



PCSS Guidance

Topic: Monitoring of liver function tests and hepatitis in patients receiving buprenorphine/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/naloxone (bup/nx) for the treatment of opioid dependence? 2) What should I do if a patient receiving bup/nx does develop evidence of acute hepatitis or worsening chronic hepatitis?

Background: An early report of adverse events related to buprenorphine treatment noted that some participants showed increases in serum aminotransferase levels, but these increases could not be directly attributed to buprenorphine.¹ That study was published prior to the availability of clinical testing for Hepatitis C so that the Hepatitis C status of the subjects was not known. A subsequent study obtained liver enzyme values on patients prior to initiation of buprenorphine and again after a minimum of 40 days of treatment with either 2, 4, or 8 mg/70 kg buprenorphine per day.² 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). In this study, higher buprenorphine doses were associated with greater odds of an increase in AST. One series of cases reported from France described 4 individuals with Hepatitis C who injected buprenorphine intravenously and developed ALT elevations 13-50 times the upper limit of normal and 1 individual with Hepatitis C and HIV who became jaundiced and had panlobular liver necrosis and microvesicular steatosis after using only sublingual buprenorphine.³ The intravenous users recovered after stopping intravenous injection, and 2 of them did not interrupt sublingual administration of buprenorphine. The HIV positive patient also recovered after stopping buprenorphine. A second series of cases from France included 7 patients who developed hepatitis while on buprenorphine.⁴ Only 1 of these patients was injecting buprenorphine. The other 6 took it as prescribed by the sublingual route. Average ALT levels were 39 times normal. All patients had

serologic evidence of Hepatitis C. Buprenorphine treatment was continued in all patients, although 3 had a dose reduction of 50%. All 7 patients recovered without apparent sequelae. An *in vitro* study with rat hepatocytes suggested that buprenorphine is a proton donor that can interfere with mitochondrial respiration resulting in necrosis of hepatocytes.⁵

It thus appears that buprenorphine may have the potential to cause elevations in transaminases and reversible hepatic injury, particularly in individuals with Hepatitis C. The precise incidence of these types of event remains uncertain, though the serious hepatic injury appears to be quite rare considering that many thousands of individuals have been treated with buprenorphine in France with only a few reported cases of hepatic injury. The National Institute on Drug Abuse Clinical Trials Network will be conducting a prospective study that will systematically assess changes in liver tests over time in opioid dependent patients randomized to be treated with either buprenorphine/naloxone or methadone. Results from this trial should provide more information about the effects of buprenorphine/naloxone on the liver.

General principles: Be aware of potential risk of liver injury with bup/nx and inform patients of risk prior to beginning medication and monitor appropriately. Intervene if evidence of liver injury occurs. Note that the clinical trials conducted in the United States with buprenorphine excluded patients with baseline transaminases greater than 3-5 times normal. 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: **Low – observational studies**

- 1) Obtain liver tests including transaminases, bilirubin, prothrombin time/INR, and albumin prior to initiating bup/nx treatment.
- 2) Obtain Hepatitis B and C panels prior to initiating bup/nx in patients whose serostatus is unknown and who have risk factors for these viral infections.
- 3) Periodically monitor liver tests during bup/nx treatment. There is no empirical evidence currently to guide the frequency of monitoring. Therefore, the frequency of monitoring may be determined by physician discretion.
- 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 bup/nx or discontinuing bup/nx.
- 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 bup/nx, the best clinical practice when possible is to check liver tests and hepatitis testing prior to initiation of therapy.

References

1. Lange WR, Fudala PJ, Dax EM, Johnson RE. Safety and side-effects of buprenorphine in the clinical management of heroin addiction. *Drug Alcohol Depend* 1990;26:19-28.
2. Petry NM, Bickel WK, Piasecki D, Marsch LA, Badger GJ. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. *Am J Addict* 2000;9:265-9.
3. Berson A, Gervais A, Cazals D et al. Hepatitis after intravenous buprenorphine misuse in heroin addicts.[comment]. *Journal of Hepatology*. 2001;34:346-50.
4. Herve S, Riachi G, Noblet C et al. Acute hepatitis due to buprenorphine administration. *Eur J Gastroenterol Hepatol* 2004;16:1033-7.
5. Berson A, Fau D, Fornacciari R et al. Mechanisms for experimental buprenorphine hepatotoxicity: major role of mitochondrial dysfunction versus metabolic activation.[comment]. *Journal of Hepatology*. 2001;34:261-9.

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:

Randomised trial = **high**

Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations

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