Naltrexone for Alcohol Use Disorder

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Q. What is naltrexone?

A. Naltrexone is a medication used originally for opioid addiction that is approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol use disorder (AUD). Naltrexone is administered either in a once-daily oral formulation or by an extended-release monthly injection. The long-acting, injectable formulation may be preferred when medication adherence is a concern, but must be refrigerated and administered by a provider.

Q. What are the potential mechanisms of action underlying naltrexone?

A. The mechanism of action underlying naltrexone as a treatment for AUD is not fully understood. The stimulating and reinforcing effects of alcohol involve several neurotransmitter systems, but research has focused on the central role of mesolimbic dopamine (Ray, Chin, & Miotto, 2010). Alcohol use induces release of endogenous opioids, leading to opioid receptor activation and increased dopamine release in the nucleus accumbens. Naltrexone is an opioid receptor antagonist, and reduces the release of dopamine resulting from alcohol use, suppressing its rewarding effects. In line with these pharmacological effects, human laboratory studies have found that naltrexone reduces craving and alcohol self-administration (Hendershot, Wardell, Samokhvalov, & Rehm, 2016).

Q. Is naltrexone recommended as a front-line treatment for AUD in the Military Health System (MHS)?

A. Yes. The *2015 VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders* gives a "*Strong For*" strength of recommendation to naltrexone (both oral and extended release) for patients with moderate-severe alcohol use disorder.

The MHS relies on the VA/DoD clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

Q. Do other authoritative reviews recommend naltrexone as a treatment for AUD?

A. Yes. Other authoritative reviews and guidelines have substantiated the use of naltrexone as a treatment for AUD.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: A 2014 AHRQ comparative effectiveness review of pharmacotherapy for adults with AUD in the outpatient setting found moderate evidence supporting the efficacy of oral naltrexone (50mg/day) for improving alcohol consumption outcomes (Jonas et al., 2014).
- Cochrane: A 2010 systematic review of opioid antagonists for alcohol dependence found that oral naltrexone reduced the risk of heavy drinking and decreased drinking days compared to placebo (Rosner et al., 2010).

Q. What conclusions can be drawn about the use of naltrexone as a treatment for AUD in the MHS?

A. Along with acamprosate and topiramate, naltrexone has met the burden of evidence for inclusion in VA/DoD guidelines and is considered a front line pharmacological treatment for AUD. The CPG states that there is insufficient evidence to recommend one of these medications over another, and that

these medications should be used in conjunction with a psychosocial intervention. Providers should take into account factors such as potential adverse effects, comorbidities, and availability to inform treatment choice for patients with AUD.

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