Should Long-Acting Depot Intramuscular Naltrexone Be Prescribed Every 3 Weeks for Alcohol Use Disorder?

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Alcohol use disorder is estimated to affect more than 75 million people each year and poses a major health issue worldwide.[1] Treatment options include several pharmacologic interventions, but the optimal duration and efficacy of these medications are not well established. Naltrexone is a first-line medication for alcohol use disorder and is available in oral and depot injection forms. Naltrexone is an antagonist of the μ-opioid receptor and is thought to reduce the reinforcing effects of alcohol through modulation of endogenous opioid.[2,3] Naltrexone is metabolized to 6β-naltrexol, which undergoes extensive glucuronide conjugation in the liver. The plasma concentration and elimination half-life of naltrexone and main metabolite 6β-naltrexol correlate with the degree of opioid antagonism in an individual according to various studies.[4] In the United States, depot preparations of naltrexone are administered every 4 weeks at 380 mg. Clinical trials found that depot naltrexone 380 mg administration every 4 weeks reduced heavy drinking by 25% after 24 weeks compared to placebo.[5] There are limited data on the efficacy of depot naltrexone 380 mg at dosing regimens outside of this 4-week schedule. We present the case of a patient with repeated alcohol use and increased cravings for alcohol at 3 weeks post injection. This report suggests that more frequent dosing regimens may increase naltrexone efficacy.

Case Report

The patient is a 37-year-old man with a past history of alcohol use disorder. He was prescribed long-acting naltrexone 380 mg intramuscularly every 4 weeks. He has been a patient in the clinic for the past 4 months and has received the injection 4 times, with each injection administered every 4 weeks. Each month, his cravings start to get worse at around 3 weeks post injection. He reports no use of drugs or alcohol for the first 3 weeks after the injection but does use alcohol during the fourth week. This pattern of continued relapse caused the patient to request treatment at 3 weeks and was the catalyst for this report.

Discussion

This case highlights the need for additional studies to evaluate the efficacy of depot naltrexone at different dosing intervals. Currently, the recommendation for dosing every 4 weeks is based on diminished blood naltrexone levels. At 4 weeks, naltrexone levels have been shown to decrease to below 1 ng/mL. At 3 weeks, blood naltrexone levels are higher at about 4 ng/mL.[5] It is reasonable to assume that clinical efficacy could be improved by preventing blood naltrexone levels from diminishing to such low levels. A study[6] has shown that naltrexone 380 mg reduced heavy drinking when compared to 190-mg injections. This component of the study[6] indicates that a higher naltrexone blood level from the 380-mg injection compared to 190 mg did improve efficacy. Using this same approach, it is reasonable to assume that dosing 380 mg every 3 weeks would increase blood naltrexone levels and also improve clinical efficacy.

A potential drawback of increased dosing intervals would be an increased potential for side effects. A randomized controlled trial[6] showed that the clinically significant side effects of naltrexone 380 mg compared to placebo were nausea, fatigue, decreased appetite, dizziness, and injection site reactions. There are also potential drawbacks in regard to naltrexone toxicity with more frequent dosing. Due to the variable half-lives of naltrexone and 6β-naltrexol, it would be prudent to conduct a research trial examining the potential adverse effects prior to implementing a 3-week naltrexone dosing regimen in clinical practice. The optimal time or schedule to measure blood levels would also need to be researched, as side effects such as hepatotoxicity have been seen with high doses of daily naltrexone.[7] Other studies[8,9] have not found toxic effects. Naltrexone has been shown to block μ-opioid receptors for 28 days, so further research would be useful considering that the injection date would precede the normal occupation period of naltrexone on the opioid receptor and that side effects could be associated with high peak plasma levels during the first week of overlap with the prior injection or result due to accumulation over several months.[9,10] The peak plasma effect after the injection and the long-term effects after several months of 3-week dosing would need to be studied. Liver function tests should be monitored, and it could be beneficial to obtain blood plasma levels so that the presence or absence of side effects could be correlated with them. A research project is warranted to

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evaluate the safety of this regimen prior to use in a clinical setting.

The depot injection of naltrexone has been shown to reduce heaving drinking in alcohol use disorder. By working as a long-acting treatment, depot injection naltrexone increases patient compliance, especially compared to daily oral dosing. This report highlights that there are few data regarding alternative dosing regimens for injection naltrexone. Our patient shows that the one-dose-fits-all approach for alcohol use disorder should be examined more closely. There may be therapeutic benefit to maintaining higher blood naltrexone levels with more frequent dosing.

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