Alcohol and Alcoholism, 2019, 1
doi: 10.1093/alcalc/agz014
Letter to the Editor

Letter to the Editor

Therapeutic Drug Monitoring and the Clinical Significance of Naltrexone Blood Levels at the Time of a First Drink: Relevance to the Sinclair Method

John C. Umhau, MD, MPH, CPE*

Alcohol Recovery Medicine, 10804 Rock Run Drive, Potomac, MD 20854, USA, Fort Belvoir Community Hospital, Fort Belvoir, Virginia, United States, and Food and Drug Administration, Silver Spring, MD, United States

*Corresponding author: Alcohol Recovery Medicine, 10804 Rock Run Drive, Potomac, MD 20854, USA. E-mail: John.Umhau@jhu.edu

Re: Brünen *et al.* 'Therapeutic Drug Monitoring of Naltrexone and 6β-Naltrexol During Anti-craving Treatment in Alcohol Dependence: Reference Ranges'

The recent report by Brünen (Brünen *et al.*, 2019) notes that clinical trials with naltrexone have been less successful than expected and suggests that the reason for this insufficient clinical response is low drug concentration in the brain. Brünen supports this postulate by demonstrating that plasma concentrations of naltrexone (plus the major metabolite, 6-ß-naltrexol) are predicative for treatment response and yet are highly variable between individuals. Treatment response was indexed by the reduction of alcohol craving assessed with the Obsessive-Compulsive Drinking Scale (OCDS). Brünen goes on to describe a therapeutic range of 17–50 ng/ml (measured 8 hours after dosing) as necessary for treatment response. This report provides clear evidence that plasma concentrations of naltrexone have clinical relevance and suggest that therapeutic blood monitoring has the potential to guide clinicians in the future.

This study can also guide today's clinician. In Brünen's report, 8 hours after a 50 mg naltrexone dose, the mean concentration of naltrexone plus 6-ß-naltrexol was 18 +/- 13 ng/ml. However, this is at the lowest end of the estimated therapeutic range of 17–50 ng/ml. Since the systemic availability of naltrexone and 6-ß-naltrexol are linearly related to the administered dose (Meyer *et al.*, 1984), and only about half of the patients given a standard 50 mg dose reached the therapeutic range, many patients will require a greater dose than this. Considering the high inter-individual variability noted, many patients may require more than three times as much for naltrexone to have a significant clinical effect. A fear of inducing hepatotoxicity, however small, is likely to restrain clinicians from using such higher doses.

Alternately, today's clinician may consider timing the dose in relationship to drinking to maximize therapeutic effectiveness (Sinclair, 2001). Targeted dosing in which naltrexone is used one hour prior to drinking takes advantage of two facts. First, craving for alcohol is not constant, but is entrained to various stimuli associated with drinking. The strongest stimulus occurs after taking a first drink; people with alcohol dependence sometimes describe the sensation as a 'manic' feeling which drives them to drink excessively. Second, plasma concentrations of naltrexone and 6-ß-naltrexol both peak at one hour after a single 50 mg oral naltrexone dose. At 1 hour, the concentration of naltrexone is four times greater than it is at eight hours (Meyer *et al.*, 1984). Naltrexone dosing targeted to occur one hour prior to drinking will give a peak concentration at the time of the first drink, when craving is greatest, and this may maximize therapeutic effectiveness. Targeted dosing with naltrexone has become popular with clinicians and patients pursuing pharmacological extinction following the method described by Sinclair, and his recommendation to dose naltrexone one hour before drinking is likely to be critical for success (Sinclair, 2001). An important benefit of this method is that it can engage patients in therapy who are unwilling to accept abstinence as an initial treatment goal. Considered another way, targeted naltrexone may prove to be a helpful method of harm reduction in selected and motivated patients who can eventually be persuaded to seek abstinence as their craving for alcohol is reduced over time with therapy.

Until therapeutic naltrexone blood level testing becomes available to guide naltrexone therapy, targeted dosing provides an alternative way to achieve therapeutic plasma concentrations when most needed while minimizing the risk of hepatoxicity. Dosing targeted to block the rewarding effects of a first drink of alcohol may prevent a 'slip' from progressing to a heavy drinking relapse. Although additional studies are needed to relate naltrexone concentrations at different times after dosing to the treatment response as quantified by relapse to heavy drinking, Brünen's report is an important milestone in the therapeutic use of naltrexone.

REFERENCES

Brünen S, Bekier NK, Hiemke C, *et al.* (2019) Therapeutic drug monitoring of naltrexone and 6β-naltrexol during anti-craving treatment in alcohol dependence: reference ranges. *Alcohol Alcohol* **54**:51–5.

Meyer M, Straughn A, Lo M, *et al.* (1984) Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration. *J Clin Psychiatry* **45**:15–9.

SInclair JD. (2001) Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. *Alcohol Alcohol* **36**:2–10.

