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

February 24, 2023

Stop Stigma Now (SSN; 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 1st line treatments, and that extended-release naltrexone is a "2nd 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).

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).

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 (31, 32). In a commentary (33) on the largest of the two randomized trials to date comparing XR-NTX with buprenorphine-naloxone (34), it was noted that "total overdoses, fatal and non-fatal, did not differ between groups, but the numbers 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 (35) 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:

1. Wakeman SE, et al. Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. JAMA Netw Open. 2020; 3(2).
   free: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2760032
   ("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.)
2. Morgan JR, et al. Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. Drug Alcohol Depend. 2019 Jul 1;200:34-39.
   free: https://www.sciencedirect.com/science/article/pii/S0376871619301310?via%3Dihub

("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.

3. Larochelle MR, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. Ann Intern Med. 2018; 169(3):137- 145. https://www.acpjournals.org/doi/abs/10.7326/m17-3107
("Compared with no MOUD, methadone was associated with decreased all-cause mortality (adjusted hazard ratio [AHR] 0.47 [CI, 0.32 to 0.71]) and opioid-related mortality (AHR 0.41 [CI, 0.24 to 0.70]. Buprenorphine was associated with decreased all-cause mortality (AHR 0.63 [CI, 0.46 to 0.87]) and opioid-related mortality (AHR 0.62 [CI, 0.41 to 0.92]). No associations between naltrexone and all-cause mortality (AHR 1.44 [CI, 0.84 to 2.46]) or opioid-related mortality (AHR 1.42 [CI, 0.73 to 2.79]) were identified."). Note that in this study patients treated with both XR-NTX and oral naltrexone were included and were not separately analyzed. Also, there were fewer patients treated for a shorter duration with naltrexone (1099 persons treated for a median of 1 month) vs. buprenorphine or methadone (3022 patients treated with buprenorphine for a median of 4 months, and 2040 patients treated with methadone for a median of 5 months, respectively.)
4. Ma J, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. Mol Psychiatry. 2019; 24(12):1868-1883.
(One conclusion is that naltrexone reduces mortality. Two naltrexone studies were reviewed: one of oral naltrexone, and one of implantable naltrexone; none with injectable naltrexone.)
5. Ajazi EM, et al. Revisiting the X:BOT Naltrexone Clinical Trial Using a Comprehensive Survival Analysis. J Addict Med 2022 Jul-Aug; 16(4):440-446.
(Reanalyzed data in Lee JD et al (31), including probable & possible overdoses, and using a time-to-event analysis. A near-significant increased association with overdose of about two-fold was found in the XR-NTX group compared to the buprenorphine-nx group. (HR: 2.10; 95% CI: 0.86, 5.14). During the treatment (i.e. maintenance) phase the risk of overdose was 3.81 (CI: 1.01, 14.36) times higher in the XR-NTX group compared to the buprenorphine-nx group in a Per Protocol analysis).
6. Lee, JD, et al. Commentary on Ajazi et al (2021) Re-analysis of the X:BOT Trial.
J Addict Med. 2022 Jul-Aug; 16(4):382-385.
7. Treatment Improvement Protocol (TIP) 63 Updated 2020. Substance Abuse and Mental Health Services Administration. free: https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document/PEP21-02-01-002 ("for XR-NTX, treatment retention is higher than for treatment without OUD medication and treatment

with placebo; treatment retention is lower than with opioid receptor agonist treatment." pg. 2-19 . . . "methadone, extended-release injectable naltrexone and buprenorphine were each found to be more effective in reducing illicit opioid use than no medication in randomized clinical trials. . . Methadone and buprenorphine treatment have also been associated with reduced risk of overdose death").

8. Jarvis BP, et al. Extended-release injectable naltrexone for opioid use disorder: a systematic review. Addiction 2018; 113(7):1188–209. free: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5993595/ ("Many individuals intending to start extended-release naltrexone (XR-NTX) do not, and most who do start XR-NTX discontinue treatment prematurely, two factors that limit its clinical utility significantly.")
9. Wakeman SE, Lee J, Alvanzo AAH, eds. Pocket Addiction Medicine. Wilger's Kluwer Health, 2023. Pgs. 9-67 – 9-68). https://www.vitalsource.com/products/pocket-addiction-medicine-sarah-e-wakeman-joshua-d-v9781975166397
10. ASAM Public Policy Statement on Treatment of Opioid Use Disorder in Correctional Settings. July 15, 2020. https://www.asam.org/advocacy/public-policy-statements/details/public-policy-statements/2021/08/09/asam-public-policy-statement-on-treatment-of-opioid-use-disorder-in-correctional-settings
11. World Health Organization Model List of Essential Medicines, 21st List, 2019. Geneva: World Health Organization; 2019. https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1
12. Clinical Guidelines Program - Treatment of Opioid Use Disorder - New York State Department of Health AIDS Institute. Updated January 2021. free: https://www.hivguidelines.org/substance-use/oud/#tab_5
13. Dickson-Gomez J, et al. "You're Not Supposed to be on it Forever": Medications to Treat Opioid Use Disorder (MOUD) Related Stigma Among Drug Treatment Providers and People who Use Opioids. Subst Abuse. 2022 Jun 27; 16:11782218221103859. ("…while acknowledging that naltrexone may be appropriate for some patients, the scientific consensus is that opioid agonist forms of MOUD (methadone and buprenorphine) are the "gold standard of addiction care" and are the most effective for retaining people with OUDs in care and reducing illicit drug use.")
14. Tsai AC, et al. Stigma as a fundamental hindrance to the United States opioid overdose crisis response. PLoS Med. 2019 Nov 26; 16(11):e1002969. "Gold-standard, first-line treatment of OUDs consists of opioid agonist medication (methadone) or partial agonist medication (buprenorphine.)"
15. Gustavson AM, et al. Early impacts of a multi-faceted implementation strategy to increase use of medication treatments for opioid use disorder in the Veterans Health Administration. Implement Sci Commun. 2021 Feb 15; 2(1):20.

free: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7885503/
("When M-OUD is contraindicated or not acceptable to the patient, antagonist medication (naltrexone) can be considered with the greatest promise shown with injectable naltrexone administered once per month."

16. Wakeman SE, et al. Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. JAMA Netw Open. 2020; 3(2). IBID
17. Jordan CJ, et al. Progress in agonist therapy for substance use disorders: Lessons learned from methadone and buprenorphine. Neuropharmacology. 2019 Nov 1; 158:107609. free: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6745247/
("Clinical observations indicate low clinical success rates and poor compliance to naltrexone as a treatment for opioid abuse . . .")
18. Davis CS, et al. Legal and policy changes urgently needed to increase access to opioid agonist therapy in the United States. Int J Drug Policy. 2019; 73:42.
(The "public health crisis of opioid-related harm . . . could be dramatically reduced through increased access to opioid agonist therapy with the medications methadone and buprenorphine. . .[with] overwhelming evidence of their efficacy . . . their use is considered the "gold standard" for OUD treatment. . . both methadone and buprenorphine treatment often reduce overdose-related and all-cause mortality risk in opioid-dependent individuals by 50% or more.")
19. Bach P, et al. Leveraging the role of community pharmacists in the prevention, surveillance, and treatment of opioid use disorders. Addiction Science & Clinical Practice 2019; volume 14, Article number: 30.
free: https://ascpjournal.biomedcentral.com/articles/10.1186/s13722-019-0158-0
("Opioid agonist therapy (OAT) with methadone or buprenorphine remains the most effective, evidence-based approach for the treatment of OUD. An extensive body of research supports the effectiveness of OAT at decreasing the use of illicit substances, at reducing criminal activity, at preventing transmission of bloodborne infections, and at protecting against overdose death.")
20. Bell J, et al. Medication Treatment of Opioid Use Disorder. Biol Psychiatry. 2020 Jan 1; 87(1):82-88. ("Oral methadone has the strongest evidence for effectiveness. . . Most experience has been with methadone, which remains the gold standard against which other medications have been compared. . . Naltrexone produces no positive opioid effects, and this may contribute to erratic compliance, early dropout, and a resulting increased risk of fatal overdose.")
21. Gastberger S, et al. Concomitant Heroin and Cocaine Use among Opioid-Dependent Patients during Methadone, Buprenorphine or Morphine Opioid Agonist Therapy. Eur Addict Res. 2019; 25(4):207-212.
("Among all the treatment methods developed so far, opioid agonist treatment (OAT) is the most effective therapy for opioid dependence.")

22. Wakeman SE. Why It's Inappropriate Not to Treat Incarcerated Patients with Opioid Agonist Therapy. AMA J Ethics. 2017 Sep 1; 19(9):922-930.
free: https://journalofethics.ama-assn.org/article/why-its-inappropriate-not-treat-incarcerated-patients-opioid-agonist-therapy/2017-09
("Decades of evidence supports opioid agonist therapy as a highly effective treatment that improves clinical outcomes and reduces illicit opioid use, overdose death, and cost. . . The most effective treatment for opioid use disorder involves maintenance treatment with the opioid agonist medications methadone and buprenorphine . . . The opioid antagonist naltrexone is the third medication that has been FDA-approved for opioid use disorder and can be considered for people with less severe opioid use disorder and a high likelihood of abstinence.")
23. Priest KC, et al. Expanding Access to Medications for Opioid Use Disorder: Program and Policy Approaches from Outside the Veterans Health Administration. J Gen Intern Med. 2020 Dec; 35(Suppl 3):886-890.
free: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7609303/
("Despite decades of availability, access to lifesaving medications for opioid use disorder (MOUD) such as first-line opioid agonist therapy (OAT) (i.e., methadone and buprenorphine) and extended-release naltrexone is sub-optimal.")
24. Tormohlen KN, et al. Evaluating the role of Section 1115 waivers on Medicaid coverage and utilization of opioid agonist therapy among substance use treatment admissions Health services research. 2020; 55(2):232-238.
free: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7080398/
("The most effective treatments for OUD are opioid agonist therapies (OAT) including methadone and buprenorphine . . .")
25. Peckham AM, et al. Leveraging pharmacists to maintain and extend buprenorphine supply for opioid use disorder amid COVID-19 pandemic. Am J Health Syst Pharm. 2021 Feb 15; zxab003. free: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7929456/
("There is an urgent need to expand access to medications for opioid use disorder (MOUD), particularly the opioid agonists methadone and buprenorphine, which are superior to other treatment options in reducing mortality and facilitating recovery. . . The most concerning access restrictions are for opioid agonist treatments (OAT), buprenorphine . . . and methadone . . . given their superiority to other MOUD in decreasing opioid-related mortality.")
26. FDA Prescribing Information for Vivitrol
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021897s020s023lbl.pdf
27. The Risk Evaluation and Mitigation Strategy (REMS) for Vivitrol
https://www.fda.gov/media/79392/download updated July 2013

28. FDA warning letter to Alkermes December 02, 2019: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/alkermes-inc-597260-12022019
29. FDA News Release December 11, 2012: https://www.fda.gov/news-events/press-announcements/fda-issues-warning-letter-not-including-most-serious-risks-advertisement-medication-assisted ("those utilizing Vivitrol for the treatment of opioid dependence should be made aware of the vulnerability to potentially fatal overdose at the end of a dosing interval, after missing a dose, or after discontinuing Vivitrol treatment. Attempts to overcome blockade may also lead to fatal overdose.")
30. National Academies of Sciences, Engineering, and Medicine 2019. Medications for Opioid Use Disorder Save Lives. Washington, DC: The National Academies Press. [see pg. 37] free: https://www.nap.edu/catalog/25310/medications-for-opioid-use-disorder-save-lives
31. Binswanger IA, et al. Commentary: Potential Risk Window for Opioid Overdose Related to Treatment with Extended-Release Injectable Naltrexone. Drug Safety. August 2018; 41: 979–980. free: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6366853/ ("In a randomized trial . . . 15 individuals had 18 overdose events in the ER injectable naltrexone arm, compared with 8 individuals who had 10 overdose events in the buprenorphine-naloxone group . . . not statistically significant, but the relative proportion of individuals with overdoses was nonetheless concerning (5.3% vs. 2.8%) . . Overall, prior data about overdose risk associated with extended-release naltrexone is difficult to interpret due to inconsistent and poorly described procedures for ascertaining overdoses across studies.")
32. Saucier R, et al. Review of case narratives from fatal overdoses associated with injectable naltrexone for opioid dependence Drug Saf, 41 (2018), pp. 981-988 https://pubmed.ncbi.nlm.nih.gov/29560596/
33. Lott, DC. Comment: Extended-release naltrexone: good but not a panacea. The Lancet, 2018 Jan 27; 391(10118), 283–284. https://pubmed.ncbi.nlm.nih.gov/29150200/
34. Lee JD, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. The Lancet. 2018; 391(10118):P309-318, free: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5806119/
35. Reece AS. Favorable mortality profile of naltrexone implants for opiate addiction. J Addict Dis. 2010; 29:30–50.

****