



RESEARCH ARTICLE

A Study on Effect of Buprenorphine- Naloxone Maintenance Treatment on Liver Function in Opioid Dependence Patients

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ABSTRACT

Background: Buprenorphine–naloxone is widely used for maintenance treatment of opioid dependence. Although generally well tolerated, its potential effects on liver function warrant attention, particularly during long-term treatment. Evidence regarding hepatic biochemical abnormalities among patients receiving maintenance treatment remains limited. **Aim:** To assess liver function parameters in patients with opioid dependence receiving buprenorphine–naloxone maintenance treatment and to examine their association with the prescribed dose. **Methods:** This cross-sectional study was conducted at the Outpatient Opioid Assisted Treatment Clinic, Institute of Mental Health, Amritsar, Punjab. A total of 150 patients aged 18–60 years who had received buprenorphine–naloxone maintenance treatment for at least six months were included. Patients with identified HIV, hepatitis B or C infection, specified psychiatric comorbidities, or recent use of other psychoactive substances were excluded. Liver function parameters, including total and direct bilirubin, SGOT, SGPT, alkaline phosphatase, total protein, albumin, and globulin, were assessed. Spearman's rank correlation analysis was performed to examine the associations between the prescribed dose and liver function parameters. **Results:** Elevated total and direct bilirubin levels were observed in 10% of participants each. SGOT was elevated in 12.7%, while SGPT was elevated in 24%, representing the most frequently observed biochemical abnormality. Mean SGOT and SGPT levels were 28.42 ± 14.89 IU/L and 37.75 ± 19.62 IU/L, respectively. No statistically significant correlations were observed between prescribed dose and total bilirubin, direct bilirubin, SGOT, SGPT, alkaline phosphatase, total protein, or globulin. The correlation between the prescribed dose and serum albumin was borderline ($\rho = -0.160$, $p = 0.050$). **Conclusion:** Liver biochemical abnormalities were observed in a proportion of patients receiving buprenorphine–naloxone maintenance treatment. No consistent association between prescribed dose and liver function parameters was demonstrated, highlighting the importance of continued clinical monitoring during maintenance treatment.

Keywords: opioid dependence; buprenorphine–naloxone; liver function tests; hepatic enzymes; maintenance treatment.

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INTRODUCTION

Opioid dependence syndrome is a significant and growing public health concern. It often requires long-term treatment and comprehensive care to reduce individual risks, minimize criminal behavior, and improve long-term physical and mental health outcomes. Several types of drugs are used to treat opioid dependence syndrome, among which the buprenorphine-naloxone combination is an established and effective treatment option. The combination contains buprenorphine and naloxone in a 4:1 ratio [1].

Patients with opioid dependence may consume various types of opioids. Opioids such as tramadol, methadone, fentanyl, and oxycodone undergo hepatic metabolism, involving cytochrome P450 enzymes. Other opioids, including hydromorphone, oxycodone, and morphine, undergo hepatic glucuronidation, primarily mediated by uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7) [2]. Opioid metabolism and associated cellular processes, including lipid peroxidation and mitochondrial oxidative stress, may contribute to hepatic injury [3]. Furthermore, people who inject heroin, particularly those who share needles, are at increased risk of blood-borne infections,

including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Chronic HCV infection is an important cause of liver disease in this population and may progress to liver cirrhosis, hepatic failure, and hepatocellular carcinoma [4].

In Punjab, India, the buprenorphine–naloxone combination is a mainstay of treatment in Outpatient Opioid Assisted Treatment (OOAT) clinics for patients with opioid dependence syndrome. Although generally well tolerated, buprenorphine–naloxone may be associated with adverse effects, including potential hepatic biochemical abnormalities. Buprenorphine has been associated with liver injury, although its hepatic safety profile differs from that of methadone. Given the potential hepatic effects of opioid exposure and the increased risk of viral hepatitis among people who inject drugs, careful monitoring of liver function is important, particularly in patients with pre-existing hepatic disease or viral hepatitis [5]. However, evidence regarding the effects of buprenorphine–naloxone maintenance treatment on liver biochemical parameters remains limited. Furthermore, Indian studies examining these effects appear to be scarce, highlighting the need for further research in this population.

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MATERIAL AND METHODS

This cross-sectional study was conducted at the Outpatient Opioid Assisted Treatment (OOAT) Clinic in Amritsar, Punjab, India. Patients aged 18–60 years who were diagnosed with opioid dependence syndrome according to the International Classification of Diseases, 10th Revision (ICD-10), had received buprenorphine-naloxone maintenance treatment for at least six months, and provided informed consent were included in the study.

Patients with comorbid medical conditions were excluded. Screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) was performed. Patients with known psychiatric disorders who were receiving treatment were also excluded. Additionally, patients who had used substances other than opioids, including alcohol, benzodiazepines, barbiturates, cannabis, and stimulants, during the six months preceding enrolment were excluded, with caffeine and nicotine use being permitted.

Patients who continued to use illicit or non-prescribed opioids, including heroin, morphine, tramadol, and oxycodone, were also excluded. Opioid use was assessed using urine screening tests and information obtained from caregivers. Patients who were non-adherent to buprenorphine-naloxone maintenance treatment, as assessed using urine screening tests and

caregiver reports, and those presenting with active opioid withdrawal symptoms on clinical assessment were likewise excluded.

Sample Size

A total of 150 participants were included in the study. The sample size was estimated using the formula for cross-sectional studies with a qualitative outcome, as described in reference [6].

Sample size = $4pq/L^2$

Where,

4: 95% confidence level

p: proportion of elevated liver enzymes in patients treated with buprenorphine naloxone combination, which is 40% [5]

q: $100-p = 60\%$

L: allowable error = 8%

After substituting these values in the above formula, the sample size estimated was 150. Thus, in the present study 150 participants were enrolled using a simple random sampling method.

Ethical clearance from our institute's ethics committee for intramural projects and written informed consent from all participants were obtained.

Approximately 320 patients attending the Outpatient Opioid Assisted Treatment (OOAT) Clinic were screened, of whom 260 met the inclusion and exclusion criteria. Of these, 50 declined to provide informed consent. Among the remaining 210 patients, 60 did not complete the study because they did not return for follow-up with their laboratory reports. Consequently, 150 participants were included in the final analysis.

Participants were interviewed by the investigator to obtain sociodemographic information and a clinical history, including medical comorbidities such as hypertension, diabetes mellitus, and cardiac disorders, as well as other chronic medical conditions and current medication use.

Blood samples were collected for the assessment of liver biochemical parameters, including total bilirubin, direct bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), total protein, serum albumin, and serum globulin.

RESULTS

Table 1 describes the demographic profile of the study population. The mean age of the sample population was around 41 years and about 30% of them

were educated till mid-school. Sikhs form major study sample (85%) and only 4 % of them were unemployed. The majority of them belonged to the upper lower and

middle socio-economic class with 84% of them currently working.

Table 1: Demographic details of study population

Parameter (N = 150)		Mean $\pm$ S.D. (Min.- Max.)/ Frequency (%)
Age in years		40.63 $\pm$ 11.29 (19-60)
Education in years		6.48 $\pm$ 4.46 (0-16)
Religion	Sikh	127 (84.7%)
	Hindu	21 (14%)
	Muslim	1 (0.7%)
	Christian	1 (0.7%)
Marital Status	Married	128 (85.3%)
	Unmarried	16 (10.7%)
	Separated	3 (2.0%)
	Widowed	3 (2.0%)
Occupation	Farmer	56 (37.3%)
	Labourer	50 (33.3%)
	Employed	38 (25.3%)
	Unemployed	6 (4.0%)

Among the 150 participants, the most frequently prescribed buprenorphine–naloxone dose was 4 mg + 1 mg, used by 48 patients (32.0%), followed by 2 mg + 0.5 mg in 41 patients (27.3%). Together, these two dose regimens accounted for nearly 60% of the sample.

Higher-dose regimens of 6 mg + 1.5 mg and 8 mg + 2 mg were used by 10.0% and 8.0% of patients, respectively, while the remaining lower-dose regimens were prescribed to smaller proportions of participants [Table 2].

Table 2: Dose of Buprenorphine + Naloxone in study population

Dose in mg (N=150)	No. of Patients (%)
4 + 1	48 (32%)
2 + 0.5	41 (27.3%)
6 + 1.5	15 (10%)
8 + 2	12 (8%)
1.6 + 0.4	11 (7.3%)
0.8 + 0.2	11 (7.3%)
3.2 + 0.8	6 (4%)
1.2 + 0.3	6 (4%)

Mean liver function parameters showed total bilirubin of 0.84 ± 0.19 , SGOT of 28.42 ± 14.89 , and SGPT of 37.75 ± 19.62 . Mean total protein, serum

albumin, and serum globulin levels were 6.96 ± 0.28 , 3.90 ± 0.25 , and 3.07 ± 0.16 , respectively [Table 3].

Table 3: Values of various Blood Investigations

Sr. No.	Blood Parameters (N = 150)	Mean (S.D.)
1.	Total Bilirubin (mg/dL)	0.84 (0.19)
2.	Direct Bilirubin (mg/dL)	0.30 (0.24)
3.	SGOT (IU/L)	28.42 (14.89)
4.	SGPT (IU/L)	37.75 (19.62)
5.	ALP (IU/L)	76.20 (10.77)
6.	Total Proteins (g/dL)	6.96 (0.28)
7.	Serum Albumin (g/dL)	3.90 (0.25)
8.	Serum Globulin (g/dL)	3.07 (0.16)

Elevated total and direct bilirubin levels were observed in 10% of participants each. SGOT levels were elevated in 12.7% of participants, whereas SGPT levels

were elevated in 24% of participants. SGPT was the most frequently elevated parameter among the 150 study participants [Table 4].

Table 4: Number of patients having deranged blood parameters

Blood Parameter	High	Normal
Total Bilirubin (>1mg/dL)	15 (10%)	135 (90%)
Direct Bilirubin (>0.4mg/dL)	15 (10%)	135 (90%)
SGOT (>40IU/L)	19 (12.7%)	131 (87.3%)
SGPT (>40IU/L)	36 (24%)	114 (76%)

Spearman correlation analysis was performed to examine the association between the prescribed buprenorphine dose and liver function test parameters. The buprenorphine dose showed no statistically significant correlation with total bilirubin, direct bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, total protein, albumin, or globulin ($p > 0.05$ for all parameters). The correlation coefficients were

small in magnitude, indicating that variations in the prescribed buprenorphine dose were not associated with clinically meaningful variations in the measured liver function parameters in the study population. Overall, these findings suggest that, within the range of doses studied, buprenorphine dose was not significantly associated with alterations in the assessed liver function tests [Table 5].

Table 5: Association between buprenorphine dose and liver function test parameters

LFT parameter	Spearman rho	p value
Total bilirubin	0.082	0.318
Direct bilirubin	0.141	0.085
SGOT (AST)	0.009	0.914
SGPT (ALT)	0.034	0.683
Alkaline phosphatase (ALP)	-0.073	0.372
Total protein	-0.120	0.142
Albumin	-0.160	0.050
Globulin	0.156	0.057

DISCUSSION

The present cross-sectional study assessed liver function parameters in 150 patients with opioid dependence receiving buprenorphine–naloxone maintenance treatment for at least six months. The study characterized the pattern of liver biochemical abnormalities and examined the association between the prescribed buprenorphine–naloxone dose and selected liver function parameters. The findings provide insight into hepatic biochemical profiles among patients receiving maintenance treatment in an outpatient opioid-assisted treatment setting.

In the present study, elevated total and direct bilirubin levels were observed in 10% of participants each. Although the group mean values were not markedly elevated, a proportion of participants exhibited abnormal liver biochemical parameters. Group means alone may not adequately reflect the distribution of abnormalities among individuals; therefore, the proportion of participants with values exceeding the specified reference limits provides complementary information about the observed biochemical abnormalities.

The proportion of participants with elevated

transaminase levels in the present study was higher than that reported in some previous studies of buprenorphine-based treatment. Soyka *et al.*, (2014) reported that approximately 1–2% of patients had predominantly mild elevations in liver enzymes, with none meeting the criteria for drug-induced liver injury. No serious liver-related adverse events were reported, although two non-serious cases of elevated liver enzymes were documented [7]. Similarly, Saxon *et al.*, (2013), in a study involving 1,269 opioid-dependent participants receiving buprenorphine or methadone, found no evidence of liver damage during the initial six months of treatment in either group [8]. These findings generally support the hepatic tolerability of buprenorphine-based maintenance treatment. However, direct comparisons with the present study should be made cautiously because of potential differences in participant characteristics, baseline hepatic status, laboratory reference limits, treatment exposure, and outcome definitions.

Vergara-Rodriguez *et al.*, (2011) found no measurable hepatic toxicity associated with buprenorphine–naloxone treatment among patients with HIV infection and opioid dependence. Their analysis revealed no significant changes in median AST or ALT

values over time [9]. Fareed *et al.*, (2014) similarly reported that AST and ALT elevations generally remained below twice the upper limit of normal and were not clinically significant, supporting a relatively low risk of clinically significant liver toxicity during long-term buprenorphine treatment [10]. These findings suggest that mild biochemical abnormalities during treatment do not necessarily indicate clinically significant hepatic injury. Nevertheless, the higher proportion of elevated SGPT levels observed in the present study warrants clinical attention and further investigation, particularly because pretreatment liver function results were unavailable.

Evidence from studies involving patients with viral hepatitis highlights the importance of considering underlying hepatic disease when interpreting liver enzyme abnormalities. Petry *et al.*, (2000) evaluated liver enzyme levels in opioid-dependent patients with a history of hepatitis who received buprenorphine. AST and ALT levels were significantly elevated in this subgroup, and the probability of an increase in AST was associated with the buprenorphine dose [5]. The authors emphasized the need for careful monitoring in patients with hepatitis. Tetrault *et al.*, (2016) also reported a higher risk of liver toxicity among patients with hepatitis C virus (HCV), HIV, or HCV/HIV coinfection, suggesting that these populations may benefit from enhanced monitoring [11]. In contrast, Bogenschutz *et al.*, (2010) found no evidence of hepatotoxicity in their exploratory analysis, although HCV infection was a significant predictor of transaminase elevation [12]. Bruce and Altice (2007) reported that patients with acute HCV infection tolerated buprenorphine treatment and demonstrated improvement in transaminase levels that had been elevated in the context of acute hepatitis C [13]. Taken together, these findings suggest that liver enzyme abnormalities among patients receiving buprenorphine may be influenced by underlying viral hepatitis and other clinical factors, rather than being attributable solely to the medication.

Ciftci Demirci (2015), in a study involving adolescents, reported that buprenorphine–naloxone was generally well tolerated, although clinically insignificant elevations in liver enzymes were observed. The authors also noted that psychotropic medications might contribute to changes in liver enzyme levels during the initial stages of treatment [14]. In addition, Behan and Geier (2016) described a patient with liver dysfunction who experienced naloxone accumulation during buprenorphine–naloxone induction, potentially interfering with buprenorphine's effectiveness [15]. Although a case report cannot establish the frequency of this complication, it highlights the importance of considering hepatic status when prescribing

buprenorphine–naloxone, particularly in patients with significant liver dysfunction.

An important finding of the present study was the absence of statistically significant correlations between the prescribed buprenorphine–naloxone dose and most of the assessed liver function parameters. Spearman's rank correlation analysis revealed no statistically significant associations between the prescribed dose and total bilirubin, direct bilirubin, SGOT, SGPT, alkaline phosphatase, total protein, or globulin. The association between the prescribed dose and serum albumin was weakly negative. This borderline finding should be interpreted cautiously in view of the small correlation coefficient. The unrounded p-value and the prespecified significance threshold should be verified before classifying this association as statistically significant or nonsignificant.

The absence of a consistent dose–response relationship in the present study differs from the dose-associated increase in AST reported by Petry *et al.*, (2000) among patients with a history of hepatitis [5]. This difference may reflect variations in study populations, particularly the presence of underlying hepatic disease, as well as differences in treatment exposure and study design. The present study excluded patients with identified HIV infection, hepatitis B surface antigen positivity, and HCV infection, in accordance with the study eligibility criteria. Therefore, its findings may be more applicable to patients without these identified infections than to those with coexisting viral hepatitis or established liver disease. Furthermore, the absence of a statistically significant correlation does not establish that the medication has no hepatic effects, because the analysis cannot fully account for pretreatment differences, cumulative exposure, or other potential confounding factors.

However, liver health cannot be comprehensively assessed using aminotransferases, bilirubin, and protein measurements alone. Clinical assessment and additional investigations, such as prothrombin time/international normalized ratio and hepatic imaging when indicated, may be necessary to evaluate suspected liver dysfunction. Accordingly, the present findings should be interpreted as a description of selected liver biochemical parameters rather than a comprehensive assessment of hepatic functional capacity.

The findings have practical implications for the clinical monitoring of patients receiving long-term buprenorphine–naloxone maintenance treatment. Although the available literature generally suggests a low risk of clinically significant hepatotoxicity, mild enzyme elevations and increased risks among patients with underlying hepatic disease have been reported.

Baseline and periodic assessment of liver function may therefore be appropriate, particularly in patients with pre-existing liver disease, symptoms suggestive of hepatic dysfunction, or other risk factors for liver injury. Abnormal results should prompt clinical evaluation of potential causes rather than automatic discontinuation of maintenance treatment. Treatment decisions should balance the severity of hepatic abnormalities against the established benefits of effective treatment for opioid dependence.

Limitations

The present study has several limitations. First, the cross-sectional design precludes establishing a temporal or causal relationship between buprenorphine–naloxone treatment and liver biochemical abnormalities. Second, the absence of pretreatment liver function measurements and a comparison group limits the ability to attribute the observed abnormalities to the medication. Third, although patients with identified HIV infection, hepatitis B surface antigen positivity, and HCV infection were excluded, other potential causes of abnormal liver biochemistry may have remained unrecognized. Fourth, the study was conducted at a single outpatient treatment centre, limiting the generalizability of the findings to other populations. Finally, the dose–correlation analysis does not establish whether treatment duration, cumulative exposure, adherence, or other clinical factors influenced the measured parameters.

Future Directions

Future prospective studies should include pretreatment and serial liver function assessments, appropriate comparison groups, and systematic evaluation of potential confounders. Stratification by treatment duration, prescribed dose, and underlying hepatic risk factors may help clarify the relationship between buprenorphine–naloxone maintenance treatment and liver biochemical abnormalities.

CONCLUSION

Elevated liver biochemical parameters were observed in a proportion of patients receiving buprenorphine–naloxone maintenance treatment, with SGPT being the most frequently elevated parameter. No consistent, statistically significant association was found between the prescribed dose and the measured liver function parameters. These findings are broadly consistent with literature suggesting a low risk of clinically significant hepatic toxicity during buprenorphine-based maintenance treatment, while underscoring the importance of monitoring liver function and evaluating alternative causes of abnormal results. Given the cross-sectional design and absence of pretreatment measurements, the observed abnormalities cannot be causally attributed to buprenorphine–naloxone treatment.

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