Naloxone-Induced Acute Opioid Withdrawal in a Stabilized Extended-Release Naltrexone–Treated Patient

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The opioid epidemic that continues to rage in the United States has increasingly challenged our collective efforts to clinically manage such patients. Among the more common chronic treatments in our population has been the monthly use of extended-release naltrexone (XR-NTX). Though the putative mechanisms of action of this compound seem straightforward, the following case suggests that our understanding might, on occasion, be too simplistic.

Case Description

We report a case of a 52-year-old white man with precipitated opioid withdrawal syndrome (OWS) following a naloxone challenge 1 week prior to his scheduled fourth dose of XR-NTX injection. He was a polysubstance user (primarily heroin), and his comorbidities of relevance were hepatitis C (status posttreatment with no hepatic impairment) and microscopic stage I prostate cancer. Although his addictive history dated back decades, he was able to achieve complete sobriety from 2006 to 2009 with the assistance of regular Alcoholics Anonymous meetings. In recent years, however, he was recurrently rehospitalized for detoxification on 16 occasions, primarily for opioid dependence and withdrawal. In August 2017, 4 months prior to the events of pertinence in this report, he was started on XR-NTX treatment and immediately began testing the "adequacy" of the naltrexone blockade by injecting heroin and searching for signs of intoxication as the weeks of his monthly cycle progressed. After the third week posttreatment, he was able to experience mild intoxication, though he received each of his first 3 injections on time without developing any OWS.

Twenty-two days after his third XR-NTX injection, he appeared at the clinic after injecting heroin with no subjective experience of intoxication. He knew from his past experience that he would soon be able to overwhelm his naltrexone blockade and asked to receive his fourth dosage of XR-NTX more than 1 week early. Although he had no clinical signs of acute opioid use, he was given a naloxone challenge of 0.8 mg intramuscularly that precipitated an immediate and violent OWS. A comprehensive drug panel revealed the presence of 3,6-diacetylmorphine and fentanyl, indicating recent opioid use. Despite his experience with end-dose heroin experimentation, he was certain that this month he felt no subjective intoxication whatsoever and was convinced the XR-NTX "was still working."

Discussion

Our patient's personal anecdotes, as well as prior case reports,[1] have shown that it is possible to overcome the μ-receptor blockade of XR-NTX. The further out from the treatment, and the higher the opioid doses, the easier it may be to overwhelm the blocked μ receptors.[2] This supposition is supported by a 2011 study[2] that set out to quantify the subjective and objective effects of opioid intoxication at various points throughout the XR-NTX treatment cycle. That study noted that XR-NTX blocked the subjective sense of intoxication of administered opioids longer than the objective measures (eg, miosis).[2] This finding may explain why our patient experienced no subjective intoxication with his heroin use, but had a profound OWS after our naloxone challenge. While XR-NTX may have continued to blunt his subjective drug experience, his body was still reacting to the self-administered opioids (heroin and fentanyl). It seems that in this particular instance, the XR-NTX μ-receptor blockade was overcome by his use of opioids, enough to precipitate the naloxone-induced withdrawal, even with no reported subjective intoxication. It is curious, though, that his previous report of end-dose opioid use did not result in similar OWS on naloxone challenge during each of the previous 3 months of XR-NXT treatment.

This case suggests that one cannot be exclusively reliant on even an experienced user's subjective report of intoxication in judging the integrity of the opioid blockade and underscores the prudence of always administering a naloxone challenge prior to administering XR-NTX in patients still struggling with ongoing opioid use.

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