DRUG & ALCOHOL FINDINGS *Review analysis*

This entry is our analysis of a review or synthesis of research findings considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original review was not published by Findings; click Title to order a copy. Free reprints may be available from the authors – click prepared e-mail. The summary conveys the findings and views expressed in the review. Below is a commentary from Drug and Alcohol Findings.

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Effectiveness of naltrexone treatment for alcohol use disorders in HIV: a systematic review.

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Substance Abuse Treatment, Prevention, and Policy: 2020, 15(24).

The negative impact of alcohol use disorders can reverberate in different areas of people's lives. For people living with HIV, this can extend to their engagement with HIV treatment. Review asks whether a recommended pharmacological treatment for alcohol dependence in the general population could improve overall health outcomes for people living with HIV.

SUMMARY An estimated 40–50% of people living with HIV have a history of heavy drinking (1 2), which can affect their health outcomes in a number of ways:

• Alcohol can interfere with the functioning of the immune system – increasing the incidence of serious bacterial infections (especially tuberculosis) and liver damage.
• Alcohol consumption can adversely affect people's engagement with (and adherence to) HIV treatment, as well as their treatment outcomes risk of mortality.
• Alcohol itself can also change the metabolism of antiretroviral drugs, which are necessary to stop the HIV virus from reproducing.

Pharmacotherapy is a recommended treatment approach for alcohol use disorders (1 2). The US Food and Drug Administration has approved the medications acamprosate, disulfiram, and naltrexone (1 2), and there is strong evidence for the use of topiramate.

Very few studies have examined the outcomes of people living with HIV who receive these medication-based treatments. The featured review sought to bring an understanding about the evidence base for naltrexone, summarising and evaluating studies which have tested the effectiveness of naltrexone among people living with HIV. Naltrexone can be consumed orally, typically in daily doses, or administered via injection in an extended-release form. The wider evidence base supports its role in reducing craving, reducing the number of drinks and heavy alcohol use days, and extending the rates of abstinence.

Seven studies were analysed, including five randomised trials (1 2 3 4 5) and two smaller pilot studies (6 7). Reported outcomes included alcohol consumption, the safety of naltrexone, and adherence to HIV treatment regimens, and studies often measured these in different ways. For example, the category of drinking-related outcomes included: the average number of drinks per week; the number of days abstinent per month; the past 30-day average of drinking days; time since first heavy drinking day; average drinks per drinking day; and average change in alcohol craving. [The findings reported below include additional information from the source studies where relevant.]

Key points
From summary and commentary

Very few studies have examined the outcomes of people living with HIV who are receiving medical treatment for an alcohol use disorder.

The featured review found some evidence that the medication naltrexone can reduce alcohol consumption and improve viral suppression, without producing serious side effects.

Altogether the findings indicate that naltrexone can be used to treat alcohol-related disorders in this group of patients. However, as with the wider population, it cannot be viewed as a 'magic bullet'.

Main findings

Treatment retention

Retention in oral and injectable naltrexone differed between studies. Overall, there was no statistically significant difference between treatment groups and placebo or treatment-as-usual groups.

Drinking outcomes

Only one study recorded significantly better drinking outcomes in the naltrexone group than the placebo group: the naltrexone treatment group recorded significantly fewer heavy and abstinent drinking days in the past 30 days. Alcohol intake during the past month also significantly decreased over time for the naltrexone group according to a biological marker of alcohol consumption, offering a more objective picture of consumption and support for the benefit of naltrexone.

In another study, daily alcohol consumption dropped significantly for participants in the naltrexone group – from 7.13 standard drinking units at baseline to 0.46 at the seven-month follow-up. However, the study did not demonstrate a significant difference between the treatment and placebo group, and therefore does not provide strong evidence of naltrexone having an effect on drinking outcomes.

In three further studies there was no evidence of improved drinking outcomes associated with naltrexone:
• Among a small group of women living with HIV, there was no significant decrease in average alcohol consumption per week or significant increase in the number of abstinent days between placebo and naltrexone groups.
• In a small study of people living with HIV, there was a reduction in both groups in the average past-month drinking days over an eight-month period, but no statistically significant difference between the groups.
• Among people living with HIV who had been released from prison, there was no statistically significant difference

between naltrexone and placebo groups for the time to first heavy drinking day, average drinks per drinking day, average percent of heavy drinking days, and average change in alcohol craving.

Adherence to a treatment regimen of antiretroviral therapy

In two studies, there was no significant difference between placebo and naltrexone treatment groups in the rate of adherence to antiretroviral therapy (1 2). These studies measured the rate of adherence by the proportion of participants who followed their HIV treatment regimen more than 90% or 95% of the time.

> *"HIV treatment does not cure HIV, but it stops the virus from reproducing in your body. It can reduce the amount of virus in the blood to undetectable levels, meaning that you cannot pass on HIV."*
>
> Terrence Higgins Trust, the largest voluntary sector provider of HIV and sexual health services in the UK

HIV viral load

Treatment with antiretroviral therapy can reduce a person's viral load (ie, the amount of HIV in the blood). When the viral load is reduced to an undetectable level, this is called viral suppression.

Two studies reported a statistically significant improvement in viral suppression in injectable naltrexone groups compared with control groups:
• Extended-release naltrexone participants were significantly more likely to achieve viral suppression at six months. There was no improvement in viral load over the six-month follow-up period in the placebo group.
• HIV viral suppression changed from 92% to 82% for patients assigned to extended-release naltrexone, whereas no change was detected for the treatment as usual group at 16 weeks (1 2). [This finding was reported in two different studies by the same group of authors, but seemingly involved the same analysis of the same group of participants.]

A further two studies did not demonstrate the effectiveness of naltrexone in relation to HIV viral load (1 2).

Health of the immune system

In two studies there was no evidence of a significant difference in the average CD4 count of participants in placebo versus treatment groups (1 2). CD4 cells (also known as T-cells) are a type of white blood cell, and their count provides a measure of the health of the immune system.

Risk of death and disease

Only one study reported mortality- and morbidity-related outcomes. During a 24-week treatment period, there were no significant differences between placebo and treatment groups in their VACS Index scores, which predict risk of death and disease among people living with HIV.

Safety

Four studies examined the safety of naltrexone against reports of adverse events and serious adverse events (1 2 3 4). None of these found a statistically significant difference between placebo and naltrexone groups. However, in one of the studies there were considerably more (if not significantly more) people in the naltrexone group reporting adverse events (70% vs. 28%). The reported side effects of naltrexone included insomnia (30%), nervousness/anxiety (30%), and nausea (10%).

The authors' conclusions

The featured review was designed to evaluate the effect of naltrexone on the health outcomes of people living with HIV – including their drinking outcomes and their HIV outcomes. It found some evidence that injectable and oral naltrexone could reduce alcohol consumption and improve viral suppression, without concern that the medication would cause serious side effects, which overall suggested that naltrexone could be used to treat alcohol-related disorders in this group of patients.

The strength of the authors' conclusions were restricted by the small number of studies available, as well as limitations associated with individual studies and the pool of studies, including the variety of responses considered for evaluating the outcomes of naltrexone, the low number of study participants, and the selection of the study population from specific groups such as people in or newly released from prison.

FINDINGS COMMENTARY Alcohol use disorders can have considerable ramifications for people living with HIV, including adversely affecting their engagement with HIV treatment. The featured review pursued a productive line of enquiry about the impact of naltrexone (a treatment for alcohol dependence) on the health outcomes of people living with HIV. The authors came to the conclusion that naltrexone could reduce alcohol consumption and improve viral suppression in people living with HIV, without significant side effects, though it is important to note that there were a limited number of studies supporting these two main assertions:
• only one study recorded significantly better drinking outcomes among participants in the naltrexone group than the control group;
• only two studies reported a statistically significant improvement in viral suppression in naltrexone versus control groups.

What we can glean from these findings, in combination with the wider evidence base, is that naltrexone may be beneficial, and there appears to be no reason *not* to consider naltrexone to treat alcohol-related disorders among people living with HIV. However, as with the wider population, it cannot be viewed as a 'magic bullet'.

In 2010, a comprehensive synthesis of 50 trials with 7,793 patients found that the naltrexone does on average help more detoxified alcohol dependent patients avoid relapse, but effects are generally small and inconsistent:
• Compared to a placebo, naltrexone reduced the risk of return to heavy drinking by 17%, drinking days by about 4%, and heavy drinking days by about 3%, meaning that the drug on average avoided one additional heavy drinking day per month.

Information about HIV from the Terrence Higgins Trust:
• "HIV stands for Human Immunodeficiency Virus. 'Immunodeficiency' refers to the weakening of the immune system by the virus."
• "AIDS stands for Acquired Immune Deficiency Syndrome. It is a collection of illnesses ('syndrome') caused by a virus people pick up ('acquire') that makes their immune system weak ('immune deficiency')."
• "In the 1980s and early 90s, most people with HIV were eventually diagnosed with

• On days when alcohol was drunk, patients treated with naltrexone manage to refrain from about one more drink than they would have done prescribed a placebo.

The authors of this much larger review concluded that naltrexone can be expected to prevent heavy drinking in one out of nine patients who would otherwise have returned to a heavy drinking pattern. But, among patients who take their naltrexone regularly, benefits are likely to exceed those demonstrated in these clinical trials. Reflecting on the findings, an Effectiveness Bank commentary said that:

> *"Naltrexone's safety and the fact that it does not itself cause dependence, mean that a trial and error approach can be applied, seeing if patients who do not do well with psychosocial therapy only and are not suitable for disulfiram respond well, and discontinuing the medication if treatment cannot be well implemented or side effects outweigh any benefits. Because it generally has a modest impact, naltrexone (and other medications) are supplements to, not replacements for, psychosocial therapies."*

Naltrexone is licensed in the UK for the treatment of alcohol dependence, and endorsed in national guidance for Scotland and England and Wales. Guidance from the National Institute for Health and Care Excellence (NICE) says that naltrexone should be considered in cases of moderate and severe alcohol dependence, but only in combination with a psychological intervention targeted at drinking such as cognitive-behavioural therapy.

Other UK expert guidelines drafted by pharmacologists go further than NICE, arguing that medications including naltrexone should be the default treatment response to dependence, and only rejected if in some way contraindicated. This should, they recommend, even be the case for *non*-dependent problem drinkers who have not responded well to 'talking' therapies. Contrary to this advice, the on average small benefits from these and other medications may be one reason why medications of any kind are prescribed in the UK for a minority of patients. In 2014/15 in England about 23% of the 89,107 patients seen at specialist services solely for problems with alcohol rather than other drugs were prescribed a medication, but this included inpatients prescribed a medication to ease withdrawal rather than to sustain their recovery. The previous year, of all alcohol patients (whether or not also recorded as having other drug problems) treated as outpatients, just 16% were prescribed medications.

According to the NHS (last updated February 2020), acamprosate and disulfiram are the two most commonly-prescribed drugs for the treatment of alcohol dependence; naltrexone has yet to be included in analyses of alcohol-related prescriptions due to its overlapping use in treating opioid dependence. In England the number of prescriptions for alcohol dependence rose sharply from 109,112 in 2005 to 196,064 in 2015, a rise largely accounted for by acamprosate, prescribed 139,226 times in 2015 compared to 52,479 for disulfiram. Since 2012 disulfiram has been on a downward trajectory while acamprosate continued rising up until 2015, after which it seems it has been on a steady decline.

Because they work in different ways, responses to these medications may differ depending on the characteristics of the patients, such as severity of dependence and their treatment goals. For example, while acamprosate ameliorates the negative feelings experienced during alcohol dependence and withdrawal which induce dependent drinking, naltrexone seems to dampen the rewarding effects of drinking.

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AIDS."
• "Now, thanks to modern antiretroviral treatment, very few people in the UK develop serious HIV-related illnesses."
• "If left untreated, infection with HIV progresses through a series of stages: from flu-like seroconversion illness, through infections associated with the symptomatic stage, leading to late-stage HIV or AIDS."

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