Drug and Alcohol Dependence 128 (2013) 71–76

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: A randomized trial

Andrew J. Saxon[a], Walter Ling[b], Maureen Hillhouse[b,*], Christie Thomas[b], Albert Hasson[b], Alfonso Ang[b], Geetha Doraimani[b], Gudaye Tasissa[c], Yuliya Lokhnygina[c], Jeff Leimberger[c], R. Douglas Bruce[d], John McCarthy[e], Katharina Wiest[f], Paul McLaughlin[g], Richard Bilangi[h], Allan Cohen[i], George Woody[j], Petra Jacobs[k]

[a] Veteran's Affairs Puget Sound Health Care System, 1660 South Columbian Way, Room 116 ATC, Seattle, WA 98108, United States
[b] University of California, Los Angeles, Integrated Substance Abuse Programs, 1640 S. Sepulveda Blvd., Suite 120, Los Angeles, CA 90025, United States
[c] Duke Clinical Research Institute, Room 0311 Terrace Level, 2400 Pratt St., Durham, NC 27705, United States
[d] Yale University School of Medicine, 135 College Street, Suite 323, New Haven, CT 06510, United States
[e] Bi-Valley Medicine Clinic, Inc., 310 Harris Avenue, Suite A, Carmichael, CA 95838, United States
[f] CODA, Inc., 1027 East Burnside Street, Portland, OR 97214, United States
[g] Hartford Dispensary, 335 Broad Street, Manchester, CT 06040, United States
[h] Connecticut Counseling Center, 60 Beaver Brook Road, Danbury, CT 06810, United States
[i] Bay Area Addiction Research & Treatment, 15325 Del Gado Drive, Sherman Oaks, CA 91403, United States
[j] University of Pennsylvania School of Medicine, 150 South Independence Mall West, Suite 600, Philadelphia, PA 19106-3475, United States
[k] National Institute on Drug Abuse, Clinical Trials Network, 6001 Executive Boulevard, Room 3105, Bethesda, MD 20892-9557, United States

ARTICLE INFO

Article history:
Received 15 May 2012
Received in revised form 2 August 2012
Accepted 3 August 2012
Available online 22 August 2012

Keywords:
Liver function
Buprenorphine
Methadone
Treatment outcome

ABSTRACT

Background: Buprenorphine/naloxone (BUP) and methadone (MET) are efficacious treatments for opioid dependence, although concerns about a link between BUP and drug-induced hepatitis have been raised. This study compares the effects of BUP and MET on liver health in opioid-dependent participants.
Methods: This was a randomized controlled trial of 1269 opioid-dependent participants seeking treatment at 8 federally licensed opioid treatment programs and followed for up to 32 weeks between May 2006 and August 2010; 731 participants met "evaluable" criteria defined as completing 24 weeks of medication and providing at least 4 blood samples for transaminase testing. Participants were randomly assigned to receive BUP or MET for 24 weeks. Shift table analysis determined how many evaluable participants moved between categories of low and elevated transaminase levels. Predictors of moving from low to high transaminase levels were identified.
Results: Changes in transaminase levels did not differ by medication condition. Baseline infection with hepatitis C or B was the only significant predictor of moving from low to elevated transaminase levels; 9 BUP and 15 MET participants showed extreme liver test elevations and were more likely than those without extreme elevations to have seroconverted to both hepatitis B and C during the study, or to use illicit drugs during the first 8 weeks of treatment. MET participants were retained longer in treatment than BUP participants.
Conclusions: This study demonstrated no evidence of liver damage during the initial 6 months of treatment in either condition. Physicians can prescribe either medication without major concern for liver injury.

1. Introduction

The United States is gripped by an epidemic of opioid addiction involving both heroin (Substance Abuse and Mental Health Services Administration, 2009) and diverted prescription opioids (Volkow and McLellan, 2011). To date, the most effective treatment for opioid addiction is opioid agonist therapy with either methadone (MET) or buprenorphine (BUP; Mattick et al., 2008). The use of BUP has expanded considerably since its introduction into the U.S., but data from early studies raised concerns about possible hepatotoxicity (e.g., Berson et al., 2001a,b). As part of The Food and Drug Administration's (FDA) approval of buprenorphine products in 2002, a Phase IV hepatic safety study to document the relative safety of prolonged exposure to buprenorphine compared to the standard of care for opioid agonist therapy (methadone) was required.

* Corresponding author. Tel.: +1 310 267 5308; fax: +1 310 312 0552.
E-mail address: hillhous@ucla.edu (M. Hillhouse).

0376-8716/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.drugalcdep.2012.08.002

One retrospective study found that patients diagnosed with hepatitis B or C receiving treatment with BUP had significant increases in transminase levels, whereas patients without hepatitis did not (Petry et al., 2000). Several case reports describe patients with hepatitis C who developed severe, acute hepatitis while either misusing BUP by injection or when taking it sublingually as directed, although some of these patients either remained on BUP at a lower dose or were re-challenged with it without further evidence of liver injury (Berson et al., 2001a,b; Hervé et al., 2004; Zuin et al., 2009). A potential theoretical mechanism was proposed to explain BUP hepatotoxicity involving disruption of mitochondrial respiration via proton donation by BUP (Berson et al., 2001a,b).

With increasing numbers of physicians prescribing BUP to patients with underlying liver disease, there is a need to determine if BUP poses any significant risk of hepatotoxicity. Thus, the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) in collaboration with Reckitt Benckiser Pharmaceuticals, designed this prospective, 24-week, open-label, randomized, controlled, phase IV study to examine the comparative effects of BUP (as the combination, buprenorphine/naloxone) and MET on indices of liver health in opioid-dependent patients seeking agonist replacement therapy. Although participants were randomized to medication condition, this study was designed to compare liver results from the two conditions with no specific hypothesis. Liver function, drug use, adverse events, and retention data were collected from participants randomly assigned to BUP or MET.

2. Methods

2.1. Participants

Individuals were recruited at eight federally licensed opioid treatment programs across the United States. Eligibility criteria included being age 18 or older, meeting DSM-IV-TR criteria for opioid dependence, and not having an alanine amino transferase (ALT) or aspartate amino transferase (AST) value >5 times, or alkaline phosphatase (ALP) value >3 times the upper limit of normal (ULN). Eligibility criteria were included to ensure that participation would be safe and included exclusion criteria based on medical and psychiatric conditions such as cardiopathy, liver disease, and acute psychosis. Additionally, individuals were excluded who had poor venous access such that venipuncture could not be accomplished.

The FDA required a minimum of 300 evaluable participants on each medication. Because this study was descriptive in design, the target randomization was not based on analysis criteria, and no power analysis was computed. The criteria for "evaluable" were completion of 24 weeks on assigned medication and provision of at least half of the eight liver tests scheduled between weeks 1 and 24, at weeks 1, 2, 4, 8, 12, 16, 20, and 24. Test windows included ± 2 days for weeks 1 and 2, and ± 7 days for all other weeks. To reach this goal, the initial randomization scheme of 1:1 (BUP:MET) was changed to 2:1 in December 2007 (18 months after initiation) because of higher dropout in the BUP condition.

2.2. Procedures

The study was approved by the institutional review boards at participating sites, and participants provided written informed consent. Recruitment occurred between May 2006 and October 2009 with follow-up assessments through August 2010. Oversight was also provided by the NIDA CTN Data Safety and Monitoring Board. Fig. 1 depicts the flow of patients through the study. Screening assessments included serum chemistries, ALT, AST, ALP, bilirubin, prothrombin time, albumin, CBC, urinalysis, and pregnancy tests (females). Human immunodeficiency virus (HIV) and hepatitis B and C serologies were obtained within one week following randomization. Participants who tested negative for these viral infections at the beginning of the trial were re-tested at 24 weeks or at early termination when possible to ascertain seroconversion events during the trial.

Eligible participants returned to the clinic for induction after abstaining from opioids for 12–24 h to present in mild opioid withdrawal (Clinical Opiate Withdrawal Scale score ≥ 8; Wesson and Ling, 2003) or as deemed appropriate by the study physician. Participants were stratified by site and normal versus abnormal transaminase levels and randomized either to open-label MET or BUP and inducted onto medication. Dosing was designed to reflect current dosing standards, and wide variety in both induction dosing and maintenance dosing was allowed, including dose changes across the study duration.

The initial dose of BUP could range from 2 to 8 mg with an additional amount given for persistent withdrawal to a maximum total first day dose of 16 mg. BUP could be further increased in subsequent days to a maximum of 32 mg. The mean maximum daily BUP dose was 22.1 mg (sd = 8.2; median = 24 mg).

The maximum initial dose of MET was 30 mg with an additional amount given for persistent withdrawal to a maximum total first day dose of 40 mg. MET could be increased in subsequent days by 10 mg increments. No specific maximum was set for MET. The mean daily maximum MET dose was 93.2 mg (sd = 42.2; median = 90 mg).

For both medications, study physicians were encouraged to increase doses in response to withdrawal symptoms or opioid use or craving. Participants came to the clinic daily for observed medication administration except Sundays and holidays or when take-home medications were permitted by local regulations. Participants were titrated to an appropriate medication dose typically over the first few medication days for BUP and over several weeks for MET, remained on study medication for the full 24 weeks, and were then tapered off medication over ≤ 8 weeks or referred for ongoing clinical treatment.

Although not specifically addressed in the study protocol or operations manual, both the BUP and MET groups were scheduled identically for clinic visits. No data were collected to document this, but there is no reason to believe that the groups differed in terms of contact with staff or referrals for ancillary services. Weekly assessments included urine drug screens and adverse event assessments. Self-reported drug use data were collected every four weeks; as noted, liver tests occurred at weeks 1, 2, 4, 8, 12, 16, 20, and 24. The Fagerstrom Test for nicotine dependence was obtained at screening to determine rates of heavy smoking (Heatherton et al., 1991). The HIV Risk Behavior Survey was obtained at screening, at week 12, and at week 24 to determine rates of unsafe injection drug use (Needle et al., 1995).

2.3. Outcome measures and statistical analyses

Analyses of transaminase levels via shift tables include data from the evaluable subsample. Other analyses use data from all randomized participants except where specified.

The primary outcome, a shift table analysis of changes in ALT and AST from baseline, sorted evaluable participants into 1 of 5 categories based on a threshold of 2X ULN (chosen because a large proportion of participants would likely have minor elevations in transaminase levels as a consequence of pre-existing liver disease). Shift table categories include:

(1) Baseline transaminases (both ALT and AST) that were ≤ 2X upper limit of normal (ULN) and remained at this level throughout the study;