

Extended Release Naltrexone (Vivitrol®)

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Overview

The U.S. Food and Drug Administration (FDA) has approved three medications for use in treating opioid dependence: methadone, buprenorphine, and naltrexone.¹ Extended release naltrexone, brand name Vivitrol®, is a once-monthly injection intended to help prevent relapse to opioid use.² Naltrexone, the active ingredient in Vivitrol, attaches to certain opioid receptors in the brain and blocks the euphoric feelings associated with opioid use for approximately 30 days.³ In other words, it prevents a person from feeling “high” if they use opioids during the month after they receive the injection. In order to take Vivitrol, a person must be free from all opioid use, including opioid medications, for at least 7-14 days.⁴ Because it must be used after detoxification from opioids, it has no role in lessening the symptoms of withdrawal.⁵ Vivitrol was approved by the FDA to treat opioid dependence on October 13, 2010.⁶ Currently, it is only approved for the treatment of opioid dependence in the United States and Russia.⁷ Vivitrol can be prescribed by any healthcare provider and can be administered at opioid treatment programs (OTPs).⁸

Research

Research on Vivitrol is limited. Some data shows that long-acting, sustained release forms of naltrexone, such as Vivitrol, are well tolerated and can be effective in preventing opioid use relapse, especially in long-term treatment spanning multiple months.⁹ While Vivitrol is costly at approximately \$1,100 per injection, some data suggests that it is cost effective¹⁰ and that its use may reduce other costs associated with inpatient treatment, emergency room visits, and other health care.¹¹

Because Vivitrol is relatively new, few studies

have been performed and the resulting small body of research is not sufficient to prove Vivitrol’s effectiveness on a broad scale. Most of the existing studies contain small sample sizes,¹² use a large majority of male participants and lack research on effectiveness in females,¹³ and only include a small minority of participants who needed detoxification prior to a Vivitrol injection.¹⁴ Currently, no studies have compared Vivitrol’s clinical effectiveness to other medications for the treatment of opioid dependence such as methadone or buprenorphine, which have been proven effective in study after study.

Concerns

In addition to concerns about both the quantity and quality of the data supporting the use of Vivitrol for opioid dependence, there are a number of other areas of concern.

Requires Detoxification

Given that Vivitrol cannot be administered until 7-14 days after last opioid use, a detoxification period is required. Studies show, however, that detoxification has very low success rates¹⁵ and can be a significant barrier for many opioid dependent people.¹⁶ Moreover, the use of opioids within 7-14 days before an injection of Vivitrol may cause sudden symptoms of opioid withdrawal at the time of injection, which may be severe enough for hospitalization.¹⁷ Alternatives to Vivitrol, such as methadone or buprenorphine, may be necessary to aid detoxification before Vivitrol can be safely administered.

Potential for Overdose

Vivitrol use may increase likelihood of overdose after injection. Because Vivitrol blocks the effects of opioids, people who use opioids after the injection may compensate with large doses to

overcome the effects of Vivitrol, resulting in overdose and death.¹⁸ Additionally, people who use opioids may be more sensitive to lower amounts of opioids after: 1) going through detoxification, 2) when the next Vivitrol dose is due, 3) if a dose of Vivitrol is missed, or 4) after stopping Vivitrol treatment. Because tolerance is lower in these circumstances, using the same amount of opioids as a person used before treatment with Vivitrol may lead to overdose and death.¹⁹

This risk warrants a significant amount of additional research on adverse events, including overdoses, associated with Vivitrol. This is particularly true in light of the overdose death rates found among patients taking the oral form of naltrexone. A review of 13 trials of medication treatments for opioid dependence in Australia found that heroin overdose rates were more than three times higher (at 6.8 per 100 person-years) for patients on oral naltrexone treatment compared with those receiving opioid agonist treatment such as methadone or buprenorphine (1.9 per 100 person-years).²⁰ And, patients who stopped oral naltrexone were 7.6 times more likely than patients on opioid agonists such as methadone or buprenorphine to experience an overdose after treatment ended.²¹

Lax FDA Approval Process

Vivitrol was approved by the FDA on the basis of then-unpublished evidence by Krupitsky et al., which found that participants who received Vivitrol injections were abstinent for significantly longer than those who received a placebo.²² However, the study's methods and results are questionable, with a scarcity of significant data on efficacy. Indeed, 54% of participants in the study did not complete the treatment protocol, and only half of those who did receive the injection received the full treatment course.²³ Moreover, it is unclear what follow-up, if any, was completed to evaluate post-treatment opioid overdose in the participants.²⁴

Additional concerns with the FDA approval of Vivitrol include inadequate assessment of risks and susceptibility to overdose, and the unethical practice of administering only a placebo when effective alternative treatments already exist.²⁵ Daniel Wolfe et al. argue that "[t]he FDA should justify why it has lowered the scientific, regulatory, and ethical standards in approving

[injectable] naltrexone for treatment of opioid dependence" and that "[FDA] approval [of injectable naltrexone] might endanger patients, and sets a precedent that unjustifiably degrades standards for all treatment of opioid dependence."²⁶

Vivitrol in Correctional Settings

Published studies evaluating the effectiveness of Vivitrol for persons pre- or post-release from a correctional facility are scant. In a 2015 study, 27 male and female prisoners received Vivitrol injections once each month for seven months (one injection prior to release and six injections after release). Of the 27 participants who received the first injection, 37% (10) completed the remaining six treatments and were less likely to test positive for opioids than those who did not complete the treatment. Those who did not complete the treatment were more likely to be rearrested than those who completed it.²⁷ These results are not statistically significant and the sample size is too small to provide evidence of effectiveness in correctional settings.

The second study recruited 308 participants with a history of opioid use who had been released from prison no more than 12 months prior. Through random assignment, 153 received an injection of Vivitrol and 155 underwent brief counseling and referral to community treatment programs. Results showed that 43% (66) of participants who received the Vivitrol injection reported relapse, compared to 64% (99) who underwent usual treatment. The time to relapse was longer in those who received Vivitrol: 10.5 weeks, compared to five weeks for those who underwent usual treatment.²⁸

While somewhat promising, the results of these studies are modest at best. Moreover, neither of these studies compared Vivitrol to other medications such as methadone and buprenorphine, both of which have proven effective at preventing relapse and recidivism among correctional populations.²⁹ Despite the lack of evidence, the Washington Post reports that around 40 jails are providing treatment with Vivitrol in the United States.³⁰ And, recently, the federal government approved spending more than \$23 million to support treatment programs in eight states that include giving monthly injections of Vivitrol to people who are incarcerated.³¹ The

programs—which cost up to \$3 million over three years—will be launched in Vermont, Wisconsin, Wyoming, Rhode Island, Illinois, North Carolina, Colorado, and Arizona.³² Meanwhile, there is a near-total lack of access to methadone and buprenorphine in U.S. correctional facilities,³³ despite the Office of National Drug Control Policy, the Centers for Disease Control and Prevention, the National Institutes of Health, the World Health Organization, and the National Commission on Correctional Healthcare all recommending that correctional systems offer methadone to treat opioid-dependent persons under legal supervision.³⁴

Given the lack of evidence in support of Vivitrol's effectiveness among incarcerated populations, it should never be offered as the sole medication to treat opioid dependence in correctional settings. Rather, to the extent it is offered at all, it needs to be one choice among other medications, such as methadone or buprenorphine, offered to treat opioid dependence for those in jails or prisons and it must be offered with full disclosure of the medication's properties and limitations. Significantly more research is needed before Vivitrol should be made available in corrections on a wide scale.

Alternatives to Vivitrol: Methadone and Buprenorphine

Two other medications have been approved to treat opioid dependence and have been rigorously studied and evaluated.

Both methadone and buprenorphine lessen the uncomfortable symptoms of opioid withdrawal and block cravings for other opioids.³⁵ Methadone was approved by the FDA to treat opioid dependence in 1972³⁶ and buprenorphine was approved by the FDA in 2002.³⁷ Methadone must be administered by a SAMHSA-certified opioid treatment program,³⁸ while buprenorphine may be prescribed in qualifying physicians' offices.³⁹ Starting in early 2017, qualifying physician assistants and nurse practitioners will also be authorized to prescribe buprenorphine.⁴⁰

Extensive research has been conducted on methadone, proving that it is highly effective in decreasing opioid use⁴¹ and mortality rates,⁴² and increasing retention in treatment,⁴³ among other benefits. Indeed, after reviewing 941 studies, the

National Institutes of Health (NIH) Consensus Development Panel concluded that the safety and efficacy of methadone has been "unequivocally established."⁴⁴ Many studies have shown that buprenorphine is also extremely effective in decreasing opioid use.⁴⁵ For more information on methadone and buprenorphine, please visit:

http://www.drugpolicy.org/sites/default/files/about_methadone.pdf

Conclusion

Vivitrol, like all medications, is not a definitively appropriate or universally efficacious treatment option. Vivitrol may be effective and safe for treating opioid dependence in those who have a high level of motivation for abstinence and who are not amenable to maintenance therapies with methadone or buprenorphine. Significantly more research is required, however, to better determine who can benefit from this particular treatment and to document and evaluate its potential risks.⁴⁶ In the meantime, suitability for Vivitrol should be determined on a case-by-case basis and only in conjunction with careful consideration of alternative, well-established treatment options such as methadone and buprenorphine.

¹ Physicians & Lawyers for Nat'l Drug Policy. "Alcohol and Other Drug Problems: A Public Health and Public Safety Priority" 40-41 (2008); *see also* Collins, G.B. & McAllister, M.S. "Buprenorphine Maintenance: A New Treatment for Opioid Dependence." *Cleveland Clinic J. Med.* 74.514 (2007): 514-16. (describing use of buprenorphine and methadone in treating opioid dependence); O'Connor, P.G. & Fiellin, D.A. "Pharmacologic Treatment of Heroin-Dependent Patients." *Annals Internal Med.* 133.40 (2000): 44-47 (describing use of naltrexone in treating opioid dependence).

² "Important Safety Information." Vivitrol.com.

<https://www.vivitrol.com/>.

³ "How Vivitrol Works to Treat Opioid Dependence After Detox." Vivitrol.com.

<https://www.vivitrol.com/HowVIVWorksOPD>.

⁴ "Vivitrol and Opioid Dependence." Vivitrol.com.

<https://www.vivitrol.com/About/OpioidDependence>

⁵ "Medication and Counseling Treatment." Substance Abuse and Mental Health Services Administration. Updated September 28, 2015. <http://www.samhsa.gov/medication-assisted-treatment/treatment>.

⁶ "FDA Approves Injectable Drug to Treat Opioid-dependent Patients." Food & Drug Administration. October 12, 2010. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229109.htm>.

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- ¹³ Lee, D., Freidmann, P., Kinlock, T., et al. "Extended Release Naltrexone to prevent opioid relapse in criminal justice offenders." *N Engl J Med* 2016; 374:1232-1242
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- ¹⁵ Kleber, H.D. "Pharmacologic treatments for opioid dependence: detoxification and maintenance options." *Dialogues Clin. Neurosci.*, 9 (2007): 455–470
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- ¹⁸ *Ibid.*
- ¹⁹ Krupitsky et al. "Injectable extended-release naltrexone for opioid dependence:a double-blind, placebo-controlled, multicentre randomised trial." *Lancet* 2011.
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