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Factors Associated with Using Opiates while under Extended-Release Naltrexone Blockade: A Descriptive Pilot Study

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Abstract

Background and Aim—Extended-release naltrexone (XR-NTX) blocks the effects of opioids for 4 weeks, yet many patients continue to use them. To learn more about why this occurs, we collected self reports on subjective effects and drug use factors from participants' most recent heroin/opiate use while under XR-NTX blockade.

Methods—Participants (N = 38) were unemployed, heroin-dependent adults enrolled in a randomized controlled trial evaluating employment-based incentives to promote adherence to XR-NTX. A subset of participants (n = 18) were asked to complete a survey about their most recent use of heroin/opiates when they provided an opiate-positive urine sample while under XR-NTX blockade. Surveys were administered weekly, and participants could complete multiple surveys throughout the trial. Participants reported how high they were (11-point scale; 0 = not at all, 10 = extremely), how much heroin/opiates they took (less, more, or about the same as usual before starting naltrexone), whether they used cocaine at the same time, and the routes of administration for heroin/opiates and cocaine (if used). All analyses were descriptive.

Results—Of the 107 surveys, 75.7% indicated being “not at all” high the last time heroin/opiates were used. 75.5% of surveys reported opiate amounts that were less than usual, and only 7.5% reported amounts larger than usual. Cocaine was used at the same time as heroin for 57.9% of surveys but typically through a different route (74.2%).

Discussion—Using heroin/opiates while under XR-NTX blockade is not strongly associated with self reports of high, taking larger than normal amounts of opiates, or taking opiates and cocaine simultaneously via the same route. Future research should incorporate measures of naltrexone concentration and more comprehensive and frequent assessments using ecological momentary assessment.

Keywords

heroin; opioids; extended-release naltrexone; challenge; blockade

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1. Introduction

Prescription opioid and heroin overdose deaths increased by 286% from 2003-2013 (Han, Compton, Jones, & Cai, 2015) and 73% from 2002-2013 (Jones, Logan, Gladden, & Bohm, 2015), respectively. During these same time periods, prevalence of opioid use disorder increased by 50% for prescription opioids and 90% for heroin. Fatal overdoses can be reduced and medical and social problems associated with opioid use disorder can be improved with medication-assisted treatments (Schuckit, 2016). Naltrexone, an opioid antagonist, is an ideal medication in theory because it blocks the effects of opioids and heroin, but has had little impact in practice due to poor compliance (Minozzi et al., 2011). An extended-release injectable naltrexone formulation (XR-NTX; Syed & Keating, 2013) that lasts for 4 weeks was developed to address issues with compliance. Although there are limited data on XR-NTX, it does appear to improve adherence (Brooks et al., 2010) and reduce opioid use compared to placebo and treatment as usual (Krupitsky et al., 2011; Lee et al., 2016).

Despite improvements over oral naltrexone, there are a number of barriers to XR-NTX's implementation (Alanis-Hirsch et al., 2016) including induction, which requires 7 to 10 days of abstinence from all opioids, and long-term adherence (DeFulio et al., 2012). In addition, even among individuals who start and adhere to XR-NTX, many continue to use opioids (Bisaga et al., 2014; Sullivan et al., 2013). Using opioids while under XR-NTX blockade has not reliably predicted treatment dropout, however, it was associated with a number of poor outcomes in a trial using naltrexone implants that produced naltrexone plasma levels similar to XR-NTX (Kunøe et al., 2010). Participants who used opioids while receiving the naltrexone implant had higher rates of non-opioid illicit drug use, injection use, sharing of injection equipment, and legal problems.

Little is known about the factors that contribute to using opioids while taking XR-NTX, and its occurrence is perplexing because XR-NTX has been shown to block the effects of a potent, high-dose opioid for at least 28 days (cumulative 13.5mg dose of hydromorphone; Bigelow, Preston, Schmittner, Dong & Gastfriend, 2012). There are several possibilities for why opioid use occurs while under XR-NTX blockade. Individuals may be able to overcome the blockade and experience a subjective high as plasma naltrexone levels decline over time. One case study reported mild intoxication in an adolescent beginning in the third week of the XR-NTX blockade interval but not earlier (Fishman, 2008). Also, in a 6-month trial of naltrexone implants, there was a trend toward more opioid use with each successive month (Kunøe et al., 2010). However, in exit interviews only 30% of participants who used opioids ever reported at least a partial high. Individuals may also try to overcome the blockade directly by taking larger quantities of opioids than usual. There are no published data examining how much opioids individuals take while under XR-NTX blockade, other than one case study in which a man injected 12-times his normal dose of heroin and experienced a nonfatal overdose while receiving a naltrexone implant (Krupitsky et al., 2006). A final possibility is that opioid use occurs in the context of polydrug use. In three trials evaluating naltrexone for heroin use (DeFulio et al., 2012; Dunn et al., 2013; & Everly et al., 2011), we showed that cocaine use was strongly associated with heroin use but it was not clear why this was the case. Detailed analyses of factors that affect opioid use while under XR-NTX

blockade are needed. In the present study, we explored these possibilities by interviewing heroin-dependent adults who provided urine samples that tested positive for opiates and who were under XR-NTX blockade.

2. Materials and Methods

2.1 Main trial

Data were collected as part of a secondary analysis in a randomized controlled trial evaluating employment-based incentives to promote adherence to XR-NTX (DeFulio et al., 2012). All participants (N = 38) were offered monthly XR-NTX and invited to attend the therapeutic workplace for 26 weeks, a model workplace designed to treat unemployed adults with substance use disorders who are living in poverty (Silverman, DeFulio, & Sigurdsson, 2012). Participants could attend the workplace each weekday for 4 hours and earn wages up to \$10 per hour for completing job skills training. Half of the participants were randomized to a condition in which they were required to take scheduled doses of XR-NTX to work and earn maximum wages, and half could work and earn maximum wages regardless of XR-NTX adherence. All study procedures were reviewed and approved by the Johns Hopkins Institutional Review Board.

2.2 Participants

Participants were unemployed, used heroin, met DSM-IV criteria for opioid dependence, were recently detoxified from opioids, were not interested in methadone or buprenorphine maintenance, and were medically approved for naltrexone treatment. The present study included a subset of participants (n = 18) from the main trial who agreed to participate and provided a urine sample that tested positive for opiates while under XR-NTX blockade.

2.3 Measures

Urine samples were collected every Monday, Wednesday, and Friday as part of the procedures for the main trial. Morphine levels above 300 ng/ml were considered positive for opiates. Six XR-NTX injections were scheduled 28 days apart, and a two-day grace period was allowed for missed appointments for participants who were required to take XR-NTX to work and earn maximum wages. Participants who had received an XR-NTX injection within 30 days were considered blocked by naltrexone.

A five-question survey was developed to gather information on participants' most recent use of heroin or other opiates. Participants who tested positive for opiates and who were under naltrexone blockade completed the survey shortly after testing positive for opiates. Participants were given the following instructions: "In the therapeutic workplace you are given a prescription for naltrexone. Our records indicate that you have been taking your prescription of naltrexone. Your urinalysis results indicate that you have recently used heroin or other opiates. We would like you to answer a few questions about your most recent experience of taking opiates after taking naltrexone. You do not have to answer these questions if you do not want to."

Participants were asked (1) How high were you the last time you took heroin/opiates? (11-point scale; 0 = not at all, 10 = extremely); (2) How much heroin/opiates did you take the last time you used, compared to how much you usually took before you started taking naltrexone? (less than usual, about the same as usual, more than usual); (3) How did you take heroin/opiates the last time you used? (IV/injection, nasal/snorted, inhaled/smoked, oral/pills); (4) Did you take cocaine at the same time? (yes, no); and if they did use cocaine at the same time, (5) How did you take the cocaine? (injection mixed with heroin; injection, not mixed; nasal/snorted, inhaled/smoked, oral).

2.4 Procedures

Each week, participants were identified who tested positive for opiates while under XR-NTX blockade and were asked to complete the survey. No more than one survey was given to each participant each week. Because administering the survey was dependent on participants' XR-NTX acceptance, recent opiate use, and attendance in the workplace, the number of surveys completed varied across participants. For comparison, two participants who tested positive for opiates but who were not blocked by XR-NTX also completed the survey.

3. Results

Three participants in the main trial refused to complete any surveys, and 4 of 18 participants included in the analysis refused to complete one or more surveys. Denial of heroin/opiate use and not wanting to be bothered were the primary reasons for refusing to complete the survey. Participant demographics are shown in Table 1. A total of 107 surveys were completed by 18 participants with each completing between 1 and 15 surveys (Table 2).

3.1 Subjective effects

Participants reported that they were “not at all” high (i.e., 0 on 11-point scale) the last time they used heroin/opiates for 75.7% of the surveys (Figure 1A). For participants who reported experiencing at least a partial high (i.e., 1 on an 11-point scale; 26 surveys from 11 participants [61.6%]), the most common ratings were 1 (19.2%), 2 (38.5%), and 3 (19.2%). The highest score for subjective high was a 6, which was reported in only one survey. For comparison, all of the 10 surveys completed by the two participants not blocked by XR-NTX reported at least a partial high, with survey ratings ranging from a 1 (20.0%) to 9 (20.0%).

3.2 Amount of opiates used

Participants nearly always reported using less opiates than usual (75.5%) or about the same as usual (17.0%; Figure 1B). Only two participants (11.1%) indicated that they had used more opiates while under XR-NTX blockade than during the period before beginning XR-NTX (8 surveys total; 7.5%).

3.3 Concurrent cocaine use with opiates and routes of administration

Thirteen participants (72.2%) reported using cocaine at the same time at least once, and this pattern of use accounted for 62 of 107 (57.9%) surveys. The most frequent combination of

cocaine and opiate use was to smoke cocaine and to snort opiates (10/13 participants, 76.9%; 42/62 surveys, 67.7%; Figure 1C). Concurrent injection of both drugs (i.e., “speedballing”) was only reported by 2 of 13 participants (14.4%) and accounted for 6 of the 62 (9.7%) surveys. Seven of the thirteen participants (53.8%) used opiates and cocaine through the same route of administration at least once but these represented just 15.0% of surveys (16 of 107).

3.4 Opiate use and subjective effects by time since last XR-NTX injection

Participants were slightly more likely to challenge the XR-NTX blockade as the time since receiving their last injection increased (Figure 1D). During the four-week blockade interval, the percentage of surveys collected increased from 21.5%, 23.4%, 26.2%, and 29.0% for Weeks 1, 2, 3, and 4, respectively. There was also an increasing trend of participants reporting feeling at least a partial high from Week 1 to Week 4 (17.4%, 28.0%, 21.4%, and 29.0% of surveys).

4. Discussion

In the present study, we conducted a preliminary analysis of the subjective effects and drug use factors associated with using opiates while blocked by XR-NTX. Similar to an earlier naltrexone implant study (Kunøe et al., 2010), only about one-quarter of instances of opiate use while taking XR-NTX resulted in any discernible euphoria or high, and those that did were mild. The vast majority of surveys indicated that although participants were using opiates, the amounts they were using were less than they typically used prior to starting XR-NTX. Participants reported using cocaine at the same time as opiates in over half of the surveys collected. However, cocaine and opiates were rarely injected together and their administration through the same route accounted for only one-quarter of all instances when they were used at the same time. As the time since participants' last XR-NTX injection increased, there was some indication that they were more likely to use and to feel the effects of opiates.

The results from these surveys are the first to our knowledge to examine more closely the counterintuitive use of opiates while taking XR-NTX. Our findings do not point to any one clear factor that is strongly associated with use, but do offer some insights. First, XR-NTX does appear to reduce or block the subjective effects of heroin. Second, taking large amounts of opiates to overcome naltrexone's effects, while possible, does not appear to be a common factor associated with use during XR-NTX treatment. Third, opiate use under XR-NTX blockade is unlikely to be an artifact of combined administration with cocaine through the same route. We observed a strong positive relationship between opiate and cocaine urine results in earlier studies of naltrexone (oral and XR-NTX) and suspected that participants' use may have been due to continuing to inject opiates with cocaine, despite naltrexone blockade. At least in the current sample, this pattern of use under XR-NTX blockade is rare. Fourth, subjective high effects from opiates are probably not responsible for most use after taking XR-NTX, at least in the 4 weeks following the injection. The slight increase observed in feeling at least some subjective effects that occurred in combination with increasing use as the naltrexone protection window closed, however, deserves further investigation.

The present study was exploratory and had several limitations. The number of participants was small and the number of surveys collected across each varied based on factors that were beyond our control (e.g., opiate use, attendance). As a result, we did not collect data on all instances of opiate use for every participant in the trial. It is possible our findings may not generalize to other populations. Although we did survey two participants who did not take XR-NTX but who used opiates, this was a limited comparison. Other limitations were the lack of specificity for some factors and the limited number of factors that were included in the survey. For example, using time since last injection as a proxy for naltrexone levels does not take into account individual differences in drug metabolism, and other potentially important variables were not measured (e.g., social factors, such as whether participants purchased and used opiates alone or used opiates with and purchased by others). Finally, there was the potential for recall bias that is inherent in all self reports.

In addition to increasing sample sizes of blocked and non-blocked participants and making future research more systematic, there are two strategies that could be explored to further elucidate factors contributing to opiate use under XR-NTX blockade. The first is to measure XR-NTX drug concentrations. Naltrexone and its active metabolite (6-beta-naltrexol) were not measured in the present study but could add valuable information about the level of protection, especially in later weeks. Not only are these levels crucial to verifying pharmacological blockade of subjective and physiological effects (Bigelow et al., 2012), there is evidence that these metabolites are associated with neural responses to heroin cues (Langleben et al., 2012). Because naltrexone blocks the physiological effects of opioids, it is possible that the influence of drug cues and other environmental factors (e.g., stress) may play more prominent roles in relapse among individuals who use while taking XR-NTX. The second strategy is to use ecological momentary assessments (Shiffman, 2009) to more frequently assess opiate use and to incorporate more in-depth measures of environmental and personal factors not included in the current study (e.g., craving, mood, stress, time, social setting). Combining biological measures and frequent real-time monitoring of contextual variables associated with challenging the XR-NTX blockade may help identify specific mechanisms that predict its occurrence.

5. Conclusion

This pilot survey study suggests that challenging the XR-NTX blockade with heroin is not strongly associated with self reports of high, with taking larger than normal amounts of opiates, or with taking opiates and cocaine simultaneously via the same route of administration. Within the 4-week window of XR-NTX blockade, subjective high from opiate use is also not likely a driving factor, although more research should investigate the small increases in use and mild high reported later in the window. This research could include biological measures of naltrexone concentration and use ecological momentary assessments to more robustly capture variables that may be relevant to using opiates under XR-NTX blockade.

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Highlights

- Individuals rarely use larger than normal amounts of opiates when challenging XR-NTX blockade
- Most who challenge XR-NTX with opiates do not report any subjective high
- Co-use of cocaine and heroin via the same route accounts for few XR-NTX challenges
- Using opiates under XR-NTX may increase slightly as the time since XR-NTX injection increases

Figure 1.

Percentage of surveys collected while participants were under XR-NTX based on (A) ratings of subjective “high” experienced while using heroin or other opiates (ratings anchors were at 0 – “not at all” and 10 – “extremely”), (B) whether the amount of heroin or other opiates used was less, the same, or more than typically used prior to taking XR-NTX, (C) the route of administration when cocaine was used at the same time, and (D) the number of weeks since receiving the XR-NTX injection. Note the different y-axis in Panel D.

Table 1

Participant demographics at intake (n = 18)

Demographic^a	
Male, %	50.0
African American, %	94.4
Age, mean (<i>SD</i>)	44.9 (8.9)
Heroin primary route of administration, %	
Snort	61.1
Smoke	5.6
Inject	33.3
Heroin dependent, ^b %	100.0
Cocaine dependent ^b , %	72.2
Past 30 day use, mean (<i>SD</i>)	
Alcohol (to intoxication)	4.7 (9.9)
Heroin	28.5 (2.3)
Other opioids	2.7 (7.4)
Sedatives	4.2 (9.7)
Cocaine	17.7 (13.7)
Cannabis	3.4 (8.2)
Lifetime use (years), mean (<i>SD</i>)	
Alcohol (to intoxication)	1.8 (4.1)
Heroin	19.1 (9.9)
Other opioids	0.9 (2.9)
Sedatives	0.4 (1.5)
Cocaine	11.6 (8.3)
Cannabis	3.6 (6.4)

^aTaken from the Addiction Severity Index – Lite unless noted otherwise^bTaken from the Composite International Diagnostic Interview.

Table 2

Summary of opiate use experience survey results under XR-NTX blockade by participant

ID	Surveys completed N	At least partial high %	Average high ^a <i>M (SD)</i>	Average amount used ^b <i>M (SD)</i>	Concurrent cocaine use %	Average weeks since injection <i>M (SD)</i>
1	3	66.7	1.3 (1.2)	2.0 (0.0)	100.0	2.9 (0.8)
2	3	100.0	2.3 (0.6)	0.0 (0.0)	66.7	2.5 (1.1)
3 ^c	1	100.0	0.0	0.0	100.0	3.0
4 ^c	1	0.0	0.0	0.0	0.0	0.7
5	15	6.7	0.1 (0.3)	0.0 (0.0)	100.0	2.3 (1.2)
6 ^c	1	0.0	0.0	0.0	100.0	3.6
7	5	0.0	0.0 (0.0)	0.0 (0.0)	100.0	2.7 (1.4)
8	12	8.3	0.1 (0.3)	0.0 (0.0)	91.7	2.4 (1.2)
9	15	0.0	0.0 (0.0)	0.1 (0.3)	53.3	2.2 (1.3)
10	11	0.0	0.0 (0.0)	0.0 (0.0)	0.0	2.4 (1.1)
11 ^c	1	0.0	0.0	0.0	0.0	2.0
12	7	71.4	1.7 (1.5)	0.2 (0.4)	85.7	2.0 (1.0)
13	15	46.7	1.0 (1.2)	0.7 (0.5)	0.0	2.0 (1.2)
14 ^c	1	0.0	0.0	0.0	0.0	1.4
15	6	33.3	1.3 (2.1)	1.8 (0.4)	66.7	2.5 (1.2)
16	6	16.7	0.2 (0.4)	0.2 (0.4)	50.0	2.3 (1.2)
17	3	100.0	5.3 (0.6)	1.0 (0.0)	66.7	3.1 (0.7)
18 ^c	1	100.0	3.0	0.0	100.0	2.7

^aBased on an 11-point scale ranging from 0 (“not at all” high”) to 10 (“extremely” high”).^bCategorized as less than usual (0), about the same as usual (1), and more than usual (2).^cMeans and percentages based on the one survey and standard deviations could not be calculated.