

## PCSS Guidance

**Topic:** Monitoring of Liver Function Tests and Hepatitis in Patients Receiving Buprenorphine (With or Without Naloxone)

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### Guideline Coverage:

This topic is also partially addressed in Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40), pages 33-34. <http://buprenorphine.samhsa.gov/Bup%20Guidelines.pdf>

### Clinical Questions:

1. How should I monitor liver function tests in patients with or without underlying chronic hepatitis who are receiving buprenorphine for the treatment of opioid dependence?
2. What should I do if a patient receiving buprenorphine does develop evidence of acute hepatitis or worsening chronic hepatitis?

### Background:

Early reports of adverse events related to buprenorphine treatment raised concerns about possible hepatotoxicity as some participants showed increases in serum aminotransferase levels (Berson et al., 2001b; Lange et al., 1990). A retrospective study found that patients with a history of hepatitis (but not those without such a history) exhibited statistically significant (but not necessarily clinically meaningful) increases in ALT (median increase=8.5 IU) and AST (median increase=9.5 IU (Petry et al., 2000). In this study, higher buprenorphine doses were associated with greater odds of an increase in AST. Several case reports describe patients with Hepatitis C (HCV) who developed severe, acute hepatitis while injecting buprenorphine or taking it sublingually (Berson et al., 2001b; Herve et al., 2004; Zuin et al., 2009). Some of these patients remained on lower dose buprenorphine or were re-challenged with it without further evidence of liver injury. Based on preclinical studies a mechanism of buprenorphine hepatotoxicity was proposed involving disruption of mitochondrial respiration via proton donation (Berson et al., 2001a).

A recent multi-center study prospectively examined hepatic safety of buprenorphine in 740 opioid dependent individuals who were at high risk for liver disease (Saxon et al., 2013). Median dose was 24 mg and participants were monitored for 24 weeks. While relatively low rates of serious exacerbation of liver injury indices was found a small number of participants (2.1%) had extreme elevation of transaminases sufficient to merit medical attention. Those with extreme elevations were more likely to have hepatitis seroconversion during the study and were using illicit drugs during the first 8 weeks of treatment suggesting that factors other than exposure to buprenorphine were responsible for observed hepatotoxicity.

In a study in adolescents (14-21yo) treated with buprenorphine for 2 or 12 weeks, liver function tests were collected at baseline and monthly afterwards (Bogenschutz et al., 2010). This study did not find evidence for hepatotoxic effects of buprenorphine. The vast majority of abnormalities seen were mild elevations (<5 upper limit of normal) and elevated values were associated with HCV. Interestingly, in this study rates of elevated transaminases associated with HCV were much lower in those maintained on buprenorphine for 12 weeks than in those who received detoxification suggesting that buprenorphine may protect against liver toxicity related to illicit opioids use.

Hepatic safety of buprenorphine was assessed prospectively for 12 months in 303 patients with HIV maintained on antiretroviral medication (Vergara-Rodriguez et al., 2011). In this population of patients at high risk for liver problems, hepatotoxicity attributable to buprenorphine/naloxone was rare at most and limited to patients with concurrent HCV infection. Moreover, no clinically significant interactions with

antiretroviral medications were noted. However, in this study, enrollment was restricted to patients with hepatic enzymes less than 5 times the upper limit of normal.

Hepatic safety was also assessed in a study of 86 women treated with buprenorphine during pregnancy with one third of the population testing positive for HCV (McNicholas et al., 2012). All HCV-negative participants had normal liver enzymes throughout pregnancy and post-partum period. While HCV-positive participants had overall higher levels of ALT, AST and GGT, buprenorphine did not affect differentially liver enzymes according to HCV-status.

In summary, data from large and diverse cohort of patients provide reassurance to providers regarding the safety of buprenorphine/naloxone in their patients. These studies suggest that liver injury from buprenorphine occurs rarely, however patients with hepatitis C are at higher risk to experience elevations in transaminases and reversible hepatic injury. Most of the evidence suggests that these elevations are related to underlying liver disease and not to the buprenorphine exposure. Serious hepatic injury appears to be quite rare considering that many hundreds of thousands of individuals have been treated with buprenorphine around the world. Moreover, maintenance on buprenorphine may have indirect beneficial effect on liver health via reduction of illicit opioid use as it may minimize the toxic impact of adulterants found in heroin or acetaminophen found in prescription analgesics.

#### **General Principles:**

Be aware of potential, though rare, risk of liver injury with buprenorphine/naloxone particularly in patients with other hepatic risk factors. Inform patients of risk prior to beginning medication and monitor appropriately. Intervene if evidence of liver injury occurs. Note that most clinical trials with buprenorphine excluded patients with baseline transaminases greater than 3-5 times normal therefore little information is available at this point to guide clinicians who are treating patients with baseline transaminases that are greater than 5 times normal.

#### **Recommendations:**

Level of evidence: **Moderate – prospective observational and randomized studies**

- 1) Obtain liver tests including transaminases, bilirubin, prothrombin time/INR, and albumin prior to initiating buprenorphine treatment.
- 2) Obtain Hepatitis B and C panels prior to initiating buprenorphine in patients whose serostatus is unknown and who have risk factors for these viral infections.
- 3) Periodically monitor liver tests during buprenorphine treatment. There is no empirical evidence currently to guide the frequency of monitoring. The frequency of monitoring may be determined by physician discretion but semi-annual frequency appears to be adequate in patients without other risk factors.
- 4) Inform patients to contact physician immediately if they develop symptoms or signs of hepatotoxicity such as fever, malaise, nausea, vomiting, abdominal distress, dark urine, clay colored stools, or icterus.
- 5) If a patient does have clinical and/or laboratory evidence of hepatotoxicity (e.g. transaminases >5X upper limit of normal, abnormal bilirubin or abnormal prothrombin time)
  - All possible causes of liver injury should be evaluated.
  - Strong consideration should be given to consulting a gastroenterologist or hepatologist.
  - Consideration should be given to lowering the dose of buprenorphine or discontinuing buprenorphine.
  - The patient should be followed with serial clinical and laboratory monitoring until evidence of hepatic injury resolves.
- 6) It is recognized that in certain clinical situations such as urgent or brief medically supervised withdrawal, it may be impractical or impossible to obtain liver tests prior to initiating treatment. Nevertheless, given the unpredictability of liver reactions, and to avoid inappropriately ascribing abnormalities to buprenorphine, the best clinical practice when possible is to check liver tests and hepatitis testing prior to initiation of therapy.

## References:

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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-