

Alcohol Use Disorders in Opioid Maintenance Therapy: Prevalence, Clinical Correlates and Treatment

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Key Words

Alcohol · Alcoholism opioids · Opioid dependence · Maintenance therapy · Buprenorphine · Methadone

Abstract

Maintenance therapy with methadone or buprenorphine is an established and first-line treatment for opioid dependence. Clinical studies indicate that about a third of patients in opioid maintenance therapy show increased alcohol consumption and alcohol use disorders. Comorbid alcohol use disorders have been identified as a risk factor for clinical outcome and can cause poor physical and mental health, including liver disorders, noncompliance, social deterioration and increased mortality risk. The effects of opioid maintenance therapy on alcohol consumption are controversial and no clear pattern has emerged. Most studies have not found a change in alcohol use after initiation of maintenance therapy. Methadone and buprenorphine appear to carry little risk of liver toxicity, but further research on this topic is required. Recent data indicate that brief intervention strategies may help reduce alcohol intake, but the existing evidence is still limited. This review discusses further clinical implications of alcohol use disorders in opioid dependence.

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Introduction

Epidemiology of Alcohol Use Disorders in Opioid Dependence

Substance use disorders, including opioid dependence, are defined by a cluster of somatic, psychological and behavioral symptoms. The worldwide prevalence of opioid use disorders is 0.4%, and about 12 million people use heroin worldwide [1–3]. In Europe, about 1.35 million individuals are affected [1]. In the USA, the 12-month prevalence of drug abuse was recently estimated at 5.7% [4]. Approximately 3.7 million individuals have used heroin at least once in their lives and 750,000–1,000,000 individuals are currently heroin dependent [5].

Opioid dependence is frequently associated with polysubstance use and alcohol use disorders (AUD), and the latter cause multiple health and social problems [3, 6–8]. This paper presents a comprehensive review of the existing literature on the prevalence and treatment of AUD in opioid dependence.

Neurobiological Interrelationships between Alcohol and Opioid Use

Opioid and alcohol abuse and dependence show some close neurobiological interrelations. In brief, like other drugs of abuse both alcohol and opioids induce dopamine

release in the ventral tegmental area and nucleus accumbens; the psychotropic effects of alcohol are in part mediated via the opioid-endorphin system [9–11]. Alcohol stimulates the release of beta-endorphin, enkephalins and dynorphin [12–16], and opioids stimulate alcohol intake via the paraventricular nucleus [17]. Opioid receptor blockade decreases alcohol intake [18–21]. Studies have provided broad evidence for a significant role of the opioid system in mediating the reinforcing effects of alcohol and the associated dopamine release in the mesolimbic brain area [15, 19, 22–26].

Clinically, both alcohol and opioids are ‘downers’, i.e. they have a strong sedative effect and cause respiratory depression. Many studies have addressed the possible role of mu-opioid receptor polymorphisms in mediating the genetic risk for alcohol or substance use in general. The OPRM1 variant was found in a recent meta-analysis to have a modest protective effect on the risk for substance use in comparison to the 1799971 (A118G ASN40/ASP40) G allele [27]. This gene variant may modulate treatment response to the opioid antagonist naltrexone, which is used for alcohol treatment [28]. ASP40-ASN40 heterozygotes may respond better than ASP40 homozygotes to naltrexone [29].

Search Methods

A systematic literature search was performed in the Medline and Pubmed databases to identify clinical and epidemiological studies on a possible association between opioid dependence and AUD. The search was not limited to certain years or languages. The indexing terms were ‘methadone AND alcoholism’ (402 citations) and ‘buprenorphine AND alcoholism’ (48 citations). In addition, the terms ‘opioids and alcohol’ were screened. Papers focusing on epidemiology, diagnosis, therapy or other clinical issues were considered to be of special relevance.

Diagnosis of AUD in Opioid Dependence

A patient may present with the typical clinical picture of being intoxicated or generally drinking too much, i.e. alcohol breath, increased body sway, red skin, CNS symptoms such as irritability, anxiety and restlessness, or, in more severe cases, withdrawal symptoms such as sweating, tremor, tachycardia or increased blood pressure (table 1). A breathalyzer may help to verify alcohol consumption. Increased liver enzymes can also help to iden-

Table 1. Detection of alcoholism in opioid dependence

Detection of AUD in opioid-maintained patients		Clinical correlates of AUD in opioid-maintained patients
Clinical picture	CNS symptoms, liver disorder, behavioral symptoms	Increased mortality [49]
Intoxication	Blood alcohol concentration	Noncompliance, nonadherence, experience [133]
Withdrawal symptoms	Tremor, sweating, blood pressure increase, other clinical symptoms	Poor health, younger age, victimization, lack of social support [53, 54, 56–58, 60]
Psychometric scales	AUDIT, ASI, others	Higher dosages of opioid maintenance drug requested by non-alcohol-abusing clients [7]
Psychosocial	Deterioration	Perceived stress, low quality of life [64]

tify patients, but they have low specificity because many patients have hepatitis or other liver disorders. Increased mean corpuscular volume (MCV) or carbohydrate-deficient transferrin values are other relevant biomarkers for alcoholism [30–32]. More recently, direct alcohol metabolites, especially ethyl glucuronide, was reported to be useful for measuring alcohol consumption in patients on opioid maintenance therapy [33–35]. Also, the 5HTOL/HIAA ratio in urine was used to detect alcoholism in methadone maintenance patients [36].

The standardized Addiction Severity Index (ASI) interview or its European variant, the EuropASI [37], can be used in clinical studies to identify alcohol problems. The Alcohol Use Disorder Identification Test (AUDIT, 10 items) [38, 39] is recommended by the WHO for clinical use and to screen patients, and is frequently used in clinical studies (see below).

Prevalence of AUD in Opioid Dependence

Prevalence estimates for AUD in opioid dependence vary. Approximately one third of the patients in methadone treatment are assumed to have alcohol problems [40–42]. More recent data by and large confirm these findings. An Irish study estimated the prevalence of problem

alcohol use among patients attending primary care for methadone treatment at 35% [43]. Data from the British National Treatment Outcome Research Study (NTORS) suggest that almost half of the patients in residential programs drink alcohol and just over a third of those in community programs drink above the recommended levels [6]. A Swiss 2-year longitudinal study found occasional alcohol abuse in 38–47% of methadone patients and daily abuse in 20–24% [44]. A recent Australian study reported that 41% of opioid substitution clients were ‘AUDIT positive’, indicating excessive alcohol use [45], but only half of them believed they drank too much.

In a large German study [46] in 1,685 heroin users and patients on opioid maintenance treatment (with methadone or codeine), 28% of participants consumed more than 40 g alcohol/day. The average alcohol consumption was significantly higher in heroin users than in methadone-treated patients. Predictors of alcohol use were male sex, daily cannabis and benzodiazepine consumption, and longer duration of drug use. Meta-analyses of US clinical trials found AUD in 38 and 45% of patients seeking treatment for opioid or stimulant use, respectively [47, 48].

Clinical Correlates of AUD in Opioid Dependence

AUD are associated with an increased risk of fatal overdose [49] (see below), hepatotoxicity (especially in hepatitis-positive individuals) [50], interactions with methadone [51, 52] and negative clinical outcome [53, 54]. Hepatitis infections are very common in opioid users [55]. Prevalence estimates of hepatitis C range from 64 to 100% in many cohorts [56–62]. Chronic alcohol intake is an important risk factor for progression to hepatic cirrhosis [50].

Alcohol dependence and AUD are usually considered to be risk factors for compliance and predictors for a negative treatment outcome, although this has not been reported in all studies [63]. According to recent data, substance use, including alcohol-related problems, may be attributed to perceived stress [64]. Stress management may therefore be a suitable approach to minimize the risk of alcohol intake.

Most patients with alcohol abuse show noncompliance and nonadherence to treatment [65]. Inadequate opioid dosage during maintenance therapy may explain alcohol or other drug use in some patients. Ottomanelli [7] found that non-alcohol-abusing clients request higher doses of opioids.

Sebanjo et al. [42] evaluated the effects of excessive alcohol consumption on the health-related quality of life in

patients receiving methadone treatment and found significant impairments in various domains, including social functioning.

Genetic variables have hardly been studied to date. Wang et al. [66] reported that a kappa-opioid receptor 1 gene polymorphism is associated with alcohol use, among other things.

AUD and Mortality in Opioid-Dependent Patients

There is broad consensus that opioid-dependent patients have a substantial risk of premature death, mostly associated with fatal overdose or polysubstance intoxications [67]. Long-term studies in opioid-dependent individuals indicate a low abstinence and high mortality rate [67–70]. The all-cause mortality rate was estimated at 2.09 per 100 person-years [71]. Problem drug users were found by the European Monitoring Centre for Drugs and Drug Addiction [1] to have a 10- to 20-fold higher mortality risk than their peers. Maintenance treatment significantly reduces mortality rates compared with untreated heroin dependence [71].

AUD are associated with an increased risk of fatal overdose in opioid dependence [72] and numerous studies have identified alcohol abuse or dependence as a risk factor for mortality in opioid-dependent patients [73]. Degenhardt et al. [74] recently published a comprehensive study on causes of death in the years 1995–2005 in a large Australian cohort (n = 43,789) of opioid-dependent people. Of the 3,685 deaths, the majority (52%) were drug related and were mostly accidental opioid deaths; 3% were alcohol related and 7% were liver related (3% chronic liver disease and 3% viral hepatitis). The standard mortality ratio for the most common causes of death for alcohol-related disorders was 5.4%. Because both heavy and dependent alcohol use have been described in older opioid-dependent people [75], screening for and treatment of hazardous alcohol use is recommended for this group [74]. Another recent large (n = 68,066) retrospective cohort study also found a high mortality rate: drug- or alcohol-induced deaths accounted for 23% of the cases [76].

Brief Update on the Efficacy of Maintenance Treatment

A number of psychosocial approaches and therapies with the goal of abstinence from opioids have proven efficacy in opioid dependence, but overall abstinence rates

Table 2. AUD in opioid dependence

Study	Methods	Key findings
The effect of methadone maintenance treatment on alcohol consumption: a systematic review [8]	Systematic review of 15 studies	Alcohol use: Increased in 3 studies Decreased in 3 studies Did not change in 9 studies
Opioid maintenance therapy suppresses alcohol intake in heroin addicts with alcohol dependence [101]	Open randomized 12-month study, MET (80, 120, 160 and 200 mg) or BUP (8, 16, 24 and 32 mg) (n = 218)	Both treatments suppressed opioid and alcohol consumption (ASI scores) Highest BUP dose better than highest MET dose on alcohol craving and intake
Effects of heroin-assisted treatment on alcohol consumption [99]	Secondary analysis of self-reported alcohol consumption, CDT, ASI scores Randomized trial: heroin vs. MET	Both groups: significant reduction of alcohol use and CDT Heroin group: reduction of ASI score Effect of daily frequency of heroin dispensing (setting effect)?

BUP = Bupropione; CDT = carbohydrate-deficient transferrin; MET = methadone.

are rather low and rarely exceed 20% [77]. Maintenance treatment with full or partial opioid agonists reduces opioid consumption, criminal behavior and psychosocial and medical morbidity, including rates of HIV and hepatitis B virus infections, as indicated by many studies and meta-analyses [78–84]. The efficacy of buprenorphine and its combination with naloxone in reducing substance use and improving social and clinical functioning in opioid-dependent individuals has been demonstrated by numerous studies [84–87] and both methadone and buprenorphine are recommended as effective, first-line medications in the treatment of opioid dependence by relevant treatment guidelines [5, 88–90] and reviews [78, 80, 82, 83, 85, 91].

Role of Opioid Maintenance Therapy in Alcohol Consumption

The interaction of opioid dependence, maintenance therapy and alcohol consumption is complex (table 2). Addressing opioid dependence adequately by increasing the dose of maintenance treatment does not automatically decrease alcohol consumption [92, 93]. For example, short-term methadone maintenance therapy was reported to decrease alcohol consumption and long-term treatment to increase it as indicated by the data reviewed by Caputo et al. [94]. Hser et al. [95] reported that alcohol consumption increases whenever narcotic use decreases, and Anglin et al. [96] also claimed that alcohol and hero-

in use are inversely related. Caputo et al. [94] reported a significant reduction in daily alcohol intake in methadone-treated, nonalcoholic, opioid-dependent patients compared to nonmethadone-dependent clients. In an 18-month longitudinal cohort study on exposure to treatment for heroin addiction, Schifano et al. [97] found that heroin, benzodiazepine and polydrug abuse decreased over time, but alcohol (and cannabis) use did not. Fishman et al. [98] reported on a female patient with an addiction to prescription opioids and comorbid depression and alcohol dependence who benefited from treatment with buprenorphine.

In some European countries heroin is used to treat opioid dependence. A secondary analysis of a randomized German study comparing heroin treatment with methadone treatment [99] found a significant reduction in carbohydrate-deficient transferrin values in both groups, but a reduction in the ASI alcohol subscore only in the heroin group. Interestingly, this result was discussed with respect to setting effects: daily dispensing of heroin may have prevented this group from consuming more alcohol. A reduction in the ASI alcohol subscore was also reported in a large German naturalistic follow-up study of 1,694 patients in opioid maintenance treatment for 6–7 years; the study also found a higher rate of ‘critical’ alcohol consumption in methadone patients (36–50%) than in buprenorphine patients (24–27%) over time [100].

Some studies suggest that opioid maintenance therapy suppresses alcohol intake in heroin addicts with alcohol

dependence. In a 12-month open randomized study, the effects of methadone (80, 120, 160 and 200 mg) and buprenorphine (8, 16, 24 and 32 mg) on opioid and alcohol consumption (as measured by ASI scores) were assessed in 218 patients [101]. Both treatments decreased opioid and alcohol consumption, but the only statistically significant finding was that the highest buprenorphine dose suppressed alcohol craving and intake more than the highest methadone dose.

Srivastava et al. [8] performed a systematic review of 15 studies on the effects of methadone treatment on alcohol consumption. Three studies indicated an increase in alcohol use during treatment and 3 indicated a decrease; 9 studies did not report any change. Apparently there is no clear pattern concerning the effects of opioid maintenance therapy on alcohol consumption.

The US Substance Abuse and Mental Health Services Administration (SAMHSA) concluded the following in their clinical guidelines for the use of buprenorphine in the treatment of opioid addiction [102]: 'Pharmacotherapy with buprenorphine for opioid addiction will not necessarily have a beneficial effect on an individual's use of other drugs. It is essential that patients be referred to treatment of addiction to other types of drugs when indicated. In addition, care must be exercised in the prescribing of buprenorphine for patients who abuse alcohol... because of the documented potential for fatal interactions.' This may be true for all drugs used for opioid maintenance treatment.

Treatment of AUD in Opioid-Dependent Patients

The issue of AUD in opioid-dependent patients has been widely neglected. A 1-year follow-up study found improvements in alcohol consumption in a minority of patients only [6]. Because many patients underestimate the risks associated with their alcohol consumption, alcohol use should be regularly assessed and brief alcohol interventions performed when necessary [45].

Only a few systematic studies have been published on AUD in opioid dependence [103, 104]. When preparing their systematic Cochrane review on this topic, Klimas et al. [105, 106] identified 4 studies with 594 participants. The studies measured 6 different psychosocial interventions grouped into 4 comparisons: cognitive-behavioral coping skills training versus 12-step facilitation ($n = 41$) [107], brief intervention versus treatment as usual ($n = 110$) [108], hepatitis health promotion versus motivational interviewing ($n = 256$) [65], and brief motivational

intervention versus an assessment-only group ($n = 187$) [109]. The authors were not able to perform a meta-analysis of all the studies because of clinical and methodological differences between them. Most of the comparisons were not statistically significant, except for decreased alcohol use at 3 and 9 months with the control intervention in the study by Feldman et al. [108]. Also, at 6 months participants receiving brief motivational intervention were significantly more likely than the control group to have reduced their alcohol use by 7 or more days in the past 30 days [109]. Similar to previous reviews [103, 104], the Cochrane review was unable to recommend using or ceasing psychosocial interventions for alcohol use problems in illicit drug users: 'Given the high rates of co-occurrence of alcohol and drug problems, integration of alcohol- and drug-orientated interventions appears a logical action, but in light of this review remains without an evidence base' [105].

The same group is currently conducting a study to determine the feasibility of a complex intervention for problem alcohol use among problem drug users [110]. A new and interesting study has been performed on this topic: Darker et al. [111] studied the effectiveness of brief interventions to reduce hazardous and harmful alcohol consumption in opiate-dependent methadone-maintained patients and excluded alcohol-dependent patients. The study assessed the change in scores on the Alcohol Use Disorders Identification Test (AUDIT-C) from baseline to the 3-month follow-up in 160 patients (15 were lost to follow-up). This implementation study found a clear reduction in alcohol consumption after treatment. Brief interventions are frequently used in alcohol treatment [112], but not in treatment for addiction to illicit drugs.

So-called anti-craving drugs such as the opioid antagonists naltrexone and nalmefene [28, 113] and the putative glutamate modulator acamprosate [114] may help to reduce alcohol consumption. The first two substances precipitate opioid withdrawal and are contraindicated in opioid-dependent patients, while acamprosate has not been tested in opioid users. The anticraving drug acamprosate has no contraindication in opioid dependence and no pharmacological interactions with opioids.

The overall evidence for disulfiram as an effective medication in alcoholism is limited [115, 116] and basically restricted to supervised treatment settings. Since opioid maintenance therapy may be considered as such a supervised setting, disulfiram may fit in here. Disulfiram was also studied as a possible medication for the treatment of cocaine dependence in methadone-stabilized patients [117] and positive results were reported in patients

maintained with buprenorphine [118], but disulfiram may also work in those with current alcohol use disorder [107]. Unlike cocaine and possibly methadone, disulfiram was not found to prolong the QTc interval [119].

Hepatotoxicity in Opioid Maintenance Therapy

Hepatotoxicity must be considered when addressing AUD in opioid dependence. While methadone has been considered to be safe, clinical reports of liver injury in patients with hepatitis have raised concerns about the hepatotoxicity of buprenorphine and the buprenorphine/naloxone combination [120–126]. Hervè et al. [127] reported on 7 cases of acute cytolytic hepatitis due to buprenorphine. Five of 7 patients presented with acute icteric hepatitis without abdominal pain or fever or evidence for liver failure; after reexposure some of the patients remained on a lower dose without further evidence of liver injury.

More systematic studies found little evidence for buprenorphine hepatotoxicity. Bogenschutz et al. [128] studied 152 patients randomized to 2 weeks' detoxification with buprenorphine-naloxone or 12 weeks' treatment with buprenorphine-naloxone and obtained at least one set of transaminase measurements for 111 patients. At least one elevated aspartate aminotransferase value was found in 8 of the 60 buprenorphine/naloxone patients and 12 of the 51 detoxification patients. Hepatitis C status was significantly associated with transaminase abnormalities. Taken together, this exploratory study found no evidence for hepatotoxicity of buprenorphine.

Saxon et al. [129] performed a controlled study of 1,269 opioid-dependent, treatment-seeking patients randomized to either buprenorphine or methadone and followed them for 32 weeks. A total of 731 participants met 'evaluable' criteria, defined as completing 24 weeks of medication and providing at least 4 blood samples. Changes in transaminase levels did not differ by medication condition. The study found no evidence that buprenorphine is associated with liver injury. A recent phase IV study also found no evidence for liver toxicity associated with buprenorphine [31]. Data from a large study comparing short- and long-term effects of buprenorphine on liver function indicate that hepatitis C seroconversion was strongly associated with ALT elevations [130].

Methadone, but not buprenorphine, was found to have some rare cardiotoxic effects, including causing torsades de pointes [90]. The possibility of such side effects

must be kept in mind when treating alcohol-dependent patients with possible cardiomyopathy. ECG controls are recommended.

Conclusions

The current data indicate that AUD are a significant problem in about a third of the patients in opioid maintenance therapy and have a significant impact on morbidity and mortality. According to most studies, opioid maintenance therapy does not change alcohol consumption, at least not in the majority of cases, but dose adjustments may help to reduce the risk of substance use, including alcohol. A simple diagnostic approach such as the use of a breathalyzer may be useful to detect affected patients. More research is needed on psychosocial strategies for use in patients with alcohol abuse. It is already difficult to define effective psychosocial interventions for the treatment of opioid use [131, 132], and therefore even more difficult to suggest evidence-based treatments for comorbid alcoholic patients. Brief interventions and treatment modifications, such as more regular visits or a more intense approach without prolonged periods at home, may be helpful. In more severe cases, selective (alcohol) detoxification may be considered.

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