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Articles

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Dr Joshua D Lee, MD, Edward V Nunes Jr, MD, Patricia Novo, MPH, Ken Bachrach, PhD, Genie L Bailey, MD, Snehal Bhatt, MD, Sarah Farkas, MA, Marc Fishman, MD, Phoebe Gauthier, MPH, Candace C Hodgkins, PhD, Jacquie King, MS, Robert Lindblad, MD, David Liu, MD, Abigail G Matthews, PhD, Jeanine May, PhD, K Michelle Peavy, PhD, Stephen Ross, MD, Dagmar Salazar, MS, Paul Schkolnik, PhD, Dikla Shmueli-Blumberg, PhD, Don Stablein, PhD, Geetha Subramaniam, MD, John Rotrosen, MD

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Summary

Background

Extended-release naltrexone (XR-NTX), an opioid antagonist, and sublingual buprenorphine-naloxone (BUP-NX), a partial opioid agonist, are pharmacologically and conceptually distinct interventions to prevent opioid relapse. We aimed to estimate the difference in opioid relapse-free survival between XR-NTX and BUP-NX.

Methods

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We initiated this 24 week, open-label, randomised controlled, comparative effectiveness trial at eight US community-based inpatient services and followed up participants as outpatients. Participants were 18 years or older, had Diagnostic and Statistical Manual of Mental Disorders-5 opioid use disorder, and had used non-prescribed opioids in the past 30 days. We stratified participants by treatment site and opioid use severity and used a web-based permuted block design with random equally weighted block sizes of four and six for randomisation (1:1) to receive XR-NTX or BUP-NX. XR-NTX was monthly intramuscular injections (Vivitrol; Alkermes) and BUP-NX was daily self-administered buprenorphine-naloxone sublingual film (Suboxone; Indivior). The primary outcome was opioid relapse-free survival during 24 weeks of outpatient treatment. Relapse was 4 consecutive weeks of any non-study opioid use by urine toxicology or self-report, or 7 consecutive days of self-reported use. This trial is registered with ClinicalTrials.gov, NCT02032433.

Findings

Between Jan 30, 2014, and May 25, 2016, we randomly assigned 570 participants to receive XR-NTX (n=283) or BUP-NX (n=287). The last follow-up visit was Jan 31, 2017. As expected, XR-NTX had a substantial induction hurdle: fewer participants successfully initiated XR-NTX (204 [72%] of 283) than BUP-NX (270 [94%] of 287; p<0·0001). Among all participants who were randomly assigned (intention-to-treat population, n=570) 24 week relapse events were greater for XR-NTX (185 [65%] of 283) than for BUP-NX (163 [57%] of 287; hazard ratio [HR] 1·36, 95% CI 1·10–1·68), most or all of this difference accounted for by early relapse in nearly all (70 [89%] of 79) XR-NTX induction failures. Among participants successfully inducted (per-protocol population, n=474), 24 week relapse events were similar across study groups (p=0·44). Opioid-negative urine samples (p<0·0001) and opioid-abstinent days (p<0·0001) favoured BUP-NX compared with XR-NTX among the intention-to-treat population, but were similar across study groups among the per-protocol population. Self-reported opioid craving was initially less with XR-NTX than with BUP-NX (p=0·0012), then converged by week 24 (p=0·20). With the exception of mild-to-moderate XR-NTX injection site reactions, treatment-emergent adverse events including overdose did not differ between treatment groups. Five fatal overdoses occurred (two in the XR-NTX group and three in the BUP-NX group).

Interpretation

In this population it is more difficult to initiate patients to XR-NTX than BUP-NX, and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective. Future work should focus on facilitating induction to XR-NTX and on

improving treatment retention for both medications.

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