Should naltrexone be the first-line medicine to treat alcohol dependence in Aboriginal and Torres Strait Islander populations? An Australian perspective

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Background

There is a pressing need to improve alcohol treatment services for Aboriginal and Torre Strait Islander peoples with alcohol dependence. One component of treatment is the use of medicines including naltrexone and acamprosate. Access to these medicines among the general drinking population is poor and, anecdotally, even worse for Aboriginal and Torre Strait Islander peoples who drink.

Objectives

This article aims to review the relative efficacy and safety of naltrexone. It will also discuss reasons why it may be a preferable first-line pharmacotherapy for Aboriginal and Torre Strait Islander peoples with alcohol dependence who are seeking to change their drinking.

Discussion

The major effect of naltrexone is reducing episodic heavy drinking, a pattern often seen in Aboriginal and Torre Strait Islander peoples with alcohol dependence. Possible genetic and epigenetic factors, and practical considerations including once-daily dosing also make naltrexone an appealing agent in this population.

A higher proportion of Aboriginal and Torres Strait Islander peoples are non-drinkers, compared with their non-Indigenous counterparts. However, those who drink are more likely to consume alcohol at risky levels.[1] This polarisation of alcohol use is mirrored in a number of indigenous and marginalised groups around the world.[2,3] It is likely to reflect ongoing experience of trauma, stress and disempowerment.[4] Aboriginal and Torres Strait Islander peoples have called for improved access to treatment for alcohol problems.[5] However, there has been limited awareness of the potential role of relapse prevention medicines in treatment that is in line with the general population.

Naltrexone and acamprosate are publically subsidised as treatments to reduce relapse to alcohol dependence in Australia. Several other medicines (eg disulfiram, baclofen and topiramate) are also used in clinical practice. These medicines have improved outcomes over placebo on average across several randomised controlled trials. However, the effectiveness of each medicine has varied by study. This may reflect study design differences, including the varying nature of the individuals who drink who were treated. Objective matching strategies including allocating naltrexone treatment according to family history of alcoholism[6,7] have yielded more promising results.

There are several theoretical reasons why naltrexone may be of particular benefit to Aboriginal and Torres Strait Islander peoples with alcohol dependence who are seeking to change their drinking. These include drinking patterns, possible genetic and epigenetic influences, practical considerations (eg once-daily dosing) and the potential availability of a sustained-release preparation. This article will discuss these considerations and make the argument for increasing awareness and access to naltrexone for Aboriginal and Torres Strait Islander peoples with alcohol dependence. Many of these observations may be able to be extrapolated to dependent drinkers from indigenous or vulnerable populations around the world.

How does naltrexone work?

The pleasurable effects of alcohol are mediated in part by the release of endogenous opioids at the ventral tegmental area (VTA) of the brain. These opioids then act via gamma-aminobutyric acid (GABA) to increase dopamine release

at the nucleus accumbens,[8] which is responsible for the reward of drinking and reinforcement of drinking patterns. Endogenous opioids are also released in response to alcohol-related cues (eg the sight or smell of an alcoholic beverage). Naltrexone is an opioid antagonist. It is thought to block the direct opioid-mediated reward and cue-driven opioid effects associated with alcohol.[9] There is also evidence that naltrexone works by altering hypothalamo–pituitary–adrenocortical (HPA) axis activity in the post-withdrawal period.[10]

Does naltrexone actually work?

A 2010 Cochrane review[11] examined 50 randomised controlled trials of opioid antagonists for alcohol-use disorders. The greatest effect of naltrexone was the reduction in the return to heavy drinking. It found that 9.09 individuals need to be treated in order to prevent one individual from returning to heavy drinking. Other outcomes included a 3% reduction in heavy drinking days when compared with placebo, and around one standard drink less of alcohol consumed per drinking day. There was also a significant post-treatment effect of up to 12 months after the treatment was discontinued. A more recent meta-analysis[12] confirmed the major effect of naltrexone in reducing heaving drinking and craving. This effect exceeded that of acamprosate.

The modest effect sizes in these trials may be a consequence of several factors. None of the reviewed trials attempted to match treatment to the characteristics in those with alcohol dependence, all were of relatively short duration (median 3 months) and most studies (except 7) required detoxification before starting naltrexone. Study participants were also a mixture of alcohol-dependent and alcohol-abusing individuals. However, the latter did not make up more than 10% of the overall study population in the Cochrane analysis. These observations are important when considering how best to use naltrexone.

An episodic pattern of heavy drinking is common among Aboriginal and Torres Strait Islander peoples with alcohol dependence, who may have intermittent access to money or alcohol.[13] The main effect of naltrexone is to reduce heavy drinking episodes, which may be particularly useful to this population. Naltrexone also has advantages where complete abstinence may not be immediately achievable (or required).

How best to use naltrexone?

Use in active drinkers or following detoxification?

Further analysis of the COMBINE study data[14] after 12 months on naltrexone found the effect was greater for those with a higher percentage of drinking days ('slip ups') during the study period.[15] It is theorised that drinking alcohol while the opioid system is blocked helps those who drink to 'learn' that alcohol is no longer rewarding.[16] Naltrexone extinguishes the reward of drinking, which helps to also extinguish cue-related craving. This may also explain the after-treatment effect as individuals who return to drinking after ceasing naltrexone take a period of time to 're-learn' the pleasurable effects of drinking.

Given this finding, it has been suggested that naltrexone may be best started when the individual is actively drinking.[16] A recent meta-analysis found naltrexone was effective if it was given before detoxification, but had a larger effect size when given after detoxification.[12] However, the authors note these results may be confounded by the patients' motivation. For instance, people more motivated to become abstinent may be more likely to have entered into detoxification.

Regardless of this, there are practical advantages to a medicine that is effective when it is started while the person is still drinking (which does not appear to be the case with acamprosate) . Naltrexone treatment may help an individual with alcohol dependence to reduce alcohol consumption in the lead up to stopping altogether. The individual may then experience less harm while drinking and milder withdrawals on stopping. This approach also allows clinicians to seize the 'window of opportunity' when a patient is motivated to change. These benefits are also important given the limited availability of withdrawal management services broadly, particularly for Aboriginal and Torres Strait Islander peoples.[17]

Targeted therapy

Therapy where the patient takes the opioid antagonist only during times of increased craving or during drinking episodes, rather than continuously, has been found to be effective.[18] This may be an appealing option for Aboriginal and Torres Strait Islander peoples who drink if they are exposed to episodic risk triggers (eg funerals and travel from a dry area to an area where alcohol is available).

What can we learn from genetics?

Naltrexone appears to be more effective in those carrying a mutation in the mu opioid receptor gene *OPRM1* (*A118G*). Secondary analysis of the COMBINE trial found the patient group that received medical management plus naltrexone and carried the *OPRM1* mutation almost doubled the proportion of patients with 'good clinical outcome' (from around 50% to around 90%).[19] About one in 10 African Americans, one in three Caucasians and one in two Asians carry the *OPRM1* mutation. Allelic frequencies in the Aboriginal and Torres Strait Islander population are unknown, but may be relatively high given their possible historical journey from Asia to Australia.[20] Genetic testing is not routinely available and can be subject to ethical pitfalls. However, these considerations provide a theoretical reason to consider the potential benefit of naltrexone for Aboriginal and Torres Strait Islander peoples with alcohol dependence who want help in changing their drinking.

Theoretical advantage in those with a history of trauma

There are well-defined links between early life traumas with early onset (adolescent)

drinking and adult alcohol dependence.[21] There is some evidence that epigenetic changes in response to early life stressors create changes in the relationship between opioid neurotransmission and endogenous reward circuits. Early life stressors in opioid-naïve rats led to methylation of the gene for brain derived growth factor (BDGF). This resulted in an epigenetic change in the distribution of BDGF expression, inducing a shift from a dopamine-independent to a dopamine-dependent opioid reward system.[22,23] It is not known whether similar changes may also be triggered or perpetuated by ongoing trauma in adult life or how reversible they are. Naltrexone may therefore play a particular role in those with alcohol dependence following early life stressors. Aboriginal and Torres Strait Islander peoples experience a disproportionate burden of early life stressors and in some cases, symptoms of post-traumatic stress disorder (PTSD). Research into the role of naltrexone in treating alcohol dependence in individuals exposed to early life stressors may help inform clinical practice.[24]

Family history of alcohol-use disorder may be a useful composite measure of genetic and epigenetic factors, as naltrexone may be more effective in individuals with a family history of alcohol misuse.[6]

Safety

The major contraindication to naltrexone is opioid dependence with ongoing use or long-term continuous opioid therapy. Naltrexone can precipitate a potentially life-threatening opioid withdrawal in this context. However, naltrexone has a relatively good safety profile in most other settings. Concerns that opioid antagonists might precipitate alcohol withdrawal when given to an active drinker have been unfounded.[16]

There have been concerns that naltrexone may worsen anhedonia in patients with depression by blocking natural endogenous opioid 'highs', which is relevant given the high degree of psychiatric comorbidity in Aboriginal and Torres Strait Islander peoples with alcohol dependence.[25] However, this has not been a common clinical finding and was not found to be a safety concern in the Cochrane review.[11] This was supported by a recent study examining naltrexone treatment in patients experiencing depression with alcohol dependency.[26] Any theoretical risk of naltrexone reducing mood must be balanced against the well-established effects of alcohol in contributing to depression.

There is a handful of case reports of naltrexone causing an idiosyncratic hepatitis. However, these were typically at much higher doses than currently recommended and not in the context of alcohol treatment.[27] Current Australian guidelines recommend patients whose transaminases are greater than five times the normal upper limit should avoid using naltrexone.[28] This poses a problem where delay in receiving laboratory test results can result in missed opportunities for responding to an individual's desire for help, particularly in remote areas. These guidelines contrast with the now large body of evidence that found naltrexone does not cause significant hepatotoxicity, even in the context of liver cirrhosis or hepatitis.[27] Clinical experience also suggests naltrexone is a far better alternative to alcohol in terms of risk of liver disease. The lack of ability to perform blood tests before treatment should not be a barrier to accessing naltrexone.

Alternatives to naltrexone

Acamprosate is the only other subsidised pharmacotherapy for alcohol dependence in Australia. It has a theoretical benefit in individuals whose drinking is driven mainly by a need for relief of withdrawal symptoms. However, there is poor adherence in individuals with stressful lives and this may limit treatment success as acamprosate should be taken three times per day. Naltrexone appears to be more effective for heavy episodic drinkers and those who have not been through detoxification.[11]

Disulfiram can have potential benefits in individuals who are keen to stop drinking, where other treatments have failed and drinking is causing major adverse social impacts. It is more effective when dosing is supervised. One Aboriginal and Torres Strait Islander patient found disulfiram helpful and 'culturally appropriate' because it physically 'punishes' a behaviour that is causing harm (ie drinking). However, complex comorbidity (eg diabetes, cardiovascular and respiratory disease) may increase the risks associated with a disulfiram reaction and preclude its use in many individuals. Disulfiram is also not currently subsidised in Australia.

Topiramate and baclofen are not registered with the Therapeutic Goods Administration (TGA) or subsidised by the Pharmaceutical Benefits Scheme (PBS) for use in Australia for alcohol dependence. The price of topirimate will also be a barrier to many individuals. Nalmefene is an opioid antagonist like naltrexone. It has the possible advantage of more effective binding to central opioid receptors.[29] However, it is not currently registered for use in Australia.

Practical issues

Access to medicines to treat alcohol dependence in Australia appear to be poor. Only 5% of people with alcohol dependence were estimated to have been prescribed naltrexone or acamprosate in 2001.[30] Physicians' perceptions of low patient adherence and pessimism over drinking outcomes are major factors contributing to this underuse.[31] Aboriginal and Torres Strait Islander peoples often struggle to gain access to medicines to treat chronic disease[32,33] and, anecdotally, their access to medicines to treat alcohol dependence is also very low. Medicines that are subsidised by the PBS are available at low cost or for free for eligible Aboriginal and Torres Strait Islander peoples who have registered with the Close the Gap scheme. Increased awareness of alcohol pharmacotherapies among prescribers

and in the community may help increase access to these medicines.

The PBS subsidy for naltrexone in Australia requires 'a goal of maintaining abstinence'. It does not state if this is a short-term or long-term goal, and does not mention harm reduction (by decreasing heavy episodic drinking). These details should be addressed. It is important that health staff and patients are aware that the medicine should continue if drinking resumes as relapse is very common in those with alcohol dependence. Continued naltrexone treatment is likely to result in a reduced amount consumed, which leads to less harm.

Extended-release formulations of naltrexone are not currently registered for routine use in Australia, but are available in the US. Preliminary data on the use of sustained-release injectable naltrexone (Vivitrol) to treat alcohol-use disorder has found it to be safe, improves quality of life and feasible in a primary care setting.[34] It is provided as a monthly intramuscular injection. This product is not yet available in Australia. Some patients are accessing six-monthly naltrexone implants instead via a special-access scheme. However, there is ongoing controversy over this arrangement.[35] Extended-release preparations of naltrexone may be a viable treatment option in the future for those who wish to change their drinking. This is especially true given difficulties with intermittent access to medicines in Aboriginal and Torres Strait Islander populations and the multiple stressors which impact on medication adherence.

Conclusion

There is a need for improved access to multimodal treatment for alcohol dependence among Aboriginal and Torres Strait Islander peoples. This need may well extend to other indigenous or vulnerable populations worldwide. Anecdotally, access to medicines to treat alcohol dependence is particularly poor among Aboriginal and Torres Strait Islander peoples. This is likely to be contributed to by pessimism about outcomes among physicians and a lack of awareness among patients. There are several reasons why naltrexone may be a good first-line pharmacotherapy to stop alcohol dependence for Aboriginal and Torres Strait Islander peoples. These benefits include the effectiveness of naltrexone in reducing episodic heavy drinking, possible genetic and epigenetic factors, practical considerations (eg once daily dosing) and possible future availability of an extended-release formulation. Future research should focus on these areas, and acceptability and accessibility of these medicines to Aboriginal and Torres Strait Islander peoples with alcohol dependence, and the optimal approach to provide this treatment in a culturally secure and accessible way.

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