Published in final edited form as:

Addiction. 2020 November ; 115(11): 2188–2190. doi:10.1111/add.15153.

Reply to Kunoe (2020) and Ghosh and Singh (2020) regarding: Nunes et al., Opioid use and dropout from extended-release naltrexone in a controlled trial: implications for mechanism. Addiction. 2020 Feb;115(2):239-246.

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Our paper, “Opioid use and dropout from extended-release naltrexone in a controlled trial: implications for mechanism” (Addiction. 2020 Feb;115(2):239-246) [1] generated interest from readers [2,3] on how to interpret the findings, and the role of cognitive and motivational processes, as opposed to conditioning, that may underlie patients’ differing behavioral responses to blocked opioid use.

We appreciate Dr. Kunoe’s close reading of our paper. His commentary [2] highlights the potential complexity underlying antagonist treatment for opioid use disorder (OUD) and important directions for future research. Our paper emphasized the mechanism of extinction [1] because of the impressive phenomenon that naltrexone, at adequate blood levels, fully blocks the subjective and reinforcing effects of opioids, at least for most patients [4] and aids in mitigating most opioid use. We also discussed cognition and expectancy as mechanisms—the patient experiences the blockade and knows that the effects of future doses of opioids will be blocked, or has been instructed that there will be blockade and thus expects it.

Dr. Kunoe argues that cognition and motivation are the more useful models [2], and he has a point. Patients in our study undoubtedly varied in their motivation entering the trial, wavered during the trial, and likely expected blockade. We were unable to confirm our hypothesis (p=0.051) that more patients on active extended-release injection naltrexone than placebo would have no evidence of opioid use at all [1]—a phenomenon that could not depend on extinction. However, the surprising proportion of patients on placebo with no opioid use suggests the importance of motivation or expectancy. The observation that some patients likely understood and accepted the blockade, while others needed to test and

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directly experience this, highlights an important role for cognitive-motivational processes. Motivational incentives combined with cognitive-behavioral therapy has shown promise for improving outcome of treatment for OUD with buprenorphine [5] and oral naltrexone [6]. Dr. Kunoe's own study of drug use and subjective experience after a 6-month naltrexone implant suggests further important behavioral dimensions [7]. As in our study, some patients never used opioids after implantation, while others continued to use intermittently. The latter group showed greater severity and worse prognosis, including lower functioning and more non-opioid drug use. A minority reported experiencing some degree of opioid high.

We also appreciate Drs. Ghosh and Singh's observation that taking opioids, and experiencing blockade, or no blockade, could indeed result in unblinding, which could then influence a patient's subsequent behavior [3]. This process can be viewed as a component of cognition or expectation: a patient's believing he or she may be on naltrexone and blocked either at the outset, or upon testing the blockade. In a placebo-controlled study of an antagonist such as naltrexone, it is difficult to preserve the blind once a patient uses opioids. Ethical concerns have also been raised about conducting double-blind, placebo-controlled studies of naltrexone in OUD, given the potential consequences of incorrectly believing oneself to be blocked, and not offering known effective medication to patients with a dangerous illness. Yet it is important to note that in our study, many patients who experienced unblocked use did not drop out; rather, they continued to accept placebo injections and remained mostly abstinent—possibly also due to the psychosocial intervention offered; a finding which supports the importance of cognitive processes affecting behaviors.

Craving is another dimension of patients' experience that exerts an effect on treatment outcome. While the experience of craving is subjective, Hulse et al. 2010 have suggested that reductions in craving are a direct pharmacologic effect of naltrexone, in that higher blood levels of naltrexone were associated with lower craving, which in turn predicted lower relapse risk in treatment with naltrexone implant vs. oral naltrexone [8]. Recent neuroimaging studies of extended-release naltrexone have demonstrated reduced responses to opioid-related stimuli in the nucleus accumbens and medial orbito-frontal cortex during XR-naltrexone treatment [9] further supporting pharmacodynamic mechanism.

We agree with Dr. Kunoe that future research should do more to measure the motivation, subjective experience and cognitions of patients before and during treatment with naltrexone or other medications for opioid use disorder. Despite the pharmacological effects of these medications, too many patients continue to use or discontinue treatment and do poorly, and we need to better understand the reasons. Identifying biomarkers or cognitive or behavioral traits that characterize those subgroups of patients most, or least, likely to have successful outcomes with a particular medication for OUD is an emerging area of clinical research. Such efforts would support the adoption of a Precision Medicine model to optimize treatment efficacy for opioid use disorder.

Acknowledgments

Declaration of Interests:

EVN has participated as an unpaid consultant for Braeburn-Camurus, Pear Therapeutics, and Alkermes, Inc., has served as an investigator on a multi-site trial funded by Braeburn-Camurus, and has received medication for NIDA funded studies from Reckitt Benckiser (Indivior) and Alkermes, Inc., and has received a digital therapeutic for an NCCIH funded study from Pear Therapeutics. AB has received study medication from, and served as an investigator and an unpaid consultant to, Alkermes, Inc., and received study medication from, and served as an unpaid consultant to Go Medical Industries Pty. He has also received honoraria and consultation fees from consulting groups and for educational activities. EK has been a consultant for Alkermes and has previously received research funding for a study from Alkermes, Inc. At the time the work to which this commentary refers was conducted NN and BLS were employees of Alkermes, Inc. and may be shareholders of Alkermes, Inc. SA and MAS are employees and may be shareholders of Alkermes, Inc. MAS previously received study medication from Alkermes for a NIDA-funded investigation.

References:

1. Nunes EV, Bisaga A, Krupitsky E, Nangia N, Silverman BL, Akerman SC, Sullivan MA. Opioid use and dropout from extended-release naltrexone in a controlled trial: implications for mechanism. Addiction. 2020 Feb;115(2):239–246. [PubMed: 31313402]
2. Kunøe N Commentary on Nunes et al. (2020): Blocked opioid use in antagonist treatment-time for cognitive and user-centered perspectives. Addiction. 2020 Feb;115(2):247–248. [PubMed: 31758629]
3. Ghosh A, Singh P. Extension as the behavioral mechanism of the naltrexone-extended release for opioid dependence: could there be an alternate explanation? Addiction 2020, [in press]. doi: 10.1111/add.15105
4. Sullivan MA, Vosburg SK, Comer SD. Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin. Psychopharmacology (Berl). 2006 Nov;189(1):37–46. [PubMed: 16972105]
5. Carroll KM, Weiss RD. The Role of Behavioral Interventions in Buprenorphine Maintenance Treatment: A Review. Am J Psychiatry. 2017 Aug 1;174(8):738–747. [PubMed: 27978771]
6. Nunes EV, Rothenberg JL, Sullivan MA, Carpenter KM, Kleber HD. Behavioral therapy to augment oral naltrexone for opioid dependence: a ceiling on effectiveness? Am J Drug Alcohol Abuse. 2006;32(4):503–17. [PubMed: 17127538]
7. Kunøe N, Lobmaier P, Vederhus JK, Hjerkinn B, Gossop M, Hegstad S, Kristensen Ø, Waal H. Challenges to antagonist blockade during sustained-release naltrexone treatment. Addiction. 2010 Sep;105(9):1633–9. [PubMed: 20707781]
8. Hulse GK, Ngo HT, Tait RJ. Risk factors for craving and relapse in heroin users treated with oral or implant naltrexone. Biol Psychiatry 2010 Aug; 68(3): 296–302. [PubMed: 20537615]
9. Shi Z, Wang A-L, Jagannathan K, Fairchild VP, O'Brien CP, Childress AR, Langleben DD. Effects of extended-release naltrexone on the brain response to drug-related stimuli in patients with opioid use disorder. J Psychiatry Neurosci 2018 Feb; 43(3): 170036. [PubMed: 29485031]