhep.2016.11.011.
9. Altamirano J, López-Pelayo H, Michelena J, et al. Alcohol abstinence in patients surviving an episode of alcoholic hepatitis: Prediction and impact on long-term survival. Hepatology 2017;66(6):1842–53. doi: 10.1002/hep.29338.
10. Rabiee A, Mahmud N, Falker C, Garcia-Tsao G, Taddei T, Kaplan DE. Medications for alcohol use disorder improve survival in patients with hazardous drinking and alcohol-associated cirrhosis. Hepatol Commun 2023;7(4):e0093. doi: 10.1097/HC9.0000000000000093.
11. Malik AK, Niu B, Singh AD. S1413 Naltrexone after hospitalization for patients with alcohol use disorder and alcohol-associated liver disease reduces risks of hepatic decompensation and mortality. Am J Gastroenterol 2023;118(10S):S1078. doi: 10.14309/01.ajg.0000955292.97711.40.
12. Sinclair JD. Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. Alcohol Alcohol 2001;36(1):2–10. doi: 10.1093/alcalc/36.1.2.
13. Oasa S, Sezgin E, Ma Y, et al. Naltrexone blocks alcohol-induced effects on kappa-opioid receptors in the plasma membrane. Transl Psychiatry 2024;14(1):477. doi: 10.1038/s41398-024-03172-8.
14. Trøstheim M, Eikemo M, Haaker J, Frost JJ, Leknes S. Opioid antagonism in humans: A primer on optimal dose and timing for central mu-opioid receptor blockade. Neuropsychopharmacology 2023;48(2):299–307. doi: 10.1038/s41386-022-01416-z.
15. Lee MC, Wagner HN Jr, Tanada S, Frost JJ, Bice AN, Dannals RF. Duration of occupancy of opiate receptors by naltrexone. J Nucl Med 1988;29(7):1207–11.
16. Weerts EM, Kim YK, Wand GS, et al. Differences in δ- and μ-opioid receptor blockade measured by positron emission tomography in naltrexone-treated recently abstinent alcohol-dependent subjects. Neuropsychopharmacology 2008;33(3):653–65. doi: 10.1038/sj.npp.1301440.
17. Bednarczyk EM, Wack D, Haka M, et al. Duration of human MU opiate receptor blockade following naltrexone: Measurement by 11C-carfentanil pet. Clin Pharm Ther 2005;77(2):26. doi: 10.1016/j.clpt.2004.11.099.
18. Pharmaceutical Benefits Scheme. Naltrexone. Commonwealth of Australia, [date unknown]. Available at www.pbs.gov.au/medicine/item/8370M [Accessed 8 May 2025].
19. Drug and Alcohol Services South Australia. Naltrexone in alcohol dependence. SA Health, Government of South Australia, 2023. Available at www.sahealth.sa.gov.au/wps/wcm/connect/36098502-08d9-4093-9689-4f28f4cacfe1/Naltrexone+in+alcohol+dependence+-FINAL+2023.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-36098502-08d9-4093-9689-4f28f4cacfe1-oX8qE5T [Accessed 8 May 2025].
20. Haber PS, Riordan BC. Guidelines for the treatment of alcohol problems: A review of the evidence. Australian Department of Health; Specialty of Addiction Medicine, Faculty of Medicine and Health, The University of Sydney, 2021. Available at https://alcoholtreatmentguidelines.com.au/pdf/guidelines-for-the-treatment-of-alcohol-problems.pdf [Accessed 10 March 2025].
21. Kranzler HR, Tennen H, Penta C, Bohn MJ. Targeted naltrexone treatment of early problem drinkers. Addict Behav 1997;22(3):431–36. doi: 10.1016/S0306-4603(96)00064-0.
22. Center for Substance Abuse Treatment. Chapter 4–Oral naltrexone. In: Incorporating alcohol pharmacotherapies into medical practice. Substance Abuse and Mental Health Services Administration (US), 2009. Available at www.ncbi.nlm.nih.gov/books/NBK64042 [Accessed 10 March 2025].
23. McPheeters M, O'Connor EA, Riley S, et al. Pharmacotherapy for alcohol use disorder: A systematic review and meta-analysis. JAMA 2023;330(17):1653–65. doi: 10.1001/jama.2023.19761.
24. Song M, Song YM. The effect of shared decision-making by mental health nurses on medication adherence in patients with alcohol use disorders: Provider-patient communication pathway model. J Health Commun 2023;28(11):777–88. doi: 10.1080/10810730.2023.2268561.
25. Quintrell E, Russell DJ, Rahmannia S, Wyrwoll CS, Larcombe A, Kelty E. The safety of alcohol pharmacotherapies in pregnancy: A scoping review of human and animal research. CNS Drugs 2025;39(1):23–37. doi: 10.1007/s40263-024-01126-8.
26. Kouimtsidis C, Duka T, Palmer E, Lingford-Hughes A. Prehabilitation in alcohol dependence as a treatment model for sustainable outcomes. A narrative review of literature on the risks associated with detoxification, from animal models to human translational research. Front Psychiatry 2019;10:339. doi: 10.3389/fpsyt.2019.00339.
27. Roose SP, Rutherford BR, Wall MM, Thase ME. Practising evidence-based medicine in an era of high placebo response: Number needed to treat reconsidered. Br J Psychiatry 2016;208(5):416–20. doi: 10.1192/bjp.bp.115.163261.
28. Pfohl DN, Allen JI, Atkinson RL, et al. Naltrexone hydrochloride (Trexan): A review of serum transaminase elevations at high dosage. NIDA Res Monog 1986;67:66–72.
29. Vannier AG, Shay JE, Fomin V, et al. Incidence and progression of alcohol-associated liver disease after medical therapy for alcohol use disorder. JAMA Network Open 2022;5(5):e2213014. doi: 10.1001/jamanetworkopen.2022.13014.
30. Thompson R, Taddei T, Kaplan D, Rabiee A. Safety of naltrexone in patients with cirrhosis. JHEP Rep Innov Hepatol 2024;6(7):101095. doi: 10.1016/j.jhepr.2024.101095.
31. Crowley P. Long-term drug treatment of patients with alcohol dependence. Aust Prescr 2015;38(2):41–43. doi: 10.18773/austprescr.2015.015.
32. Brett J, Ivers R, Doyle M, Lawrence L, Conigrave K. Should naltrexone be the first-line medicine to treat alcohol dependence in Aboriginal and Torres Strait Islander populations? An Australian perspective. Aust Fam Physician 2015;44(11):815–19.
33. Dzidowska M, Lee KSK, Conigrave JH, et al. Supporting alcohol brief interventions and pharmacotherapy provision in Australian First Nations primary care: Exploratory analysis of a cluster randomised trial. BMC Prim Care 2024;25(1):351. doi: 10.1186/s12875-024-02598-9.

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