Viewpoint

A Statement on the Pharmacology of Reinstatement: Naltrexone and Relapse to Opioid Seeking

This issue of the Journal of Pharmacology and Experimental Therapeutics includes an article by Withey et al. that addresses an important challenge in the seemingly unending quest for effective and safe pharmacological approaches to the treatment of opioid use disorders (OUDs). One focus of the article is on the use of chronic naltrexone, a μ-opioid receptor antagonist, to block “reinstatement” of a number of full and partial μ-opioid receptor agonists in squirrel monkeys. An additional objective of the research was to examine the effects of chronic naltrexone administration on the antinociceptive effects of the same drugs used in the reinstatement experiments. The rationale behind this portion of the publication is related to naltrexone’s ability to block μ-opioid receptor–mediated effects that include antinociception. Opioid pain management may be challenging in patients undergoing treatment with extended-release naltrexone. The article serving as the basis for this Viewpoint could be viewed as a companion publication to Withey et al. (2019), who studied the effects of chronic buprenorphine under similar conditions and with comparable drugs. Together, they provide valuable information on issues surrounding both reinstatement and antinociception with chronic administration of naltrexone and buprenorphine.

The study of reinstatement of drug-seeking behavior in laboratory animals has become standard as one of the experimental approaches to aid in guiding the development of potential medications to treat relapse to drug use. Susceptibility to relapse is, among other variables, frequently believed to be related to craving, which has emerged as an important indicator of drug seeking and relapse. Gauld et al. (2023), following an extensive network analysis of opioids and other drugs, concluded that craving is a potential central marker of addiction, connecting to the entire symptom network regardless of the specific substance, and can be used to aid and facilitate the understanding and treatment of SUDs.

As used in the accompanying article to this Viewpoint, the study of reinstatement typically follows a period where access to an abused drug, such as oxycodone, usually by self-administration, is followed by discontinuation of the drug’s availability (extinction). When responding (sometimes referred to as “drug seeking” behavior) has declined to low levels, it can frequently be reinstated by the brief administration of the original drug (a “priming” stimulus) or by a drug having a similar mechanism. This was the technique used in the present study. Reinstatement can also occur following the presentation of a stimulus (“cue”) previously associated with drug delivery (e.g., Blackwood et al., 2019) by exposure to the context in which the drug has been administered previously (e.g., Venniro et al., 2016; Bossert et al., 2019) or by some form of stress, such as foot shock (Grella et al., 2011; Fulenwider et al., 2020). A few studies with rodents have examined the effects of acute naltrexone administration on a priming dose of oxycodone (Leri and Burns, 2005) and following context-induced reinstatement after oxycodone self-administration had been extinguished (Bossert et al., 2019). Both of these studies reported that naltrexone decreased or attenuated oxycodone-induced reinstatement of responding. Of interest in the present article is whether chronic administration of the opioid receptor antagonist naltrexone would block reinstatement when primed with the training drug, oxycodone, and by the different μ-opioid receptor agonists.

Studies of reinstatement produced by any of the approaches mentioned above are difficult to conduct with humans, and the absence of this information is one of the primary objectives and areas of focus for this manuscript. Withey et al. (2024) also point out that there were a limited number of studies conducted prior to the approval of long-acting naltrexone, suggesting that the article in this issue would address some of the missing information. Since the approval of extended-release naltrexone (Vivitrol or XR-NTX), a number of reviews have appeared indicating rather robust effects in increases in the period of opioid abstinence,
accompanied by significant reductions of craving and relapse (Kjome and Moeller, 2011; Syed and Keating, 2013; Jarvis et al., 2018).

Currently, there are four Food and Drug Administration approved medications for the treatment of opioid use disorders: methadone, buprenorphine, a combination of buprenorphine and naloxone (Suboxone), and extended-release naltrexone (XR-NTX). Naltrexone was patented in 1967 and approved for medical use in 1984. The oral formulation was shown not to be terribly effective for the treatment of OUDs due primarily to a lack of compliance. Although sustained-release preparations of naltrexone were attempted in use in 1984. The oral formulation was shown not to be terribly effective for the treatment of OUDs due primarily to a lack of compliance. Although sustained-release preparations of naltrexone were attempted in the 1970s, difficulties with biocompatibility limited widespread use. A long-acting injectable version of naltrexone, XR-NTX, was approved in the United States in 2006 as an intramuscular injection every 4 weeks or monthly for the treatment of alcohol dependence. In 2010, XR-NTX (Vivitrol) was approved by the US Food and Drug Administration as an extended-release intramuscular injection of naltrexone for the prevention of relapse to opioid dependence following opioid detoxification.

Prior to the initial approval of XR-NTX, a few studies were conducted with a predecessor, Depotrex, a drug that is not currently available (Kjome and Moeller, 2011). Depotrex, an injectable depot formulation of naltrexone, was studied in a small number of heroin-dependent individuals. Following a period of detoxification to prevent precipitated withdrawal, subcutaneous administration of Depotrex produced a long-lasting antagonism of the effects of intravenous heroin in humans that included a dose-related blockade of the positive subjective effects (Comer et al., 2002). In a subsequent study, Depotrex was shown to suppress craving for heroin as well as for other drugs and also antagonized the subjective, reinforcing, and physiologic effects of heroin (Sullivan et al., 2006).

Subsequent studies with XR-NTX in individuals with OUD have shown significant differences in the proportion of weeks of confirmed abstinence that were higher in the XR-NTX group compared with placebo. In addition, XR-NTX produced an anticraving effect and fewer relapses to dependence and also doubled the median length of retention in the study. The reduction in the craving effect of XR-NTX occurred rapidly and was apparent in week 1 of the study (Krupitsky et al., 2011). A subsequent open-label study by Lee et al. (2018) compared the effects of XR-NTX with those of buprenorphine-naloxone (BUP-NX). More participants in the BUP-NX group were successfully inducted into the study than in the XR-NTX group, indicating that it was more difficult to initiate treatment with XR-NTX due to the need to detoxify before starting treatment; this step is not needed with BUP-NX. As an example, in the Lee et al. (2018) study, out of 283 subjects randomly assigned to XR-NTX treatment group, there were 79 induction failures compared with 17 out of 287 subjects randomly assigned to the BUP-NX group. Almost all induction failures had an early relapse, but for those that were successful in initiating medication, the two drugs were equally effective, leading Lee et al. (2018) to conclude that if induction to either medication is successful, XR-NTX and BUP-NX are comparably effective.

With this backdrop, there are several interesting and noteworthy features of the studies conducted by Withey et al. (2024). First is the use of a behavioral procedure, novel in the context of reinstatement studies, that integrated daily delivery of naltrexone via an indwelling subcutaneous catheter along with intravenous access to oxycodone that maintained lever-press responding of four male squirrel monkeys. Responding that produced oxycodone following 30 lever-press responses [fixed-ratio (FR) 30 or FR 30 schedule] alternated with periods in the experimental session when responding produced only saline. Oxycodone consistently maintained high levels of responding, with much lower levels of responding during portions of the schedule when only saline was available. Reinstatement was studied on days when only the intravenous saline sessions were in effect. On these days, intramuscular doses of either a full agonist (heroin, methadone, or oxycodone) or a partial agonist (nalbuphine, butorphanol, or buprenorphine) preceded the experimental session as potential priming doses—probing for possible reinstatement. During the reinstatement sessions, responding produced only saline. This unique experimental design provides the opportunity to study reinstatement repeatedly, in the same animal, and with several different doses of a range of drugs. Methadone, heroin, and oxycodone all reinstated responding when administered before chronic naltrexone administration was initiated. Chronic administration of naltrexone blocked reinstatement at doses of these agonists that previously produced reinstatement. However, the subsequent shift to the right of the dose-response curves indicated that higher doses could reinstate responding to levels comparable to those prior to naloxone treatment. The lower efficacy partial agonists also reinstated responding prior to the administration of chronic naltrexone but differed during chronic naltrexone administration, suggesting pharmacological differences between these partial agonists and between the full agonists.

A second feature of this study, also unique, was the examination of antinociception using a warm-water tail withdrawal procedure that was conducted with a separate set of four male squirrel monkeys. There were several cycles throughout the experimental session when cumulative doses of the drugs could be
administered, and the latency to withdraw the tail from water was assessed. Prior to chronic treatment with naltrexone, all drugs produced graded increases in the latency to withdraw the tail from each of the warm-water temperatures (50, 52, and 55° C), suggesting an antinociceptive effect. Following chronic treatment with naltrexone, with the exception of nalbuphine, all drugs produced a distinctive rightward shift in the dose-response curves. Measures of operant responding were decreased dose dependently for all drugs, were shifted to the right during chronic administration of naltrexone, and were decreased or eliminated at the higher doses of all drugs.

Third, a comparison of this study with that of Withey et al. (2019), who studied the effects of chronic buprenorphine under comparable conditions to those in the present publication, permits a useful evaluation of these two different treatment options. As just two examples of the differences between these two drugs, oxycodone was able to fully surmount the antagonistic effects of naltrexone, whereas with buprenorphine, peak levels of oxycodone self-administration decreased by approximately 50%. Further, chronic naltrexone treatment led to rightward shifts in the dose-response functions for priming with all full opioid agonists, suggesting competitive antagonism; in contrast, chronic buprenorphine led to rightward and downward shifts with the same agonists, suggesting to the authors that naltrexone and buprenorphine attenuate the reinforcing and relapse-related effects (“reinstatement”) through qualitatively different mechanisms.

There are also differences observed clinically between naltrexone and buprenorphine that have been reported. For example, Jarvis et al. (2018) concluded that many individuals that start XR-NTX discontinue treatment prematurely. This is due to the fact that individuals need to be fully detoxified before receiving XR-NTX to prevent precipitated withdrawal, whereas this is not necessary with buprenorphine. The substantial induction hurdles accompanying induction into treatment with XR-NTX shown in the Lee et al. (2018) study are a recognized limitation of XR-NTX and a distinct advantage of BUP-NX. This is particularly critical because the drop-out rate to enter treatment is very high during this transition period, and relapse is frequent.

Fourth, the assessment of complete dose-response functions in all phases of these experiments is another distinct strength. All too often, reinstatement studies as well as many other published studies have used only a single dose of a drug to study reinstatement. This limitation potentially obscures the rich data that accompanies the determination of full dose-response curves. Withey et al. (2024) point out that the inability of the lower-efficacy partial agonists to surmount naltrexone antagonism may complicate the prescribed use of opioid drugs for pain. In all likelihood, this insight would not have been achieved were only single doses examined.

Finally, another strength of this manuscript is evident in the value of using a self-administration schedule other than an FR1 where every response produces drug or saline. The use of an FR 30 response schedule in these studies generated robust and reproducible behavior across all conditions. The use of different schedules of reinforcement with greater intermittency may also provide greater translational value, more faithfully reflecting the robust and enduring nature of substance use disorders.

In summary, the publication by Withey et al. has several positive contributions beyond the objective of addressing a knowledge gap in the study of naltrexone as a medication to treat OUDs. The article unquestionably provides valuable information on the study of reinstatement and nociception during chronic naltrexone administration. In doing so, it illustrates fundamental procedural and experimental approaches to be employed more widely in future behavioral studies of reinstatement. Studies incorporating these approaches may also aid in addressing and overcoming some of the challenges associated with naltrexone treatment of OUDs, such as the substantial induction hurdles.

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References


