Review Article

Effects of Buprenorphine on Liver Enzymes in Patients without a History of Liver Disease

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Abstract

Background & Objective: Buprenorphine (BUP), a synthetic opioid, treats pain and opioid use syndrome. The potential of BUP to cause liver toxicity has not been fully evaluated. The present literature review was designed to investigate the impact of BUP treatment on liver function in patients without a previous history of liver diseases.

Materials & Methods: A literature review was implemented within databases of Scopus, PubMed, ISI, and Cochran until February 2022. Studies published in English were included in this study. Retrieved citations were screened and data were extracted by at least two independent reviewers.

Results: Of the 1853 studies screened citations, 14 research reports were eligible. Overall, among the randomized controlled trial, four studies reported hepatotoxicity in patients who had a history of hepatitis C or hepatitis B seroconversion under BUP treatment.

Conclusion: No strong evidence was found for hepatotoxicity of BUP in this study. Elevation in the liver enzyme levels in some patients may be related to other factors such as infectious diseases, illicit drugs, alcohol consumption, environmental pollutants, and chronic diseases. More experimental and clinical studies should be conducted to address this question.

Keywords: Buprenorphine, Liver, Toxicity, Hepatitis

Introduction

BUP, a semi-synthetic opioid, is increasingly administrated as a first line standard treatment for opioid dependence due to its high safety and efficacy compared to other opioids (1). It is a synthetic analog of thebaine, which is an alkaloid compound derived from the poppy flower. BUP is a potent analgesic that acts on the central nervous system (CNS). Numerous studies have confirmed the safety of BUP maintenance treatment in opioid addiction (1). It is as effective as methadone and is generally safe and well-tolerated (2). However, BUP offers some potential pharmacologic advantages over methadone in the management of opioid addiction, such as decreased respiratory depression, less sedation, fewer withdrawal symptoms, lower risk of toxicity at higher doses,

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and decreased risk of diversion (3). According to previous studies, the mortality rate of BUP was lower than methadone in patients who are being under treatment. Nevertheless, the mortality rate was increased in the first 12 months after discontinuing drugs (4). Additionally, it was found that the risk of overdose due to BUP was lower than methadone (5). Common adverse effects of BUP include headache, constipation, insomnia, asthenia, dizziness, somnolence, and sweating. Another main side effect of BUP treatment is psychological or physical dependency (6). There are several studies indicating liver damage, respiratory failure, and nervous system problems such as memory loss and cognitive function after BUP administration (7, 8). The previous studies indicated a risk of increased liver function tests (LFTs) for patients with hepatitis C undergoing BUP treatment maintenance or misusing BUP (9, 10). However, their findings are controversial. On the one hand, there have been several reports and case series of acute, clinically apparent liver injury arising after treatment with BUP. Almost all patients with this injury had concurrent chronic hepatitis C, and several appeared to resolve the chronic infection with the acute liver injury. On the other hand, several studies reported no significant pattern of liver enzyme elevations or hepatotoxicity following BUP therapy. Based on our knowledge, this is the first literature review in this context. The present literature review was designed to investigate the impact of BUP treatment on liver function in patients without a previous history of liver diseases. This study provides a review of the existing literature to help clinicians and patients better understand the approaches to microdosing of buprenorphine in various clinical settings and populations.

Materials & Methodes

Pharmacokinetics of BUP

Human and animal studies have investigated the absorption, distribution, metabolism, and excretion of BUP (11). BUP is metabolized by N-dealkylation to form the active metabolite Nor-BUP, and both undergo subsequent glucuronidation (12). The cytochrome P450 (CYP) enzymes (especially CYP3A4 iso-enzyme) catalyze the N-dealkylation of BUP to nor-BUP in the liver (13). BUP undergoes extensive first-pass metabolism and therefore has very low oral bioavailability (14). However, most of the BUP administered sublingually may escape the first-pass metabolism and enter the systemic circulation (15). Approximately 80%-90% of BUP is excreted through the biliary system, where 10% of a dose can be detected in the urine (14). BUP has relatively high bioavailability with sublingual absorption (35%–55%)(16). Its sublingual administration causes a longer half-life than the intravenous injection. There are two tablet forms of BUP including only BUP and mixes of BUP with the opioid antagonist naloxone (NLX)(17). NLX has been a highly effective evidence-based tool to reduce opioid overdose-related mortality and morbidity (18). A sublingual dose of BUP/NLX leads to a quick opioid-withdrawal syndrome. NLX decreases the side effects of BUP and elevates its safety (19). The inhibition of BUP metabolism is not associated with opioid toxicity, i.e., respiratory depression, though it decreases the plasma levels (20).

Mechanism of Action

Mechanism of action describes the way BUP affects cell function or impacts a specific target within a cell. BUP is a partial opioid agonist (21). BUP has a slow onset of action. When taken sublingually, the peak effect is between three and four hours after administration. It also has a long duration of action, with a half-life of around 38 hours, meaning that it will stay active in the body for a long time after taking it, preventing withdrawal symptoms all day long (22). Its mechanism of action occurs at the μ-opioid receptor. BUP binds to μ-opioid receptors throughout the body, including inside the brain, and induce endorphins that produce euphoria and block pain (23). BUP is a potent Schedule III opioid with high binding affinity at the μ-opioid receptor that behaves as a partial agonist on the basis of in vitro studies (24). Although BUP has less capacity to activate receptors or induce

multiple signaling pathways than full μ-opioid receptor agonists, it still effectively stimulates the analgesic signaling pathway from the μ-opioid receptor. Moreover, other opioid receptors may also contribute to efficacy and tolerability of BUP. BUP is a full agonist at the opioid receptor-like 1 (ORL1), which may contribute to analgesia, and it is an antagonist at the δ- and κ-opioid receptors (25). These receptors decrease constipation, dysphoria, and abuse potential and are involved in reducing mental depression (26). However, μ-opioid receptor also can lead to the side effect of constipation. BUP exhibited a relative ceiling effect for respiratory depression after binding to μ-opioid receptors (27). Although, the risk of respiratory depression appears to be lower than that of analgesic doses of full μ-opioid receptor agonists, there is still a risk of respiratory depression with BUP (28). However, our current knowledge about BUP receptors and their interactions needs further studies.

Drug-BUP interaction

Drug-BUP interaction is exerted via pharmacokinetic and pharmacodynamic interactions (29). Pharmacokinetic interactions are comprised of inhibition/induction of hepatic CYP enzymes and affect glucuronidation, the function of the drug transporter P-glycoprotein, and drug absorption (30). Other mechanisms include blood-brain barrier alteration. Pharmacodynamic interactions occur between BUP and depressant agents of CNS including alcohol, another opioid, or psychotropic agents (31). The BUP action is lower than that of methadone. BUP converts to nor-BUP in sublingual adsorptions via CYP3A4 (32). BUP is not the main inducer/inhibitor of P450 enzymes, but it competes with drugs metabolized by the pathway. BUP is a weak inhibitor of CYP3A4. This inhibition property is not dose-dependent. Plasma BUP levels may be reduced by CYP3A4 inhibitors, although the opioid toxicity might be reduced by the partial agonist effect of BUP (33). BUP metabolism and its reduced plasma level might be the result of CYP3A4 inducers, which leads to opioid withdrawal (34). BUP pharmacokinetics is also gender-dependent. For example, in a study, women showed higher plasma concentrations for BUP and its metabolites than men. It is reported that BUP interacts with several antidepressants and antiviral drugs (35). It seems that there is a link between drug-drug interactions and mortality associated with BUP since such interactions cause P-glycoprotein inhibition (36). P-glycoprotein is a drug transporter with a crucial protective role that can contribute to the incidence of respiratory distress following the administration of BUP (37). However, in vitro studies reported nor-BUP as a substrate of human P-glycoprotein. Pharmacodynamic interactions may be related to other CNS depressants, including alcohol and benzodiazepines. Co-administration of diazepam in high doses with BUP may increase the effects of psychedelic drugs and reduce psychological performance (38). According to animal studies, such regimens could also alter respiratory functions. BUP alters the profiles of desmethyl flunitrazepam and flunitrazepam (FZ)(39). High-dosage BUP consumed concomitantly with benzodiazepines (BZDs) including FZ may cause life-threatening respiratory depression (39). Furthermore, BUP and FZ combination caused a toxic impact on rat ventilation. Active benzodiazepine and alcohol consumption are clinically risk factors for relapse in BUP maintenance (39). The BUP respiratory outcomes with and without NLX are similar in animal models (40). Note that the respiratory effects of BUP are higher if being co-administered with diazepam compared to its combination with NLX. Indeed, BUP-associated death occurs in co-administration with other psychotropic agents (40). Thus, psychotropic drugs should be administered to opioid addicts cautiously.

Search strategy

A literature review was implemented within databases of Scopus, PubMed, ISI, and Cochran until October 2021. Studies published in English were included in this study. Retrieved citations

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were screened and data were extracted by at least two independent reviewers. We used database-specific combinations of the following index terms and text words: buprenorphine, buprenorphine/naloxone, liver enzymes, hepatotoxicity, transdermal buprenorphine, buprenorphine-dosing protocol. Our search for these databases generated 1853 results. Two authors blindly screened all articles obtained through the search, based on titles and abstracts, to identify relevant articles for full-text consideration. After excluding all duplicates (543 studies) and completely off-topic titles (1296 studies), 14 citations were left.

Remaining citations were manually screened by two authors for exclusion based on their titles and abstracts, that is, those clearly incompatible with the purpose of our review or those written in languages other than English. The authors reviewed and determined each article based on the title and the abstract. A total of 14 papers meeting the criteria were included in the review. Table 1 & Figure 1 demonstrate the search strategy and keywords used ("Buprenorphine" and "liver enzymes" and "Buprenorphine" and "hepatotoxicity".

Study	Key criteria keywords
Lange, 1990	Heroin-dependent subjects Participants in this treatment research study were not required to have clinical laboratory parameters of liver function within the limits of normal in order to qualify for inclusion.
Singh, 1992	Abused BUP subjected (mean 14 months)
Assadi, 2004	Addicted outpatient that met DSM-IV criteria for opioid dependence. No pregnancy or lactation, clinically unstable medical illness, liver transaminases exceeding twice the upper limit of normal, history of psychosis, mania or severe major depression, concurrent dependency to alcohol, antisocial or borderline personality
Di Petta, 2005	Addicted polydrug abusers with previous methadone treatment No pregnancy, acute active liver or chronic liver diseases
Lofwall, 2005	Outpatient opioid-dependent subjects No pregnancy , mental and chronic medical diseases
Gerra, 2006	Heroin-dependent subjects met the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders; American Psychiatric Association, 1994. No exclusion criteria are applied to select patients in the public health system. All the patients were evaluated using a self-report and observer-rated questionnaire, a psychometric test, and a psychiatric diagnostic screening

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Table 1. Inclusion criteria of selected studies

Fiellin, 2008	Opioid-dependent subjects No alcohol or benzodiazepines dependency, psychotic or major depression
Bogenschutz, 2010	Opioid dependent subjects No pregnancy or lactation, serious medical conditions, and under psychotropic medication.
Strain, 2011	Opioid dependent subjects met the DSM-IV-TR, age 18–65 years No pregnancy or lactation, serious medical conditions, and under psychotropic medication, concurrent dependency to alcohol and sedative-hypnotics, active aphthous stomatitis or oral herpes, dental caries requiring immediate medical intervention, and no ongoing prescription medications that interact with the P450 3A4 system.
Saxon, 2013	Opioid-dependent subjects meet DSM-IV-TR Not having ALT and AST value > 5 times, or ALP value >3 times the upper limit of normal (ULN)
Al-Tawil, 2013	Healthy individuals without chronic condition requiring frequent analgesic therapy, no-smoking in 89.2% pf participants
Ciftci Demirci, 2015	Heroin-dependent adolescents with normal liver enzymes
Fareed, 2017	Patients had nor-buprenorphine level in urine Important risk factors for hepatotoxicity including HCV were adjusted in this study
Haight, 2019	Opioid-dependent subjects meet DSM-IV-TR Moderate or severe alcohol, cocaine or cannabis use disorders.

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Exploded keywords were included and MESH terms for MEDLINE and modified truncation according to the different search platforms.

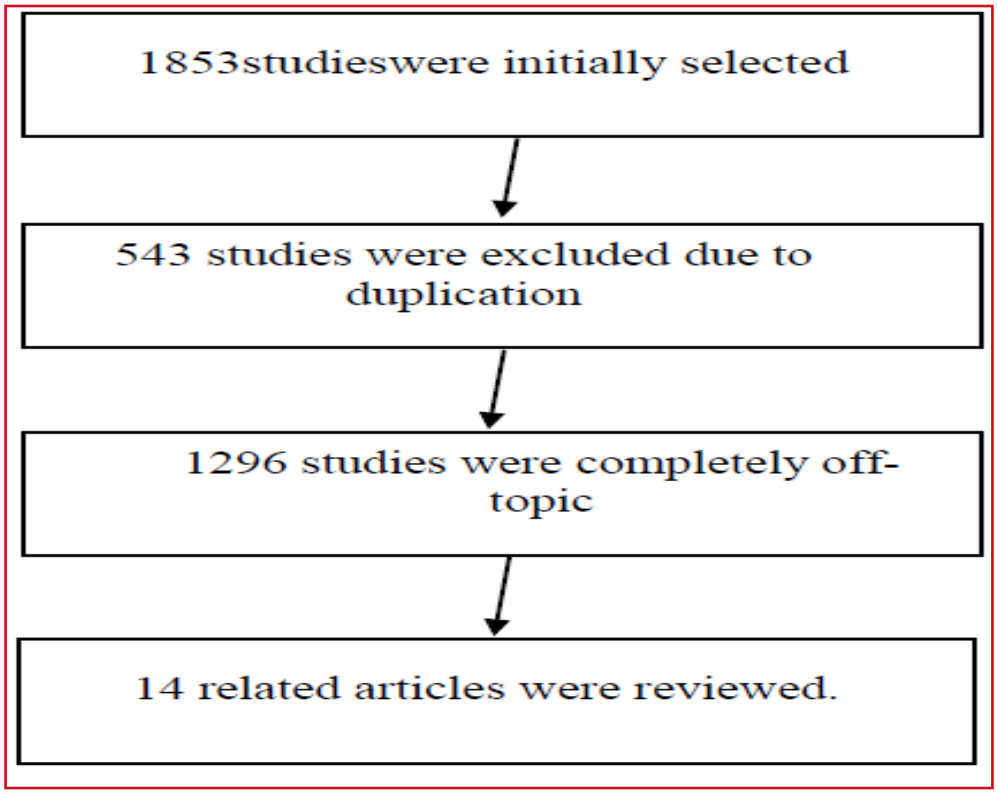

Figure 1. Search strategy

Study characteristics and liver outcome findings

Among the selected studies, twelve papers were randomized clinical trials (RCTs). Details of these studies are summarized in Table 2.

Table 2. Characteristics of the selected studies

Lange, 1990	**USA**	**Clinical trial**	**Heroin**	**Group 1: BUP (8 mg) for 18 days, from day 19-36 daily**	**M:8**	**26-45**	**Sublingual 36 days**	**12 (71%) of patients had higher levels of ALT and AST, those elevations could not be directly related to BUP.**
				Group 2: BUP (8mg) for 18 days, from day 19-36 alternate days.	**M:10**			
Singh, 1992	India	Case report	Abused BUP (60 mg)		M:18	Average 26	IV Mean 14 months	No change in the liver function.

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				Experimental group: BUP 12 mg in 8 divided doses during 24 h	M:17 F:3	32.2 ± 6.2	IM 24h	No patient had abnormal ALT at the end. Five patients had AST levels above the upper limit at the end.
Assadi, 2004	Iran	Clinical trial	Opioid	Conventional group: BUP administration as follows: 3 mg/day on day 1 3 mg/day on day 2 2.7 mg/day on day 3 1.2 mg/day on day 4 0.6 mg/day on day 5	M:20	30.5± 8.9	IM 5 days	Five patients at the end of the study had ALT levels above the upper limit of normal. ALT levels never exceeded twice the upper limits of normal. Eight patients at the end showed AST levels above the normal upper limit. AST level of one patient in this group exceeded twice the upper normal limit
Di Petta, 2005	Italy	Clinical trial	Polydrugs	BUP (average dose 28 mg) treatment group	M:610 F:40	Average 30	Sublingual 3o months	No change in the liver function.
Lofwall, 2005	USA	Clinical trial	Opioid	BUP (average dose 8.9 mg) treatment group	M:57 F:27	32.5± 5.7	Sublingual 16 weeks	There is no evidence that BUP is selectively related to abnormal liver function compared with methadone.
				Methadone (average dose 54 mg) treatment group	M:59 F:21	32.7 ± 6.0	Orally 16 weeks	
Gerra, 2006	Italy	Clinical trial	Heroin	Group 1: BUP (4mg)+naltrexone (50mg) treatment group	30	31.51± 1.3	BUP: Sublingual Naltrexone: Orally 12 weeks	No change in the liver function.
				Group 2: Naltrexone (50 mg) treatment group	30	30.29± 0.92		

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				Group 2: Naltrexone (50 mg) treatment group	30	30.29± 0.92		
Fiellin, 2008	USA	Clinical trial	Opioid	BUP/NLX (16 to 24 mg) treatment group	M: 43 F: 10	36± 9.4	Sublingual 2-5 year	No change in the liver function.
Bogenschutz, 2010	USA	Clinical trial	Opioid	BUP treatment group: 24 (31%) received 2 to 8 mg and 53 (68%) received 9 to 14 mg.	M:42 F: 32	19.14 ± 1.4	Sublingual 12 weeks	No change in the liver function.
				Detox group: 20 (27%) received 2 to 8 mg, 43 (59%) received 9 to 16 mg, and 10 (14%) received 17 to 24 mg	M:48 F:30	19.2 ± 1.6	Sublingual 2 weeks	
Strain, 2011	USA	Clinical trial	Heroin	Soluble-film BUP (16 mg) treatment group	M:14 F:4	40.5	Sublingual 5 days	One patient had normal liver function at baseline but at the end, he/she had a significant increase (3 times) in the upper limit of normal. Follow-up liver function tests showed slight increase in AST (105 U/L).
				BUP/NLX (16 mg) treatment group	M:11 F:5	40.1		

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Saxon, 2013	USA	Clinical trial	Opioid	BUP (24 ± 8.2) treatment group	M:242 F:98	39.3 ± 11.3	Sublingual 24 weeks	9 (2.1%) of subjects had extreme increase in liver enzyme levels. They were more likely to have both hepatitis C and hepatitis B seroconversion during the study
Al-Tawil, 2013	Sweden	Clinical trial	-	Younger group: BUP	M:12 F:25	53.8±3.1	Transdermal patch	A transient increase in
				5 µg/h) treatment as analgesic drug				liver enzymes for two participants in the younger age group, which returned to normal at the end.
				Elderly group: BUP (5 µg/h) treatment as analgesic drug	M: 8 F:29	78.7 ± 3.3	2 weeks	
Haight, 2019	USA	Clinical trial	Opioid	Two groups under BUP-XR Group 1: six doses of BUP-XR 300 Group 2: two doses of BUP-XR 300 mg followed by four doses of BUP-XR 100 mg	Group1: M:132 F:64 Group2: M:128 F:66	18-65	Subcutaneous injection for 28 days	Increased liver enzymes for some individuals without liver injury
Ciftci Demirci, 2015	USA	Case Series	Heroin	BUP/NLX (4.79±1.76 mg/ day) treatment group	59	17.25±0.81	Sublingual 8 weeks	The liver enzyme levels at weeks 2 and 4 were significantly higher than the baseline No change in liver function at week 8.
Fareed, 2017	USA	Cross-sectional		BUP (23± 9 mg) treatment group	M:31	47±13	Sublingual 6 year	No change in liver function.

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The results of RCT studies conducted by Lofwall et al. (2005), Di Petta & Leonardi (2005), Gerra et al. (2006), Fiellin et al. (2008), Bogenschutz et al. (2010), Al-Tawil et al. (2013), and Haight et al., (2019) did not report BUP hepatotoxicity in any patient (40-44). Lofwall et al. (2005) assessed the liver consequence of BUP and oral methadone in 164 opioid-dependent patients (84 receiving BUP and 80 receiving methadone). All patients had normal baseline AST levels. However, 39.6% (n=19) of the BUP and 26.2% (n = 11) of the methadone-treated patients showed an increase in AST level during treatment. Twenty-five patients had abnormal levels of ALT at baseline (13 patients in the BUP group and 12 patients in the methadone group). Specifically, 17 out of 43 patients under BUP treatment (39.5%) and 11 out of 40 patients under methadone treatment (27.5%) showed an elevation in ALT level. These increases may be associated with other factors such as infectious diseases, illicit drugs, alcohol consumption, environmental pollutants, and chronic diseases. They suggested that the abnormality in the liver enzymes was not induced by BUP and methadone (45). Di Petta & Leonardi (2005) conducted an RCT to evaluate the efficacy and safety of high-dose sublingual BUP tablets in 650 addicted individuals with previous methadone treatment. The subjects included in the study had no history of acute or chronic liver diseases. Liver function was normal in all patients (46). Gerra et al. (2006) determined the impact of 50 mg oral naltrexone daily (Nalorex) as well as 50 mg oral naltrexone plus BUP (4 mg sublingual) on the levels of liver enzymes in 60 heroin-addicted individuals who were divided into two groups for 12 weeks. The liver function did not change in any subject (42). Fiellin et al. (2008) evaluated the effect of BUP/NLX on the liver function of 53 opioid patients with a normal liver enzyme at the baseline. BUP administration was performed at 16 mg/d and 24 mg/d doses and serum levels of liver enzymes were analyzed every 12 weeks. Result showed that the liver function did not change in any patient (43). Bogenschutz et al. (2010) assessed alterations in the serum levels of transaminase related to BUP medication. Twenty-eight out of 152 patients were found hepatitis C (HCV) positive at baseline, with four subjects being seroconverted within 12 weeks in each group. The participants were randomized into groups including 2-week detoxification with BUP/NLX (DETOX) or 12 weeks of BUP/NLX (BUP) treatment. The levels of transaminases were analyzed at baseline, 4, 8, and 12 weeks. HCV status was significantly related to ALT and AST levels. HCV status affected ALT and AST levels in subjects in the DETOX group but not in the BUP group. The increase was 5 times greater than the upper limit of the normal range. They did not find evidence of hepatotoxicity by BUP in any group (44). Al-Tawil et al. (2013) conducted an open-label RCT to study BUP transdermal patches for treating pain in healthy elderly (≥75 years) and younger (50–60 years) individuals (37 participants in each group). The subjects received BUP 5 µg/h transdermal patch for two weeks. No hepatotoxicity was reported in this study (45). An RCT (phase 3 trial) was conducted at 36 treatment centers in the USA on adults of 18-65 years who received BUP-XR (extended-release BUP) at dose 300 mg/300 mg (n= 203) and dose 300 mg/100 mg (n=201) for 28 days. Although elevation in the levels of liver enzymes was observed for some individuals under BUP-XR treatment, BUP could not cause liver damage (46). However, four studies Lange et al. (48), Assadi et al. (2004)(49), Strain et al. (2011)(50), and Saxon et al. (2013)(51) reported hepatotoxicity under BUP treatment. Lange et al. (1990) recruited 18 heroin-dependent addicts without a clinical symptom of liver disease and divided them into two BUP intervention groups. All patients completed the treatment course (36 days), and were followed for 4 weeks after discharge. They reported elevated serum levels of aminotransferase enzymes (AST or ALT) in some patients under BUP treatment.

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However, those elevations could not be directly related to BUP treatment (47). Assadi et al. (2004)(35) randomized 40 opioid-addicted patients in two BUP-treated groups. Twenty patients have been treated with BUP at a dose of 12 mg in 8 divided doses for 24 h (experimental group), while 20 patients received the following: 3 mg/day on day 1; 3 mg/day on day 2; 2.7 mg/day on day 3; 1.2 mg/day on day 4; 0.6 mg/day on day five within 24 h (conventional group) for five days. No patient had abnormal ALT, while five patients had AST levels above the upper limit in the experimental group. Also, five patients had ALT levels above the normal range in the conventional group (48). Strain et al. (2011) evaluated liver function in 34 opioid-dependent subjects. They divided patients into BUP and BUP/NLX film-treated groups. Patients received either BUP (16 mg) or BUP/NLX (16/4 mg) for five days. Liver enzymes did not change after the treatment (49). Saxon et al. (2013) conducted an RCT study with four phases to assess the liver outcomes in patients treated with BUP/NLX or methadone. A total of 1,269 participants were randomly assigned to two treated groups: firstly, at a 1:1 ratio and later at a 2:1 BUP/NLX: MET ratio. The subjects administrated for 24 weeks, and liver enzymes assessed eight times in this period. Nine participants in the BUP group and 15 participants in the methadone group showed elevated liver enzyme levels.

Discussion

Buprenorphine undergoes extensive first pass hepatic extraction and is metabolized primarily by the cytochrome P450 system (CYP 3A4)(51). BUP is well tolerated at recommended sublingual dosages, while some individuals have an increase in blood alanine aminotransferase (ALT) activity (52). The risk of diversion and toxicity of opioid prescription drugs, including BUP, causes significant concerns (53). There are two possible molecular pathways for buprenorphine-induced toxicity. First, BUP is a lipophilic tertiary amine (54). Several such drugs are taken up by mitochondria and impair fatty acid b-oxidation and/or mitochondrial energy production, causing adenosine triphosphate (ATP) depletion and cell death (55). Second, BUP depletes cellular glutathione (GSH) in cultured human hepatocytes (56). Although the Food and Drug Administration (FDA) approved the safety of BUP, data about its safety in liver is controversial (57). This literature review investigated the effects of BUP therapy on the liver function in opioid-dependent subjects without liver diseases. According to our research, there was no strong evidence confirming the association between BUP administration and increased liver enzyme levels (58, 59). However, some clinical studies indicated liver injury in BUP-treated patients. Hepatotoxicity was found only in patients who had a history of hepatitis C or hepatitis B seroconversion (60, 61). Additionally, Ciftci Demirci et al. found an increase in the liver enzymes in the participants after 2 and 4 weeks, but the liver enzymes returned to the normal range after 8 weeks. In their study, 60% of patients used psychoactive drugs so the interaction between BUP and psychoactive drugs may have been the cause of transient elevation of liver enzymes in their study (9). Although Lange et al. reported that 71% of patients had elevated ALT and AST levels, they did not report any clinical signs or symptoms related to liver injury in BUP users. They declared that those increases could not be directly associated with buprenorphine. The articles selected in the present study were conducted on patients without a history of liver diseases, and our findings did not indicate the hepatotoxicity of BUP. However, it was reported that BUP administration in patients with viral infections could trigger liver dysfunction and hepatitis. Viral hepatitis such as Hepatitis B and C were more implicated, and anti-HCV antibodies or positive HCV-RNA were positive in some patients. It is suggested that BUP could trigger hepatitis in a few patients whose mitochondrial function is already deteriorated by other toxic factors. Furthermore, Herve et al. (2004) observed that cytolysis and jaundice in their study patients

improved quickly in all subjects, and ALT levels returned to the normal range during the third week of the monitoring period. It seems that BUP can cause liver failure in susceptible patients, possibly through direct mitochondrial toxicity (62). Although a higher risk of hepatotoxicity in HCV carrier patients under BUP therapy has been found, there is not sufficient evidence for this association. In patients under treatment with BUP with positive HCV, mitochondrial dysfunction induced by viral infection caused an increased risk of hepatotoxicity (60). In conclusion, although the association between BUP administration and hepatitis is not clear, monitoring of liver function should be improved in patients with mitochondrial dysfunction induced by viral infections or other toxic factors.

Conclusion

No strong evidence was found for hepatotoxicity of BUP in this study. Elevation in the liver enzyme levels in some patients may be related to other factors such as infectious diseases, illicit drugs, alcohol consumption, environmental pollutants, and chronic diseases. More experimental and clinical studies should be conducted to address this question.

Acknowledgment

Not applicable.

Conflict of interest

The Authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

1.Mattick RP, Breen C, Kimber J, Davoli MJCdosr. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews. 2014; 2:CD002207.

2.Wiffen PJ, Wee B, Derry S, Bell RF, Moore RAJCDoSR. Opioids for cancer pain-an overview of Cochrane reviews. Cochrane Database of Systematic Reviews. 2017;7: CD012592.

3.Heo Y-A, Scott LJJCd. Buprenorphine/Naloxone (Zubsolv®): A Review in Opioid Dependence. CNS Drugs. 2018;32(9):875-82.

4.Hickman M, Steer C, Tilling K, Lim AG, Marsden J, Millar T, et al. The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom. Addiction. 2018; 113(8): 1461-76.

5.Whelan PJ, Remski KJJonirp. Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. Journal of Neurosciences in Rural Practice. 2012;3(1):45-50.

6.Pergolizzi Jr JV, Magnusson P, LeQuang JA, Breve F, Mitchell K, Chopra M, et al. Transdermal buprenorphine for acute pain in the clinical setting: a narrative review. Journal of Pain Research. 2021;14:871-879.

7.Samini M, Farkhondeh T, Azimi-Nezhad M, Samarghandian SJCMP. Impact of Buprenorphine on Learning and Memory Ability, Oxidative Status and Inflammation in the Hippocampus of Rats. Current Molecular Pharmacology. 2021;14(4):597-603.

8.Linas BP, Savinkina A, Madushani R, Wang J, Yazdi GE, Chatterjee A, et al. Projected estimates of opioid mortality after community-level interventions. JAMA Network Open. 2021;4(2):e2037259-e.

9.Ciftci Demirci A, Gunes H, Adaletli H, Bulanik E, Erdogan A. Liver enzyme levels in adolescent patients treated with buprenorphine and additional psychotropic agents. The American journal of drug and alcohol abuse. 2015;41(1):107-13.

10.Dong R, Wang H, Li D, Lang L, Gray F, Liu Y, et al. Pharmacokinetics of Sublingual Buprenorphine Tablets Following Single and Multiple Doses in Chinese Participants With and Without Opioid Use Disorder. Drugs R D. 2019;19(3):255-65.

11.Mariottini C, Gergov M, Ojanperä IJDT. Analysis, Determination of buprenorphine, norbuprenorphine, naloxone, and their glucuronides in urine by liquid chromatography–tandem mass spectrometry. Drug Testing and Analysis. 2021;13(9):1658-67.

12.Sychev DA, Ashraf GM, Svistunov AA, Maksimov ML, Tarasov VV, Chubarev VN, et al. The cytochrome P450 isoenzyme and some new opportunities for the prediction of negative drug interaction in vivo. Drug Design, Development and Therapy. 2018;12:1147-1156.

13.Coe MA, Lofwall MR, Walsh SL. Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations. Journal Addict Medical. 2019;13(2):93-103.

14.Van Hoogdalem MW, Johnson TN, McPhail BT, Kamatkar S, Wexelblatt SL, Ward LP, et al. Physiologically-Based Pharmacokinetic Modeling to Investigate the Effect of Maturation on Buprenorphine Pharmacokinetics in Newborns with Neonatal Opioid Withdrawal Syndrome. Clinical Pharmacology & Therapeutics (CPT). 2022;111(2):496-508.

15.Blazes CK, Morrow JD. Reconsidering the Usefulness of Adding Naloxone to Buprenorphine. Frontiers in Psychiatry. 2020; 11: 549272.

16.Soyka M. New developments in the management of opioid dependence: focus on sublingual buprenorphine-

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[DOR: 20.1001.1.22285105.2022.12.3.2.0]

[DOI: 10.18502/jabs.v12i3.10710]

naloxone. Substance abuse and rehabilitation. 2015;6:1-14.
17.Irvine MA, Oller D, Boggis J, Bishop B, Coombs D, Wheeler E, et al. Estimating naloxone need in the USA across fentanyl, heroin, and prescription opioid epidemics: a modelling study. Lancet Public Health. 2022;7(3):e210-e8.
18.Chiang CN, Hawks RLJD, dependence A. Pharmacokinetics of the combination tablet of buprenorphine and naloxone. Drug and Alcohol Dependence. 2003;70(2):S39-S47.
19.Maharao N, Venitz J, Gerk PMJB, Disposition D. Use of generally recognized as safe or dietary compounds to inhibit buprenorphine metabolism: potential to improve buprenorphine oral bioavailability. Biopharmaceutics & Drug Disposition. 2019;40(1):18-31.
20.Soyka MJDicn. Treatment of opioid dependence with buprenorphine: current update. Dialogues in Clinical Neuroscience. 2022;19(3):299-308.
21.Martin SA, Chiodo LM, Bosse JD, Wilson AJAoIM. The next stage of buprenorphine care for opioid use disorder. Annals of Internal Medicine. 2018;169(9):628-35.
22.Erdoğan A, Topcuoğlu M, Coşkun MN, Cinemre B, Kulaksızoğlu B, Kuloğlu MMJHPC, et al. Comparison of naltrexone implant and oral buprenorphine-naloxone in the treatment of opiate use disorder. Human Psychopharmacology. 2022;37(2):e2813.
23.Webster L, Gudin J, Raffa RB, Kuchera J, Rauck R, Fudin J, et al. Understanding Buprenorphine for Use in Chronic Pain: Expert Opinion. Pain Medicine. 2020;21(4):714-23.
24.Yamamoto T, Shono K, Tanabe SJJoP, Therapeutics E. Buprenorphine activates μ and opioid receptor like-1 receptors simultaneously, but the analgesic effect is mainly mediated by μ receptor activation in the rat formalin test. The Journal of Pharmacology and Experimental Therapeutics. 2006;318(1):206-13.
25.Stein C, Machelska HJPr. Modulation of peripheral sensory neurons by the immune system: implications for pain therapy. Pharmacological Reviews. 2011;63(4):860-81.
26.Dahan A, Yassen A, Bijl H, Romberg R, Sarton E, Teppema L, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. The British Journal of Anaesthesia. 2005;94(6):825-34.
27.Dahan A, Yassen A, Romberg R, Sarton E, Teppema L, Olofsen E, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. British Journal of Anaesthesia. 2006;96(5):627-32.
28.Garimella T, Wang R, Luo WL, Wastall P, Kandoussi H, Demicco M, et al. Evaluation of drug-drug interaction between daclatasvir and methadone or buprenorphine/naloxone. Journal of the International AIDS Society. 2014;17(4):19628.
29.Feng H-P, Guo Z, Caro L, Marshall WL, Liu F, Panebianco D, et al. No Pharmacokinetic Interactions Between Elbasvir or Grazoprevir and Buprenorphine/Naloxone in Healthy Participants and Participants Receiving Stable Opioid Agonist Therapy. Clinical and Translational Science. 2018;11(6):562-72.
30.Etaee F, Asadbegi M, Taslimi Z, Shahidi S, Sarihi A, Soleimani Asl S, et al. The effects of methamphetamine and buprenorphine, and their interaction on anxiety-like behavior and locomotion in male rats. Neuroscience letters. 2017;655:172-8.
31.Caille F, Goislard M, Kuhnast B, Auvity S, Goutal S, Tournier NJJoLC, et al. An original radio-biomimetic synthesis of C-11-nor-buprenorphine for PET imaging. Nuclear Medicine and Biology. 2019;62(1):S237-S8.
32.Holmquist GLJPM. Opioid metabolism and effects of cytochrome P450. Pain Medicine. 2009;10(suppl_1):S20-S29.
33.Van Hoogdalem MW, Wexelblatt SL, Akinbi HT, Vinks AA, Mizuno TJP.therapeutics: A review of pregnancy-induced changes in opioid pharmacokinetics, placental transfer, and fetal exposure: Towards fetomaternal physiologically-based pharmacokinetic modeling to improve the treatment of neonatal opioid withdrawal syndrome. Pharmacology & Therapeutics. 2021:108045.
34.Moody DE, Fang WB, Morrison J, McCance-Katz E. Gender differences in pharmacokinetics of maintenance dosed buprenorphine. Drug Alcohol Depend. 2011;118(2-3):479-83.
35.McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. The American journal on addictions. 2010;19(1):4-16.
36.Brown SM, Campbell SD, Crafford A, Regina KJ, Holtzman MJ, Kharasch ED. P-glycoprotein is a major determinant of norbuprenorphine brain exposure and antinociception. The Journal of pharmacology and experimental therapeutics. 2012; 343(1):53-61.
37.Lintzeris N, Mitchell TB, Bond AJ, Nestor L, Strang J. Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. Drug Alcohol Depend. 2007;91(2-3):187-94.
38.Pirnay S, Megarbane B, Declèves X, Risède P, Borron SW, Bouchonnet S, et al. Buprenorphine alters desmethylflunitrazepam disposition and flunitrazepam toxicity in rats. Toxicological sciences. 2008;106(1):64-73.
39.Cohier C, Chevillard L, Risède P, Roussel O, Mégarbane B. Respiratory effects of buprenorphine/naloxone alone and in combination with diazepam in naive and tolerant rats. Toxicology letters. 2014;228(2):75-84.
40.Balhara YPS, Jain R. A urinalysis-based study of buprenorphine and non-prescription opioid use among patients on buprenorphine maintenance. J Pharmacol Pharmacother. 2012;3(1):15-9.
41.Gerra G, Fantoma A, Zaimovic A. Naltrexone and buprenorphine combination in the treatment of opioid dependence. Journal of psychopharmacology

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[DOR: 20.1001.1.22285105.2022.12.3.2.0]
[DOI: 10.18502/jabs.v12i3.10710]

(Oxford, England). 2006;20(6):806-14.
42.Fiellin DA, Moore BA, Sullivan LE, Becker WC, Pantalon MV, Chawarski MC, et al. Long-term treatment with buprenorphine/naloxone in primary care: results at 2-5 years. The American journal on addictions. 2008;17(2):116-20.
43.Bogenschutz MP, Abbott PJ, Kushner R, Tonigan JS, Woody GE. Effects of buprenorphine and hepatitis C on liver enzymes in adolescents and young adults. Journal of Addiction Medicine. 2010;4(4):211-6.
44.Lofwall MR, Stitzer ML, Bigelow GE, Strain ECJAD, Treatment T. Comparative safety and side effect profiles of buprenorphine and methadone in the outpatient treatment of opioid dependence. Addictive Disorders & Their Treatment. 2005;4(2):49-64.
45.Di Petta G, Leonardi CJHA, Problems RC. Buprenorphine high-dose, broad spectrum, long-term treatment: A new clinical approach to opiate alkaloid dependency. Heroin Addiction And Related Clinical Problems. 2005;7(3):21-5.
46.Al-Tawil N, Odar-Cederlöf I, Berggren AC, Johnson HE, Persson J. Pharmacokinetics of transdermal buprenorphine patch in the elderly. European journal of clinical pharmacology. 2013;69(2):143-9.
47.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(1):19-28.
48.Assadi SM, Hafezi M, Mokri A, Razzaghi EM, Ghaeli P. Opioid detoxification using high doses of buprenorphine in 24 hours: a randomized, double blind, controlled clinical trial. Journal of substance abuse treatment. 2004;27(1):75-82.
49.Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. Clinical pharmacology and therapeutics. 2011;89(3):443-9.
50.Saxon AJ, Ling W, Hillhouse M, Thomas C, Hasson A, Ang A, et al. Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: a randomized trial. Drug Alcohol Depend. 2013;128(1-2):71-6.
51.Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GEJCP, Therapeutics. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clinical Pharmacology & Therapeutics. 1994;55(5):569-80.
52.Ruhl CE, Everhart JE. Upper limits of normal for alanine aminotransferase activity in the United States population. Hepatology (Baltimore, Md). 2012;55(2):447-54.
53.Soyka M. Buprenorphine and buprenorphine/naloxone intoxication in children - how strong is the risk? Current drug abuse reviews. 2013;6(1):63-70.
54.Vodovar D, Chevillard L, Caillé F, Risède P, Pottier G, Auvity S, et al. Mechanisms of respiratory depression induced by the combination of buprenorphine and diazepam in rats. The British Journal of Anaesthesia. 2022;128(3):584-95.
55.Wajner M, Amaral AU. Mitochondrial dysfunction in fatty acid oxidation disorders: insights from human and animal studies. Bioscience Reports. 2015;36(1):e00281-e.
56.Berson A, Fau D, Fornacciari R, Degove-Goddard P, Sutton A, Descatoire V, et al. Mechanisms for experimental buprenorphine hepatotoxicity: major role of mitochondrial dysfunction versus metabolic activation. The Journal of Hepatology. 2001;34(2):261-9.
57.Lavonas EJ, Severtson SG, Martinez EM, Bucher-Bartelson B, Le Lait MC, Green JL, et al. Abuse and diversion of buprenorphine sublingual tablets and film. Journal of substance abuse treatment. 2014;47(1):27-34.
58.Singh R, Mattoo S, Malhotra A, Varma VJAPS. Cases of buprenorphine abuse in India. Acta Psychiatrica Scandinavica. 1992;86(1):46-8.
59.Fareed A, Scheinberg K, Gale RB, Stout S, Vayalapalli S, Drexler KJAD, et al. Effect of Buprenorphine on liver function tests for patients undergoing long-term maintenance treatment. Addictive Disorders & Their Treatment. 2014;13(3):133-7.
60.Hervé S, Riachi G, Noblet C, Guillement N, Tanasescu S, Goria O, et al. Acute hepatitis due to buprenorphine administration. European Journal of Gastroenterology & Hepatology. 2004;16(10):1033-7.
61.Petry NM, Bickel WK, Piasecki D, Marsch LA, Badger GJJAJoA. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. The American Academy of Addiction Psychiatry. 2000;9(3):265-9.
62.Zuin M, Giorgini A, Selmi C, Battezzati PM, Cocchi CA, Crosignani A, et al. Acute liver and renal failure during treatment with buprenorphine at therapeutic dose. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. Digestive and Liver Disease. 2009;41(7):e8-e10.

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