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BRAINSTORMS—Clinical Neuroscience Update

Antagonist treatment is just as effective as replacement therapy for opioid addiction but neither is used often enough

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ISSUE:

One of the most malignant illnesses in psychiatry is opioid addiction. This disorder has resulted in a current epidemic of addiction, overdose, and death that continues in large part because of the lack of robust treatments and the surprising lack of utilization of the treatments that are available.

Take-Home Points

- The mainstay of treatment for opioid addiction is detoxification and abstinence, but this is largely ineffective with >90% of those in recovery relapsing. Despite the availability of psychopharmacology treatments, few with opioid addiction receive them.
- For the minority who do receive psychopharmacologic treatment, the most commonly utilized is opioid replacement therapy (especially with buprenorphine/naloxone, and to a lesser extent, methadone), which may reduce short term relapse rates to as little as 50% in some studies.
- Much less commonly utilized is opioid antagonist therapy with naltrexone, perhaps because it requires detoxification prior to initiation and until now it has not been clear how effective opioid antagonist therapy is compared to opioid replacement therapy.
- Two prominent studies have now shown that the two available psychopharmacology treatments for opioid addiction are largely comparable both in their effectiveness in preventing relapse and in their safety. Of course, neither treatment will work if it is not administered. Perhaps it is time to redouble our efforts to implement the two available psychopharmacologic treatments to a much higher proportion of those with opioid addiction.

Introduction

Opioid abuse, addiction, and overdoses have become a vast epidemic throughout the world.[1] According to the World Health Organization and the National Institute on Drug Abuse, only about 10% of those with opioid dependence are being treated.[1–5] For those who do receive standard treatment with detoxification and abstinence, over 90% eventually relapse, 60% of them in the first week of sobriety, and 80% within a month after discharge from a detox program.[3–5]

Much of the public health effort to stem this epidemic has been directed at measures to prevent addiction by more responsible prescribing of opioids by health care professionals.[1,2,6] Perhaps understandably, because so few opioid addicts are in treatment, and outcomes are so dismal for those who do get treatment, little emphasis has been put on increasing the use of psychopharmacologic therapies for opioid addiction that are available but little used, namely opioid antagonist therapy and opioid replacement therapy (sometimes called medication-assisted therapy, MAT, or opioid medication treatment, OMT).[7] Now that it is clear that opioid antagonist therapy has comparable effectiveness and safety to opioid replacement therapy,[8,9] the time may be right to expand the availability and use of both of these treatments and for psychopharmacologists to become more involved in the treatment teams for opioid addicts.

Starving in the Midst of Plenty? Two Underutilized Psychopharmacologic Treatments for Opioid Addiction

Buprenorphine is a high affinity mu-opioid partial agonist that also acts as a partial agonist/antagonist at kappa opioid receptors with high affinity and at delta opioid receptors with lower affinity.[10,11] Due to its high affinity for the mu opioid receptor, buprenorphine is not easily displaced from the mu opioid receptor.[10,11] This means it is difficult for someone addicted to opioids to "dose over" with an abused opioid while taking buprenorphine, so that buprenorphine must be first discontinued in order for other opioids to act at the mu opioid receptor. Buprenorphine is given sublingually in a formulation combined with naloxone, a mu opioid antagonist that is not absorbed sublingually but will reduce the chances of diversion by injection (ie, naloxone blocks the effects of injected buprenorphine but not sublingual buprenorphine).[1,2,6–11] Due to the fact that treatment with buprenorphine/naloxone can begin without having a person addicted to opioids go through full detoxification, it is administered to patients in mild opioid withdrawal, making it much easier to initiate than naltrexone, which requires full detoxification before it can begin.[8–11] Buprenorphine/naloxone medication has gained favor among many outpatient treatment programs.

Naltrexone is an orally absorbed mu opioid antagonist also available in a long-acting injectable formulation that only has to be given every 30 days.[1,2,6–12] Long acting injectable technology is gaining favor in the treatment of schizophrenia and mania with antipsychotics,[13] but its use for substance abuse (either alcoholism or opioid addiction) has never gained great traction in the addiction community as a treatment. Reasons given for this lack of uptake in the treatment of opioid addiction seem to be related both to the hassle of needing to be fully detoxified in order not to risk going into precipitated withdrawal and until recently to questions about whether naltrexone is as effective as buprenophrine-naloxone.[8,9] Medication costs, insurance coverage, logistics of getting medications, and economic incentives to prescribers may also favor the use of buprenorphine-naloxone over injectable naltrexone. Many patients in treatment programs simply cannot or will not become fully detoxified and thus are not candidates for injectable naltrexone.[8,9,12] On the other hand, long-acting injectable technology considerably enhances compliance for those who can initiate naltrexone, and for 30 days the patient cannot "dose over" injectable naltrexone with an illicit opioid and obviously cannot discontinue naltrexone until the next injection is due, unlike buprenorphine which can be quickly discontinued and abuse of an illicit opioid can begin immediately.[12]

Two Comparable Psychopharmacologic Treatments for Opioid Addiction

Opioid replacement therapy with buprenorphine/naloxone given sublingually every day has been compared to opioid antagonist therapy with naltrexone given by injection every 30 days in two recently published landmark studies.[8,9] In one 12-week study from Norway, extended release injectable naltrexone was as safe and effective as buprenorphine-naloxone in maintaining short-term abstinence from illicit opioids.[8] In a second study from the US, 24 weeks long, there was a shorter detoxification run-in period than in the Norwegian study, and more failures to initiate naltrexone.[9] Although buprenorphine-naloxone was superior to injectable naltrexone in preventing relapse in the entire population studied, more than one-quarter of participants dropped out of naltrexone treatment before it was even begun due to failure to get through detoxification and start treatment. If treatment was successfully initiated in the US study, both medications were comparably safe and effective in preventing relapses.[8,9]

One thing that is interesting about the small amount of psychopharmacologic treatment ongoing for opioid addiction is that the few who get psychopharmacologic treatment only seem to get one or the other. It seems to be an either/or situation, rather than a both/and situation where one treatment, namely buprenorphine/naloxone as a step-down from illicit opioids could potentially further step down to injectable naltrexone after a period of stabilization on buprenophrine-naloxone. Instead, buprenorphine/naloxone treatment too often is indefinite or is used until the person with opioid addiction relapses, whereas treatment with injectable naltrexone only occurs, if at all, following a very rough period of full detoxification from street opioids. Why have these two treatments not been made consecutive in more studies? Also, given the neurobiology of addiction, why has long acting injectable naltrexone not been employed more often as a tool for habit reversal in those addicted to opioids (see below)?

Becoming Addicting to Opioids: Normal Reward Behavior Becomes an Involuntary Conditioned Habit

Opioid addiction is often conceptualized as an uncontrollable drive to get high and to stop craving and withdrawal, the "rewards" of using opioids.[14–17] Recent neurobiological formulations, however, regard opioid addiction as a compulsive habit that is a

conditioned response to a set of conditioned opioid stimuli, namely, the people, the process of procurement, use, paraphernalia, etc., associated with opioid abuse.[14–17] According to this formulation, exposure to the set of opioid stimuli over time leads to a weakening of control circuits due to conditioned learning.

Upon the first exposure to opioid, the reward of that stimulus is evaluated.[14–17] If the stimulus is perceived to have a favorable outcome, behavior is evoked to achieve that reward. However, if the stimulus is perceived to have an unfavorable outcome, the behavior is inhibited. When that same stimulus is presented again, the value of the reward will be remembered to either evoke the behavior or inhibit the behavior. This is called goal-directed behavior or action-outcome learning.[14–17]

However, this rapidly changes if a behavior is repeated again and again. That is, the conditioned response (ie, opioid reward) following the conditioned stimulus (craving, seeking opioids, procuring them, etc.) will be devalued, and the conditioned stimulus itself will be enough to drive behavior, regardless of the dangerous and self-destructive outcome. This has now turned into what is called stimulus-directed behavior or stimulus-response learning.[14–17] It is rather like a Pavlovian dog who salivates at the sound of the bell. In a similar sense, the "bell" for those addicted to opioids is the set of opioid stimuli. And like the dog that salivates involuntarily in response to the bell, the addicted person then compulsively uses the drug.

It is through stimulus-response learning that behaviors become habitual and eventually compulsive with loss of control. When drug taking behavior becomes compulsive, the reward no longer matters and the behavior is strictly driven by the opioid set of stimuli.[14–17] Those addicted to opioids have a bias toward paying attention to those things in the environment that are opioid stimuli, and this is called "attentional bias." Since behavior is now being controlled by habit—in other words, stimulus-directed, instead of reward- or goal-directed—the set of opioid stimuli drives drug taking behavior automatically. This may be why it is nearly impossible for someone addicted to opioids to stop using the drug in the environment where opioid stimuli abound.

Reversing Habit Learning and the Potential of Long Acting Injectable Naltrexone

Although opioid stimulus-driven drug taking as a habit will dissipate with detoxification and abstinence alone over time,[1–7] theoretically it may be possible to enhance extinction of the involuntary habit of automatic opioid use by administering long acting injectable naltrexone. That is, paradoxically, those with opioid addiction may need to take more opioids in order to reverse habit learning! They just need to take opioids in response to their usual opioid stimulus, but instead, they do not get their expected response.[14–17] That is exactly what happens when an addicted person takes an opioid after receiving long acting injectable naltrexone. The stimulus is uncoupled from the reward, and over time the habit extinguishes. This model suggests that "unlearning" can be accomplished by uncoupling the conditioned response (high from drug abuse) from the drug-associated conditioned stimuli. Anecdotally, the lead Norwegian author of one of the recent landmark studies[8] has mentioned (Lars Tanum, personal communication) that the patients who did best on injectable naltrexone often were the ones who attempted to abuse illicit opioids the most while beginning to receive long acting naltrexone injections and had the repeated experiences of failing to get high from their opioid. Perhaps here the enhanced compliance of long acting injectable naltrexone coupled with "unlearning" a habit associated with abusing a drug and not having a reward/response are underutilized potential advantages for the treatment of opioid addiction.

Conclusion

Two comparable psychopharmacologic treatments are available to significantly reduce the chance of relapse for those addicted to opioids, but both are underutilized. Hopefully two new studies comparing buprenorphine/naltrexone with long acting injectable naltrexone will stimulate further use of this psychopharmacologic approach to the treatment of addiction, and also will provoke more clinical research on how best to treat the devastating condition of opioid addiction.

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