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## LONG-ACTING INJECTABLE NALTREXONE IS NOT A FIRST-LINE TREATMENT FOR MOST INDIVIDUALS WITH MODERATE OR SEVERE OPIOID USE DISORDER

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Stop Stigma Now (SSN; [www.StopStigmaNow.org](http://www.StopStigmaNow.org)) and Doctors For America (DFA; <https://doctorsforamerica.org>) confirm that long-acting injectable naltrexone (XR-NTX) is a second-line treatment option for most individuals with moderate or severe opioid use disorder (OUD) based on currently available information, and that methadone or buprenorphine (opioid agonist therapy or OAT) are first-line treatments for most such individuals.

Health agencies and medical providers who treat opioid use disorder should communicate this to individuals considering treatment, and should also inform such individuals about all FDA-approved pharmacologic options, that the choice among available treatment options should be a shared decision between the clinician and the patient, and that any approved pharmacologic therapy may be recommended preferentially based on individual circumstances.

This position is based on the fact that, unlike OAT, injectable naltrexone has not been clearly demonstrated to reduce fatal overdose deaths (1 - 6), and has been associated with lower retention in treatment compared with OAT in some studies (7) (8). This position is also consistent with the published statements reproduced below.

The 2023 American Society of Addiction Medicine (ASAM)'s publication 'Pocket Addiction Medicine' states that methadone and buprenorphine are 1<sup>st</sup> line treatments, and that extended-release naltrexone is a "2<sup>nd</sup> line option for patients who have been counseled on risks vs. benefits and prefer it to agonist medication" (9). (The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder 2020 Focused Update does not make this distinction).

ASAM's Policy Statement on Treatment of Opioid Use Disorder in Correctional Settings states that "For individuals who do not want to be treated with methadone or buprenorphine, extended-release injectable naltrexone is an alternative option for relapse prevention during detainment and after release." (10).

MEDICATION TREATMENT FOR OPIOID ADDICTION SAVES LIVES

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The 2019 World Health Organization Model List of Essential Medicines designated methadone and buprenorphine, but not naltrexone, as “essential medicines” (11).

According to the Clinical Guidelines Program on the Treatment of Opioid Use Disorder by the New York State Department of Health AIDS Institute, updated January 2021, “Clinicians should recommend co-formulated buprenorphine/naloxone or methadone as preferred treatments for individuals with opioid use disorder. . . Clinicians should offer extended-release naltrexone to patients who prefer naltrexone for treatment or who are not able to access treatment with or reach their treatment goals with methadone or buprenorphine/naloxone” (12).

OAT has been described in recent peer-reviewed reports as the “gold standard” or most effective treatment for OUD, or that XR-NTX is appropriate for those who are unable to, or choose not to, use OAT (13 – 25).

The Food and Drug Administration (FDA) Prescribing Information for Vivitrol, the brand name of XR-NXT, notes that “. . . Any attempt by a patient to overcome the antagonism by taking opioids is especially dangerous and may lead to life-threatening opioid intoxication or fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade” (26). The Risk Evaluation and Mitigation Strategy (REMS) for Vivitrol required by the FDA states that “Using large amounts of opioids, such as prescription pain pills or heroin, to overcome effects of Vivitrol, can lead to serious injury, coma, and death” (27).

In 2019 the FDA issued a warning letter to the manufacturer of Vivitrol for not including serious risks in marketing materials (28), and a related news release (29).

A National Academies of Sciences, Engineering, and Medicine 2019 report on medications for opioid use disorder stated that “Emerging evidence suggests that patients can experience an increased risk of overdose when they approach the end of the 28-day period of the extended-release formulation” of XR-NTX (30).

Note, however, that XR-NT has been associated with a decrease on total overdose in a randomized trial (31).

Some authors have noted that the question of a possible increase in overdose rates associated with the use of XR-NTX has not been settled (32, 33). In a commentary (34) on the largest of the two randomized trials to date comparing XR-NTX with buprenorphine-naloxone (35), it was noted that “total overdoses, fatal and non-fatal, did not differ between groups, but the numbers



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were noteworthy - 18 for XR-NTX versus 10 for buprenorphine-naloxone. Considering that the study was not powered to detect overdose differences, there should be continued evaluation of how failure to complete opioid detoxification and induction onto XR-NTX might increase overdose risk."

Nevertheless, XR-NTX is an important option that may be more appropriate than OAT for particular individuals. For example, XR-NTX may be appropriate for individuals with relatively brief durations of OUD, mild OUD, those who strongly prefer it or who decline OAT, or when OAT is not available. SSN and DFA endorse the availability of all FDA-approved medications for OUD: methadone, buprenorphine, and XR-NTX.

Also, XR-NTX should be considered for individuals who have undergone medically managed withdrawal off of OAT. This should be accompanied by an explanation that, unlike OAT, it is a second-line agent for most people with moderate or severe OUD.

This statement applies to long-acting injectable naltrexone XR-NTX, and not to *implantable* naltrexone which has been associated with a reduction in mortality (36) but is not currently FDA-approved.

For the reasons noted, injectable naltrexone is currently a second line OUD treatment option, after OAT, for most individuals seeking treatment for moderate or severe OUD, and methadone or buprenorphine should be considered as first line treatments for most of these individuals.

#### ANNOTATED REFERENCES:

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("Our finding that MOUD [Medication for Opioid Use Disorder] treatment with naltrexone was not protective against overdose or serious opioid-related acute care use is consistent with other studies that found naltrexone to be less effective than MOUD treatment with buprenorphine."). (The use of either the oral and/or the injectable naltrexone formulation, XR-NTX, was not identified; XR-NTX was approved in the U.S. for OUD in 2010; this study evaluated claims data between October 3, 2014, to December 31, 2017.)
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(“Among commercially-insured patients who initiate medications for opioid use disorder, buprenorphine, but not naltrexone, was associated with lower risk of overdose during active treatment compared to post-discontinuation.”). Note that treatment with XR-NTX and or naltrexone in this study were each found to be associated with significantly higher overdose rates compared to buprenorphine, whether while on treatment or after recently discontinuing treatment.

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