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Medication Treatment for Opioid Use Disorders:

A Brief Overview with Comments on Extended Release Naltrexone

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Opioid use disorders, particularly those involving compulsive use with tolerance and withdrawal, are among the most harmful substance use disorders worldwide due to their association with mortality, morbidity and criminal behavior. Maintenance treatment using methadone or buprenorphine/naloxone have helped hundreds of thousands of patients worldwide and been the only meaningful outpatient therapies for many years. Both are controlled substances and can only be administered under conditions that are aimed to reduce diversion and abuse. Methadone, a full opioid agonist, is administered in specially licensed programs, and typically requires daily observed dosing for several months before "take home doses" are permitted.

Methadone programs have varying criteria for who can receive take-homes but they usually require negative urine tests, keeping regular appointments, absence of behavioral problems, and other indicators of a meaningful treatment response and responsible use of unsupervised medication administration.

Buprenorphine/naloxone (Suboxone®) is less tightly regulated and can be provided in primary or specialty care settings with less observed dosing by providers that received permission from the Drug Enforcement Administration after passing a course in how to use it. These differences in the level of supervision for using methadone or buprenorphine are a function oftheir abuse liability and safety. Methadone, being a full agonist, has a higher abuse liability and lower safety margin than buprenorphine, which is a partial opioid agonist. A third medication is naltrexone, a μ-opioid receptor antagonist that blocks exogenous opioids and the euphoric effects of heroin and other opioids.[1] One 50 mg oral dose provides opioid blockade for 24-36 hours, and long-term use does not cause tolerance to its blocking effect or withdrawal after it is discontinued.[2]

Naltrexone will displace opioids from their receptors thus patients need to be detoxified and free of physiologic dependence before it is administered to avoid precipitated withdrawal. Provided this condition is met naltrexone is easy to administer, safe (no serious adverse events if used as recommended), generally well tolerated, and does not have addictive potential.

Because of its blocking effect, self-administration of opioids at usual doses produces no euphoric effect so that the patient either stops using opioids or ceases taking naltrexone.[3] Like other medications, naltrexone is effective only so long as the patient takes it, thus compliance is very important.[4–6] It is facilitated by involving families or other significant others to supervise dosing; where there is strong external motivation to remain abstinent such as persons under criminal justice supervision[7] or health care professionals at risk of losing their license; or settings where naltrexone is the only available treatment option.

The earliest studies of oral naltrexone had little success due to high dropout[8,9] however a 6-month, placebo- controlled, randomized trial conducted in the late 1990s in St. Petersburg, Russia[4] in which one or more close family members (e.g., mother, spouse) agreed to supervise daily dosing and found significant differences in retention and relapse favoring naltrexone at the

end of the first month to the end of the study. At 6 months, 12 of the 27 (44%) patients in the naltrexone group remained in the study and had not relapsed compared to 4 of 25 (16%) in the placebo group ($p<0.05$).

Efforts to develop extended release naltrexone in hopes of reducing dropout were started in the 1970's[9] and realized with the approval of extended-release injectable naltrexone (XR-NTX; Vivitrol®) for preventing relapse to alcohol dependence in 2005 and for opioid dependence in 2010.[10] XR-NTX contains 380 mg naltrexone dissolved in a viscous solution that is injected into the gluteal muscle and produces an effective plasma naltrexone level for approximately 28 days. Its most common side effects involve soreness at the injection site, headaches, and nausea, however these problems typically last 1-3 days and are not severe.[11] It fills a niche created by situations in which methadone and/or buprenorphine-naloxone maintenance are unavailable or undesirable due to legal, logistic, or patient preference.

Transitioning from opioid dependence to antagonist treatment is a challenge because it requires detoxification. Methadone or buprenorphine tapers require a 7-14 day opioid-free interval before starting XR-NTX and are most effective when done on an inpatient setting, but these settings can be unavailable and/or unaffordable. Similarly, agonist tapers are not always available and non-opioid detoxification protocols based on an alpha-2 adrenergic receptor agonist such as clonidine have been widely used. Though clonidine suppresses some of the sympathetic over-activity of withdrawal it does not prevent the dysphoria and other subjective effects, thus making it marginally effective and unpopular with patients and physicians alike.

Correctional facilities are locations where detoxification is part of usual treatment and reentry is followed by community supervision with pressure to not use drugs.

XR-NTX is a logical option in these situations and has been evaluated in recent clinical trials.[12–14] One was a 24-week open label trial randomized consenting, detoxified, opioid addicted former prisoners on probation or parole to XR-NTX or the usual course of supervision and counseling with referral to community treatment programs.[14] Results were that participants assigned to XR-NTX had a longer median time to relapse than those assigned to usual treatment (10.5 vs. 5.0 weeks, $p<0.001$; hazard ratio, 0.49; 95%CI 0.36 to 0.68) and a lower rate of relapse (43% vs. 64%, $p<0.001$; OR 0.43; 95%CI, 0.28 to 0.65). Notably, there were no overdoses in the extended-release naltrexone group and seven in the usual-treatment group ($p=0.02$).

Though not approved in the U.S., an extended- release implant (Prodetoxon®) is available in Russia. It consists of a pellet that is inserted under the skin of the abdominal wall, contains 1000 mg naltrexone is a dissolvable matrix, blocks opioid effects for 2-3 months, and resulted in more time in treatment and less relapse when compared to oral naltrexone.[15] Similar outcomes were seen in a Swedish study[16] and in a study of a similarly acting implant that has been used in Australia.[17]

A recently-completed 12-month study whose preliminary findings were presented at the February 2017 CROI study in Seattle compared the Russian implant (NI) with oral naltrexone 50 mg/day (ON) for HIV+ patients who were starting antiretroviral therapy (ART).[15] The primary outcome of viral <400 copies/ml at month 12 was more common in NI than ON patients [66% vs 50%; OR (95% CI = 1.94 [1.10-3.43)]; addiction treatment completion was better on NI than ON (32% vs 17%, respectably, $p<0.05$); ART retention was better on NI (46% vs 32%; $p<0.05$); and CD4 count was higher in those who stayed on naltrexone, regardless of group assignment, vs. those who dropped out.

In conclusion, methadone, buprenorphine/naloxone, and naltrexone are all effective for treating opioid addiction, though they do not "cure" it in the sense that antibiotics cure infections. In the case of naltrexone, extended release is much more effective than the oral formulation due to its impact on adherence. How it compares with buprenorphine/naloxone or methadone maintenance in settings where all three options are available is a topic for future studies. How long patients should continue medication treatment is unclear but high relapse rates following detoxification alone or termination of a brief course of relapse prevention medication indicate that outcomes are best for most patients if the medication of choice is continued until the patient has made the life style and attitudinal changes that facilitate of sustained recovery; such changes can take months to years.

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