Naltrexone

Essential medicine status

Section: 24. Medicines for mental and behavioural disorders > 24.5. Medicines for disorders due to psychoactive substance use > 24.5.1. Medicines for alcohol use disorders

ATC codes: N07BB04

Indication	Disorders due to use of alcohol ICD11 code: 6C40
INN	Naltrexone
Medicine type	Chemical agent
List type	Core
Formulations	Parenteral > General injections > IM: 380 mg in vial (extended-release) Oral > Solid > tablet: 50 mg
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Naltrexone
DrugBank	Naltrexone

Expert Committee recommendation

The Expert Committee noted the public health importance of treatment of alcohol dependence and harmful use of alcohol from a medical, social and economic perspective. Currently, only one in six people globally with alcohol use disorder receives treatment and rates are even lower in low- and lower middle-income countries. The Committee recognized the need to identify and address the various factors that increase alcohol consumption and influence its effects, as well as the need to develop and implement appropriate policies to decrease the harmful use of alcohol. The Committee considered that the availability of pharmacotherapies for the treatment of alcohol use disorder should be seen as part of this complex strategy of interventions. The Committee noted that a large body of evidence confirmed that naltrexone improved alcohol consumption outcomes in patients with alcohol use disorders compared with placebo. The magnitude of treatment effects appeared moderate, but the Committee considered the impact at the population level would be significant. The Committee noted that the benefits of naltrexone may be greater in people whose drinking is driven by positive reinforcement. The Committee noted that naltrexone was generally well tolerated but has been associated hepatotoxic effects when used at higher doses for extended periods of time. The Committee noted that liver function tests should be performed before starting treatment and at regular intervals during treatment. The Committee noted that injectable extended-release formulations of naltrexone were more costly than the oral formulation. However, the Committee considered that the possibility of monthly administration may increase treatment persistence in some patient subgroups. The Committee noted that in head-to-head trials that compared naltrexone with acamprosate, no statistically significant difference was found between the two medications for some outcomes (e.g. return to any drinking). The Committee noted that naltrexone was one of the medicines recommended in the WHO mhGAP guidelines for treatment of alcohol use disorder and was also recommended in other international guidelines. The Committee considered that the availability of different medicines for alcohol use disorder would provide valuable options and choice for patients and clinicians. It could also facilitate increased market competition, reduce costs and improve affordable access for national health systems. The Committee therefore recommended the

inclusion of naltrexone oral tablets and extended-release injection on the core list of the EML for use in the treatment of alcohol use disorder in adults.

Background

Medicines for treatment of alcohol use disorders have not previously been evaluated for inclusion in the EML.

Public health relevance

Globally in 2016, alcohol use was the seventh leading risk factor for premature death and disability and was the leading risk factor in people aged 15 to 49 years. Worldwide, 2.8 million deaths were attributable to alcohol use. Alcohol consumption was shown to have a strong association with a higher risk of cancer, injuries and communicable disease (1). The 2018 WHO Global status report on alcohol and health recognized that the harmful use of alcohol directly affects numerous targets of the Sustainable Development Goals including those for maternal and child health, infectious diseases, noncommunicable diseases, mental health, injuries and poisonings (2). Globally in 2016, estimates suggest that the harmful use of alcohol was responsible for 3 million deaths and caused 132.6 million disability-adjusted life years (DALYs) or 5.1% of total DALYs that year. The age-standardized burden of disease and injury associated with alcohol use varied geographically across WHO regions and was highest in the African region, where it was responsible for 70.6 deaths and 3044 DALYs per 100 000 people (2). During the COVID-19 pandemic, a cross-sectional survey in the United States found that respondents reported consuming more drinks per day, more binge drinking and more alcohol consumption beyond recommended drinking limits than before the introduction of stay-at-home orders (3).

Benefits

Systematic reviews and meta-analyses A 2014 meta-analysis of 123 studies (22 803 participants) evaluated the benefits and harms of pharmacotherapy for alcohol use disorders and included 53 randomized-controlled trials (9140 participants) comparing naltrexone and placebo (4). Naltrexone was associated with improvement in alcohol consumption outcomes compared with placebo. Oral naltrexone 50 mg daily was associated with a reduced risk of return to any drinking (risk difference (RD) −0.05 (95% confidence interval (CI) −0.10 to −0.00; number needed to treat (NNT) to prevent return to any drinking = 20) and return to heavy drinking (RD −0.09, 95% CI −0.13 to −0.04; NNT to prevent return to heavy drinking = 12). A significant association was also found between oral naltrexone 50 mg daily and reduction in percentage of drinking days (weighted mean difference (WMD) −5.4, 95% CI −7.5 to −3.2) and percentage of heavy drinking days (WMD −4.1, 95% CI −7.6 to −0.6). Naltrexone extended-release injection was associated with a significant reduction in percentage of heavy drinking days (WMD −4.6, 95% CI −8.5 to −0.6), but no significant association was observed for return to any or heavy drinking. Individual randomized trials A double-blind, placebo-controlled randomized trial evaluated oral naltrexone 50 mg per day for 12 weeks as adjunct to standard rehabilitation treatment in 70 men who had undergone initial alcohol detoxification (5). Compared with placebo, naltrexone was associated with a significantly lower mean alcohol craving score (1.41 versus 3.42), non-significantly lower mean liver enzyme levels (aspartate aminotransferase: 23.6 U/L versus 50.4 U/L; gamma-glutamyl transferase 51.4 U/L versus 127.3 U/L) and significantly fewer drinking days (1.6% versus 8.3% of study days). Naltrexone treatment did not prevent study participants from sampling alcohol, however, it was associated with decreased subsequent drinking once drinking occurred (3.6% versus 14.0% of study days). Significantly fewer patients treated with naltrexone relapsed (23% versus 54%). Within the subgroup of patients who reported any drinking during the study period, significantly fewer patients treated with naltrexone relapsed (50% versus 95%). A double-blind, placebo-controlled randomized trial of 12 weeks duration compared the additive effects of pharmacotherapy (oral naltrexone 50 mg daily versus placebo) and psychotherapy (coping skills training versus standard supportive therapy) in 97 patients with alcohol dependency (6). Rates of continuous abstinence over the study period were 61% for patients receiving naltrexone and supportive therapy, 28% for patients receiving naltrexone and coping skills training, 21% for patients receiving placebo and coping skills training and 19% for patients receiving placebo and supportive therapy. The rate of relapse, defined as drinking five or more (for men) or four or more (for women) drinks on an occasion, was 34% and 43% in the naltrexone and supportive therapy group and naltrexone and coping skills training group, respectively. Compared with patients treated with placebo, those receiving naltrexone drank on fewer study days (4.3% versus 9.9%) and consumed fewer standard drinks on average during the trial (13.7 versus 38.0). The combined pharmacotherapies and behavioural interventions study (COMBINE) was a multicentre, randomized controlled trial that compared effectiveness of oral naltrexone with placebo and acamprosate (1383 participants). Patients received 16 weeks of treatment and were followed for 1 year after treatment completion (7). Participants were randomly assigned after 4 to 21 days of abstinence to

receive either naltrexone, acamprosate, acamprosate and naltrexone in combination, or placebo, with or without a combined behavioural intervention. All treatment groups experienced an increase in percentage of days abstinent, from 25% pre-study to 73% during treatment. All groups receiving medicines or placebo showed improvements in abstinent days compared with the group who only received combined behavioural intervention. Naltrexone also reduced the risk of return to heavy drinking compared with placebo (hazard ratio (HR) 0.72, 97.5% CI, 0.53 to –0.98). The PREDICT study was a double-blind, placebo-controlled randomized study in Germany that attempted to replicate the findings of the COMBINE study (8). As in COMBINE, participants (n = 426) received oral treatment with acamprosate, naltrexone or placebo. The primary outcome measure was time until the first occurrence of heavy drinking. No significant difference in time to first heavy drinking day was found between treatment groups. A subgroup analysis examined whether so-called reward drinking (drinking driven by positive reinforcement) versus so-called relief drinking (drinking driven by negative reinforcement) moderated treatment response (9). Participants who were predominantly reward drinkers who received naltrexone had an 83% lower likelihood of any heaving drinking during treatment compared with placebo. Greater effects of naltrexone in reward drinkers have subsequently been reported in other randomized trials (10–12). A multicentre, randomized, double-blind, placebo-controlled trial evaluated the efficacy and tolerability of naltrexone extended release intramuscular injection in 627 adults with alcohol dependency (13). Participants were randomized to receive 190 mg or 380 mg long-acting naltrexone or a matching volume of placebo for 24 weeks and all received standardized supportive therapy. Rates of heavy drinking decreased in both active treatment groups. Those treated with naltrexone 380 mg had about a 25% greater reduction in the rate of heavy drinking relative to participants treated with placebo (HR 0.75, 95% CI 0.60 to 0.94). Subgroup analyses showed that treatment effects were greater in men and participants with lead-in abstinence receiving naltrexone. A randomized, double-blinded, placebo-controlled trial evaluated the efficacy of combining extended-release naltrexone and behavioural harm reduction treatment for alcohol use disorder in 308 homeless adults with alcohol use disorders (14). Participants were randomized to receive: harm reduction treatment plus extended-release naltrexone 380 mg injection; harm reduction treatment plus placebo injection; harm reduction treatment alone; or usual supportive services (control group). Primary outcome measures were self-reported alcohol use (quantity and frequency), alcohol-related harm to oneself, and physical and mental health-related quality of life. Compared with the control group, participants receiving combined harm reduction treatment and naltrexone had significant improvements from baseline to 12 weeks post-treatment in peak alcohol quantity (Cohen's d –0.68), alcohol frequency (Cohen's d –0.16), alcohol-related harm (Cohen's d –0.56) and physical health-related quality of life (Cohen's d 0.43). A systematic review and meta-analysis (seven randomized controlled trials, 1500 participants) evaluated the effect of extended-release naltrexone injection versus placebo on alcohol consumption in patients with alcohol use disorder, and determined the effects of lead-in abstinence and treatment duration on efficacy (15). For drinking days per month, the pooled WMD was –2.0 (95% CI –3.4 to –0.6) in favour of naltrexone. For heavy drinking days per month, the pooled WMD was –1.2 (95% CI –0.2 to –2.1) in favour of naltrexone. Trials in which lead-in abstinence was not an inclusion criteria and trials of duration of at least 3 months reported larger reductions in heavy drinking days per month with naltrexone: WMD –2.0 (95% CI –3.52 to –0.48) and –1.9 (95% CI –3.2 to –0.5), respectively. Observational cohort studies Cohort studies have been used to evaluate the effectiveness of treatment of alcohol use disorder on relevant health care outcomes (16,17). In a Swedish nationwide cohort study covering 10 years and 125 556 individuals with alcohol use disorder, 10 872 participants received treatment with naltrexone (16). Naltrexone in combination with acamprosate (HR 0.74, 95% CI 0.61 to 0.89) or disulfiram (HR 0.76, 95% CI 0.60 to 0.96) and as monotherapy (HR 0.89, 95% CI 0.81 to 0.97) was associated with a significantly lower risk of hospitalization due to alcohol use disorder compared with those time periods when the same individual did not use any treatment. Longer duration of naltrexone use was associated with lower risk of hospitalization due to alcohol use disorder. Naltrexone was also associated with a significantly decreased risk of hospitalization due to any cause when used in combination with acamprosate or disulfiram (HR 0.80, 95% CI 0.69 to 0.94 and HR 0.77, 95% CI 0.64 to 0.94, respectively) or used alone (HR 0.89, 95% CI 0.83 to 0.96). Similarly, a cohort study of 127 480 patients in Boston, United States identified 9635 individuals with alcohol use disorder of whom 1135 had alcohol-related liver disease (17). Patients treated with naltrexone had significantly decreased odds of developing liver disease during follow-up compared with those who had no pharmacological treatment for alcohol use disorder (adjusted odds ratio (OR) 0.67, 95% CI 0.46 to 0.95) (17). For patients with a diagnosis of liver cirrhosis, those treated with naltrexone had significantly decreased odds of having hepatic decompensation compared with those who were untreated (adjusted OR 0.27, 95% CI 0.10 to 0.64).

Harms

The application did not present a summary of evidence for the harms of naltrexone. The most common adverse effects of naltrexone include nausea, vomiting, headache, dizziness, fatigue, nervousness, anxiety and somnolence. Injection site reactions

have been reported with the extended-release injection formulation. Naltrexone should not be used if a patient is currently using opioids to avoid precipitating withdrawal. Naltrexone should be discontinued if there are anticipated opioid requirements within 7 days (18). The United States Food and Drug Administration's approval label for naltrexone includes a black box warning about hepatotoxicity, which usually occurs at higher doses than those used in clinical practice. Due to hepatotoxicity and potential increases in levels of liver enzymes, liver function tests are recommended to be performed before starting treatment and at intervals of 1, 3 and 6 months, and then annually thereafter (or more frequently if baseline liver function tests are high). Naltrexone is contraindicated in patients with acute hepatitis or liver failure (18).

Cost / cost effectiveness

A 2007 prospective cost and cost–effectiveness study of the COMBINE study interventions found three of the nine interventions to be cost-effective from a treatment provider perspective: medical management plus placebo; medical management plus naltrexone; and medical management plus naltrexone and acamprosate. Estimated treatment costs per patient were US$ 409, US$ 671 and US$ 1003, respectively, using 2007 costs (20). An additional cost study using data from COMBINE examined the effect of treatment arms on social costs of alcohol dependence and outcomes at 3 years (in terms of health care use, arrests, and motor vehicle incidents in the United States) (21). Median social cost savings comparing medical management and placebo were: US$ 2547 for medical management plus acamprosate, US$ 2991 for medical management plus naltrexone, US$ 3871 for medical management plus acamprosate and naltrexone, and US$ 3277 for medical management plus acamprosate plus cognitive behavioural interventions. A substantial effect on cost differences was related to the outcomes of arrests and motor vehicle incidents (21). A health technology assessment by the National Institute for Clinical Excellence (NICE) in the United Kingdom found that the the incremental cost-effectiveness ratio of acamprosate and naltrexone compared with standard care were both within the cost–effectiveness threshold of £20 000 to £30 000 per quality-adjusted life year (QALY) (22). The finding was robust under various scenarios evaluated in the one-way sensitivity analysis. The use of extended-release naltrexone injection was reported to cost significantly more than oral naltrexone. Studies report that individuals treated with extended-release naltrexone had fewer alcohol-related inpatient days and more outpatient visits for treatment of alcohol use disorder than other medication regimens (23). Extended-release naltrexone was more likely to be refilled, was associated with fewer hospitalizations and – despite the higher cost for extended-release naltrexone itself – total health care cost was not different from that of oral naltrexone (24). Patients treated with extended-release naltrexone were also more likely to persist with pharmacotherapy compared with those treated with oral naltrexone, acamprosate or disulfiram thus resulting in lower non-pharmacy health care costs and use of inpatient and emergency services (25). In contrast to these findings, one retrospective study by a Veterans Affairs facility found that patients on extended-release naltrexone had higher health care utilization than those on oral naltrexone (26). A meta-analysis of health care utilization studies showed that extended-release naltrexone (1565 patients) had longer medication refill persistence and lower or as low health care utilization and costs compared with other pharmacotherapies for alcohol use disorder, including oral naltrexone (27). Randomized controlled data comparing extended-release naltrexone with oral naltrexone are lacking, although the results of one trial are pending which will analyse cost–effectiveness (28).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a strong recommendation that combined psychosocial and pharmacological interventions should be offered for adults with alcohol dependence (moderate certainty of evidence). Pharmacological treatments considered included acamprosate, disulfiram and naltrexone (19).

Availability

Oral naltrexone has regulatory approval globally for use in alcohol use disorder and is available in most countries in innovator and generic brands. Naltrexone extended-release injection has regulatory approval for alcohol dependence in patients who can abstain from alcohol in an outpatient setting prior to initiation of treatment. It remains under patent protection in several jurisdictions.

Other considerations

The WHO Department of Mental Health and Substance Use reviewed and provided comments on the application. The technical unit stated that the application to include naltrexone on the EML was timely and in line with guidance provided by WHO global policy

frameworks and action plans.

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