



## PCSS Guidance

**Topic:** Monitoring of Liver Function Tests in Patients Receiving Naltrexone or Extended-Release Naltrexone

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### Clinical Questions:

1. How should I monitor liver function tests in patients who are receiving naltrexone or extended-release naltrexone for their treatment of opioid and or alcohol use disorders?
2. What should I do if a patient receiving naltrexone does develop evidence of a severe elevation of liver function tests or acute hepatitis?

### Background:

Naltrexone (NTX) is an opioid receptor antagonist that blocks the reinforcing effects of opioids and reduces alcohol consumption and craving. Naltrexone can be administered orally daily, or once a month by intramuscular injection (extended-release naltrexone: XR-NTX). The oral form of naltrexone (Revia®) was approved by the FDA in 1984 for the treatment of opioid dependence and in 1994 for the treatment of alcohol dependence. XR-NTX (Vivitrol®) was FDA-approved for the treatment of alcohol dependence in 2006 and in 2010 for the treatment of opioid dependence.

XR-NTX is an extended-release, microsphere formulation of naltrexone designed to be administered by intramuscular (IM) gluteal injection every 4 weeks or once a month. After IM injection of XR-NTX, the naltrexone plasma concentration peaks in 2 hours, followed by a second peak 2-3 days later. Compared to daily oral dosing with NTX, the total naltrexone exposure is 3-4 fold higher following injection of an equivalent dose, that allows the total monthly dose of XR-NTX of 380 mg to achieve dose equivalent to 50 mg/d of oral NTX preparation given over a 28-day period (Dunbar et al., 2006). Steady state is reached at the end of the dosing interval following the first injection of XR-NTX. Naltrexone has an active metabolite 6-beta-naltrexol that has a longer half-life. Naltrexone and its metabolites are conjugated to form glucuronide by-products. Elimination of naltrexone and its metabolites occurs primarily via urine, with minimal excretion of unchanged naltrexone.

The cytochrome P450 system is not involved in naltrexone metabolism; thus co-administration with most antiretroviral therapies (ART) among HIV-infected patients, as well as newer oral treatments for HCV infection, is not expected to alter their metabolism. Hepatic impairment does not appear to significantly alter the pharmacokinetics of XR-NXT or NTX. In pre-marketing studies there were no changes in naltrexone blood levels in subjects with mild to moderate hepatic impairment (Child-Pugh classification Groups A and B); therefore dose adjustment is not necessary (Turncliff et al., 2005).

The most common side effects with NTX and XR-NTX, occurring in approximately 2% of subjects and not associated with discontinuation of study medication, include insomnia, nausea, vomiting, and headache (Revia® and Vivitrol® package inserts). Overall NTX and XR-NTX are documented safe, clinically efficacious FDA-approved medications to assist in treatment of opioid and alcohol use disorders (Garbutt et al., 2005; Krupitsky et al., 2011; Kunoe et al., 2014; Rosner et al., 2010).

Though minimal, the greatest potential risk of NTX was initially ascribed to liver toxicity as cases of hepatitis and liver dysfunction (elevated transaminase elevations), were observed during the earlier clinical trials with naltrexone. Many recent reports, however, have documented that NTX and XR-NTX pose significantly lower risk of hepatotoxicity than previously suspected, even among alcohol- and opioid-dependent persons including those with HCV and/or HIV infection (Lucey et al., 2008; Mitchell et al., 2012; Vagenas, 2014). A small number of studies examined liver function test (LFT) abnormalities among patients receiving the oral formulation of NTX. A study among alcohol-dependent men and women prescribed oral NTX did not observe LFT abnormalities; this study however did not compare the participants to a control group, nor did they have any additional significant co-morbidities (Yen et al., 2006). A similar observational study followed patients with Huntington's disease who were prescribed oral NTX also did not observe LFT changes (Sax et al., 1994). A retrospective cohort study among HIV-positive patients involved in the Veterans Administration Health care system who were alcohol-dependent receiving oral NTX also found no differences in hepatic enzyme levels (Tetrault et al., 2012).

Additionally there are numerous reports that XR-NTX also does not seem to produce hepatic enzyme abnormalities. A study among alcohol-dependent patients demonstrated no statistically significant differences among LFT enzyme levels between placebo and XR-NTX arms (Lucey et al., 2008). The original preliminary safety data, compiled by Alkermes pharmaceutical company prior to the publication of the placebo-controlled XR-NTX study among opioid-dependent persons in Russia (Krupitsky et al., 2011), did not find any severe LFT changes either (Krupitsky et al., 2010). In this Phase III double blind placebo-controlled randomized clinical trial (RCT), 250 opioid-dependent subjects who completed in-patient opioid detoxification treatment received one XR-NTX injection every 4 weeks. They were randomized in a 1:1 ratio of XR-NTX 380mg or placebo injection. After 6 monthly doses, subjects continued to an extension phase where 13 additional doses of XR-NTX 380 mg were given. Of note 42% of the group was HIV-infected and 90% was HCV-infected; however, patients with transaminase

levels greater than 3-times ULN were not enrolled. A total of 40 (32%) of the placebo group experienced  $\geq 1$  adverse event (AE) compared to N=63 (50%) of the XR-NTX group; N=4 (3%) of the placebo and N=3 (2%) of the XR-NTX group had a serious adverse event (SAE). Only 2 (2%) of the placebo discontinued the drug due to SAE, while N=3 (2%) of the XR-NTX group discontinued the study drug due to any adverse event. 53% (n=67) of the XR-NTX group and 38% (N=47) of the placebo group completed part A of the 6-month intervention. The primary reason for withdrawal within the placebo group was a positive naloxone challenge (n=17; 14%) compared with 1 (1%) of the XR-NTX group. The primary reason for the withdrawal of the XR-NTX group for N=10 (8%) was due to 'investigator judgment.' The most common clinical adverse events that were not considered serious were nasopharyngitis, insomnia, hypertension, flu-like symptoms, injection site pain, toothache, headache and respiratory tract infection. Elevations in liver enzymes (ALT, AST, and GGT) occurred in 10% of patients and were more commonly observed in the XR-NTX group than in the placebo group. There was a mean increase in XR-NTX group from baseline in ALT of 61 IU/L and AST 40 IU/L (with increases of 48 IU/L and 31 IU/L respectively in placebo group); however, the frequency of elevations in ALT, AST, and GGT above 3-times ULN was not statistically or clinically significant. Elevations in transaminases occurred primarily in patients with chronic HCV infection. Given that 42% of the population were HIV-infected and almost 90% were HCV-infected, results of this long-term study do not indicate that LFT abnormalities should be a major concern for healthcare professionals utilizing XR-NTX for treatment of opioid dependency (Mitchell et al., 2012). In addition, a more recent RCT of XR-NTX compared to TAU for persons with opioid use disorders involved in the criminal justice system was completed in the United States and again found no evidence of serious adverse events including no evidence for elevated LFTS (Lee, 2016).

One study examined the contributions to hepatotoxicity among HIV-infected prisoners prescribed antiretroviral therapy (ART) and transitioning to the community who were enrolled in two placebo-controlled randomized trials (RCT) of XR-NTX (Vagenas et al., 2014). Eighty-five HIV-infected persons who were being released to the community from prison/jail with opioid and/or alcohol dependence had been enrolled in two NIH-funded RCTs and had received at least one XR-NTX injection. More than 50% of this HIV-infected subject population was HCV antibody-positive and 39% had an axis I DSM-IV mental illness with 34% prescribed psychiatric medications, both additional hepatotoxic risk factors identified previously among persons receiving NTX. The majority (81%) were receiving ART for their HIV infection, another important potential hepatotoxic risk factor. In these RCTs, all patients had to have LFTS  $< 5x$  ULN prior to initiating an injection and could continue treatment unless LFTS were  $> 10x$  ULN and they had clinical symptoms of hepatitis and/or required hospital evaluation for hepatitis. Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) were not statistically different between persons randomized to placebo (N=24) and XR-NTX (N=61) arms over 6 months. Furthermore, a recently completed double blind placebo controlled RCT of XR-NTX was published among persons with alcohol use disorders and with HIV disease who were released to the community and there were no grade 3 or 4 hepatotoxicity events in either group after receiving 6 months of treatment (Springer et al., 2017; Springer et al, 2018a). Another

RCT of XR-NTX was published among persons with opioid use disorders and HIV and again found no grade 3 or 4 hepatotoxicity events. (Springer et al, 2018b). These results suggested that XR-NTX is safe to use among opioid and alcohol dependent HIV-infected released prisoners receiving ART with high rates of co-morbid HCV infection and mental illness.

## **General Principles**

Given this body of research that has not found any increased hepatotoxicity of XR-NTX for persons with opioid or alcohol use disorders even among those living with chronic HCV or HIV infection, a consensus was reached among experts at a “Summit of Non-Agonist Treatments” held by SAMHSA and NIDA that there is now ample evidence to support that obtaining LFTs prior to institution of XR-NTX is not warranted nor is routine monitoring of LFTs (SAMHSA et al, 2016). Despite the overall consensus that NTX and XR-NTX are safe to administer among patients with severe comorbidities including HCV and HIV infection, it is prudent to know whether a patient has underlying liver disease and monitor for usual clinical side effects and symptoms while persons are on treatment.

## **Recommendations:**

Level of evidence: **High- prospective observational and randomized placebo-controlled trials.**

1. It is not necessary to obtain baseline liver function tests including AST, ALT, and total bilirubin prior to instituting naltrexone (oral or injectable) therapy as this may limit the opportunity to provide treatment to those in need at time of need. Having a patient return after obtaining LFTs can delay effective treatment.
2. It is prudent to be aware of patients’ medical history of HIV, HCV and HBV chronic infection, however it is not recommended to check for these chronic infections as a criteria for starting treatment. It is recommended to offer screening of HIV, HCV and HBV infections as routine clinical care and offered at time of initiating XR-NTX treatment for opioid and alcohol use disorders. If chronic infections are determined, then referral to those with expertise in treatment of these infections should be offered.
3. At present there is no empirical evidence to support frequency of monitoring hepatic enzymes. Studies of HIV+ and HCV+ co-infected persons receiving XR-NTX do not indicate any changes in liver function tests warranting frequent monitoring. Clinical discretion may be used to guide further hepatic monitoring but quarterly is likely sufficient. For instance, LFTs should be obtained if a patient clinically has signs or symptoms of hepatic dysfunction, i.e. jaundice, abdominal pain, nausea and vomiting.
4. Inform patients to discuss relapse to alcohol/opioids or other drug use.
5. Inform patients to report any new medications as certain medications, including over-the-counter medications, may have associated hepatic enzyme elevations such as isoniazid for tuberculosis or acetaminophen.

6. Inform patients to contact a healthcare professional immediately if they develop abdominal pain, nausea, vomiting, fever, dark urine, clay-colored stools, jaundice, or icterus.
7. If a patient receiving NTX or XR-NTX does have clinical symptoms of severe hepatotoxicity (elevated transaminases greater than 10x ULN with symptoms mentioned above in #6 and/or requiring hospitalization or emergency room use for hepatitis), then the medication should be discontinued. All other possible causes of hepatotoxicity should be evaluated at this time besides the NTX or XR-NTX including new medications, as well as concurrent infection, relapse to alcohol or other drug use, etc. If there is no evidence that NTX or XR-NTX is the cause, then treatment can be restarted after clinical symptoms are no longer present and LFTs fall below 10x ULN.

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**PCSS Guidances use the following levels of evidence\*:**

**High** = Further research is very unlikely to change our confidence in the estimate of effect

**Moderate**= Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

**Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

**Very low** = Any estimate of effect is very uncertain.

**Type of evidence:**

Randomized trial = **high**

Observational study = **low**

Any other evidence = **very low**

\* Grading quality of evidence and strength of recommendations *British Medical Journal* 2004: 328:1490.