ONLINE EXCLUSIVE

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Q/ Does XR injectable naltrexone prevent relapse as effectively as daily sublingual buprenorphine-naloxone?

EVIDENCE-BASED ANSWER

A/ **Yes.** Monthly extended-release injectable naltrexone (XR-NTX) treats opioid use disorder as effectively as daily sublingual buprenorphine-naloxone (BUP-NX) without causing any increase in serious adverse events or fatal overdoses. (strength of recommendation: **A**, 2 good-quality RCTs).

Evidence summary

Two recent multicenter, open-label RCTs, 1 in the United States and 1 in Norway, compared monthly XR-NTX with daily BUP-NX.[1,2] Both studies evaluated effectiveness (defined by either the number of people who relapsed or self-reported opioid use), cravings, and safety (defined as the absence of serious adverse events such as medically complex withdrawal or fatal overdose).

The participant populations were similar in both mean age and mean age of onset of opioid use. Duration of opioid use was reported differently (total duration or years of heavy heroin or other opioid use) and couldn't be compared directly.

Naltrexone and buprenorphine-naloxone are similarly effective

The US study enrolled 570 opioid-dependent participants in a 24-week comparative effectiveness trial.[1] The 8 study sites were community treatment programs, and the participants were recruited during voluntary inpatient detoxification admissions. Some participants were randomized while on methadone or buprenorphine tapers and some after complete detoxification.

The intention-to-treat analysis included 283 patients in the XR-NTX group and 287 in the BUP-NX group. At 24 weeks, the number of participants who'd had a relapse event (self-reported use or positive urine drug test for nonstudy opioids or refusal to provide a urine sample) was 185 (65%) for XR-NTX compared with 163 (57%) for BUP-NX (odds ratio [OR] = 1.44, 95% confidence interval [CI], 1.02 to 2.01; $P = .036$).

The 12-week Norwegian noninferiority trial enrolled 159 participants.[2] In contrast to the US study, all participants were required to complete inpatient detoxification before randomization and induction onto the study medication.

Patients on BUP-NX reported 3.6 more days of heroin use within the previous 28 days than patients in the XR-NTX group (95% CI, 1.2 to 6; $P = .003$). For other illicit opioids, self-reported use was 2.4 days greater in the BUP-NX group (95% CI, –0.1 to 4.9; $P = .06$). Retention with XR-NTX was noninferior to BUP-NX (mean days in therapy [standard deviation], 69.3 [25.9] and 63.7 [29.9]; $P = .33$).

Randomizing after complete detox reduces induction failures

Naltrexone, a full opioid antagonist, precipitates withdrawal when a full or partial opioid agonist is engaging the opioid receptor. For this reason, an opioid-free interval of 7 to

10 days is generally recommended before initiating naltrexone, raising the risk for relapse during the induction process.

The Norwegian trial randomized participants after detoxification. The US trial, in which some participants were randomized before completing detoxification, reported 79 (28%) induction failures for XR-NTX and 17 (6%) for BUP-NX.[1] As a result, a per protocol analysis was completed with the 204 patients on XR-NTX and 270 patients on BUP-NX who were successfully inducted onto a study medication. The 24-week relapse rate was 52% (106) for XR-NTX and 56% (150) for BUP-NX (OR = 0.87; 95% CI, 0.60 to 1.25; $P = .44$).

Cravings, adverse events, and cost considerations

Patients reported cravings using a visual analog scale. At 12 weeks in both studies, the XR-NTX groups reported fewer cravings than the BUP-NX groups, although by the end of the 24-week US trial, no statistically significant difference in cravings was found between the 2 groups.[1,2]

The Norwegian trial found a difference between the XR-NTX and the BUP-NX groups in the percentage of nonserious adverse events such as nausea or chills (60.6% in the XR-NTX group vs 30.6% in the BUP-NX group; $P < .001$), and the US trial found a difference in total number of overdoses (64% of the total overdoses were in the XR-NTX group). Neither trial, however, reported a statistically significant difference in serious adverse events or fatal overdoses between the 2 groups.[1,2]

The price for naltrexone is $1665.06 per monthly injection.[3] The price for buprenorphine-naloxone varies depending on dose and formulation, with a general range of $527 to $600 per month at 16 mg/d.[4]

Editor's takeaway

Two higher-quality RCTs show similar but imperfect effectiveness for both XR-NTX and daily sublingual BUP-NX. Injectable naltrexone's higher cost may influence medication choice. JFP

References

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