Alcohol and Alcoholism, 2015, 50(4) 451–457
doi: 10.1093/alcalc/agv028
Advance Access Publication Date: 31 March 2015
Article

Article

Former Heroin-Dependent Alcohol Use Disorder Patients. Prevalence, Addiction History and Clinical Features

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Received 7 November 2014; Revised 19 January 2015; Accepted 5 March 2015

Abstract

Aims: To examine the prevalence of former heroin dependence (FHA) in Alcohol Use Disorder (AUD) patients; to compare the clinical characteristics of FHA-AUD patients versus AUD patients without any past use of heroin at alcohol treatment entry; to document the heroin dependence history of FHA-AUD patients, and review treatment strategies for this group.
Methods: Retrospective case review of 448 consecutive AUD patients.
Results: The annual entry of FHA-AUD showed stability over the study period of 3 years overall 60/448 (13.3%). FHA-AUD patients showed higher concomitant use of cocaine, benzodiazepines, cannabis and hallucinogens than other heroin addicts. They consumed higher amounts of alcohol at the beginning of their alcohol dependence history, and reached a high maximum level of alcohol consumption, than other AUD patients, and tended to have more physical disorders. The most important signals of FHA-AUD were polyabuse and older age at the time of presentation. FHA-AUD patients tended to have had a severe pattern of heroin dependence associated with inadequate agonist opiate treatment.
Conclusions: The prevalence of FHA-AUD patients is not negligible. This may relate to previous inadequate treatment of heroin addiction contributing to the development of severe AUD. For these patients we propose a reconsideration of 'soft' (low dose) agonist opiate treatment.

INTRODUCTION

Opioid agonist treatment (AOT) is an effective programme for the treatment of heroin dependence (Gronbladh *et al.*, 1990; Giacomuzzi *et al.*, 2003; Mattick *et al.*, 2003, 2008, 2009; Gibson *et al.*, 2008). It should, however, be noted that the magnitude of the gains achieved through AOT can be strongly influenced by how treatment is delivered (Benyamina and Stöver, 2012; Dale-Perera *et al.*, 2012; Fischer *et al.*, 2012). To achieve the best results it is critical to optimize the AOT. Vincent P. Dole, together with Marie Nyswander and Mary Jeanne Kreek, clarified how to optimize treatment (Dole *et al.*, 1966), and the treatment has survived challenges from professional sceptics, ideologically hostile agencies, competitive modalities, and even from well-intentioned clinicians in methadone programmes who have prescribed inadequate doses of the medication (Dole, 1999). No matter how much time has gone by, we still need evidence to prove how important it is to optimize treatment. Successful outcomes are achieved when

patients take adequate doses and stay in treatment over the long term (Dole and Joseph, 1978; Lowinson *et al.*, 1992; Dole, 1994; Kritz *et al.*, 2009). Indeed, higher doses of agonist opioids are more effective than lower ones in reducing illicit opioid use (Schottenfeld *et al.*, 1997; Maxwell and Shinderman, 1999) and, when taking higher doses, patients tend to stay in treatment longer (Johnson *et al.*, 2000). That is true, no matter whether it is methadone or buprenorphine that is being considered (Farre *et al.*, 2002).

Although the best techniques for optimizing AOT are now known, they are not always applied (Benyamina and Stöver, 2012; Dale-Perera *et al.*, 2012; Fischer and Stöver, 2012; Fischer *et al.*, 2012; Goulão and Stöver, 2012; Stöver, 2012); when this happens treatment outcomes tend to worsen, and extreme attention should be paid to the possibility of subsequent use of sedative drugs such as alcohol and benzodiazepines (Mitcheson *et al.*, 1970; Maremmani and Shinderman, 1999; Lubrano *et al.*, 2002).

Increases in alcohol consumption during AOT programmes have been observed alongside dwindling heroin use, suggesting a negative correlation between the two, at least in programmes that employ lower dosages of methadone (Green *et al.*, 1978; Anglin *et al.*, 1989; Maremmani and Shinderman, 1999; Maremmani *et al.*, 2007; Stenbacka *et al.*, 2007). Similar observations can be applied to benzodiazepine use (Maremmani and Shinderman, 1999; Vogel *et al.*, 2013).

There is growing evidence that alcohol use is a common problem among people who use heroin and other illicit opiates (McCusker, 2001)—in other words, not only among former heroin-dependent patients (Ryder *et al.*, 2009). The close linkage between these two substances has been well documented (Green *et al.*, 1978). A history of exposure to opiates and subsequent opiate use disorder is a frequent background in subjects who apply for alcohol abuse treatment. The maximum levels of alcohol consumption seem to rise as heroin use dwindles, in some cases to nothing; this highlights a predictable shift from regular opiate abuse to regular heavy alcohol use (Ceccanti and Vitali, 2009); one should bear in mind the tendency to use alcohol as a substitute for heroin (Lehman *et al.*, 1990). In addicts' natural environment, before any therapeutic setting has been established, alcohol consumption may compensate for the lack of available heroin (due to poverty, somatic impairment or temporary supply shortages), so becoming a common means of self-handling in a situation of opiate craving (Noble *et al.*, 2002). This can also happen when heroin-dependent patients are prematurely removed from agonist opioid medications, which directly favours, or fail to counter, a switching evolution of heroin dependence towards alcoholism, probably to obtain relief from symptoms of narcotic craving without relapsing into the use of heroin (Bickel *et al.*, 1987; Ottomanelli, 1999). Conversely, if alcohol-abusing heroin-dependent patients are prompted to take action by entering methadone treatment, that may forestall their alcohol consumption in the short term, so indicating a rapid direct action of opioid agonism on alcohol craving in this population (Caputo *et al.*, 2002).

The purpose of the present paper is 3-fold:

- First, to analyse the prevalence of former heroin addiction in AUD patients requesting treatment for Alcohol Use Disorders (AUD) at Alcohol Units (FHA-Alcoholic patients).
- Second, to compare the clinical characteristics of former heroin-dependent AUD patients and AUD patients without any past use of heroin (NFHA-Alcoholic patients) at alcohol treatment entry.
- Third, to describe the heroin dependence history and previous treatment of these patients.

METHODS

A comparative cohort study was designed to compare the demographic, clinical and diagnostic characteristics of AUD patients with and without past heroin use. All patients included in the study signed an informed consent form. The competent ethics committees, in accordance with internationally accepted criteria for ethical research, approved both the consent form and the experimental procedures.

Since 2004, the Centre for the Assessment and Treatment of Alcohol-Related Pathology, La Sapienza University, at the Umberto I University Hospital in Rome has been using a clinical protocol that comprises a detoxification unit, which may be followed by a long-term outpatient psychopharmacological approach to prevent relapses. Patients displaying major psychomotor excitement, aggressive, and suicidal behaviour, or major psychotic symptoms were referred to the local psychiatric inpatient unit. For these patients, the initiation of the outpatient treatment was postponed.

We considered all consecutive AUD patients, according to DSM-IV TR criteria, who had been referred for treatment to the outpatient clinic, during the years 2004–2007. Previous studies had been performed with this sample (Ceccanti and Vitali, 2009; Pacini *et al.*, 2010b).

All patients were evaluated after the resolution of acute withdrawal to avoid, in the diagnostic process, possible interferences arising from the acute phase of their illness.

Assessment

Alcoholism-related information was collected by means of the Drug Addiction History Questionnaire (DAH-Q) (Maremmani and Castrogiovanni, 1989)—alcohol version, administered by a psychiatrist. The DAH-Q is a multiscale questionnaire comprising these categories: sociodemographic information, physical health, mental health, substance abuse, treatment history, social adjustment and environmental factors. DAH-Q was specifically designed to register information regarding illicit drug users. For patients who were also alcoholics, we further registered the number of alcohol units per day at evaluation time and maximum lifetime.

Psychiatric Diagnostic Evaluation Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version was administered. It is specifically adapted for Axis I structured clinical interviewing for use in clinical settings (First *et al.*, 1997) and covers the DSM-IV diagnoses most commonly seen by clinicians. According to our criteria, there was a 'dual diagnosis' when we determined the presence of both alcohol dependence and an autonomous psychiatric disorder. Autonomy of additional psychiatric syndromes was assessed with reference to an independent course with respect to substance abuse, and the specificity of symptoms with respect to expected intoxication or withdrawal pictures.

Regarding bipolar spectrum diagnoses, both the history of earlier hypomanic episodes, and temperamental characteristics were explored using the criteria listed in the SID, the Semi-structured Interview for Depression (Cassano *et al.*, 1989). All information was gathered from the patient and at least one close relative (usually parents, siblings); in addition, all available clinical records were carefully examined. Inquiries on temperamental attributes focused on the habitual self of the patient during periods free of affective episodes—the sources being patients and their significant others (Akiskal and Mallya, 1987).

Statistical analysis

We compared FHA-AUD patients and all AUD patients with reference to: demographic data, physical health, psychiatric diagnoses,

substance abuse and social adjustment. The variables that showed statistically significant differences ($P < 0.05$) for an association with past heroin use were included in separate logistic backward regression analyses comprising the issue of belonging to the FHA-AUD patients group as a dependent variable. Then we described FHA-AUD patients by reviewing their heroin dependence history and treatment history. Statistical analyses were carried out using the SPSS package. As this is an exploratory study, statistical tests were considered significant at the $P < 0.05$ level.

RESULTS

The study included 448 patients of whom 338 (75.4%) were male, and mean age was 44 years (SD = 9; min 19 max 74). Most were single (155, 34.6%), had had <8 years of education (230, 51.3%) and were employed (344, 76.8%). Sixty AUD patients were former heroin-dependent patients (FHA-AUD patients). Of these, 50 (83.3%) were males, of mean age 43 ± 6 years. They were characterized by the concomitant use of cocaine (75.0%), benzodiazepines (25.9%) and cannabinoids (65.0%). The other 388 AUD patients (mean age 44 ± 1 years) had never used heroin; 228 (74.2%) were male.

The prevalence of FHA-AUD patients at this clinic was 15/99 (15.1%) in 2004; there were 22/159 (13.8%) new cases in 2005, and 16/151 (10.5%) in 2006. Reviewed cumulatively in 2007, cases of this type totalled 60/448 (13.3%).

Table 1 compares FHA-AUD patients and NFHA-AUD patients on demographic characteristics, psychiatric comorbidity, social adjustment and drug addiction history. No differences emerged as to age ($P = 0.580$), gender ($P = 0.127$), civil status ($P = 0.289$), unemployment rates ($P = 0.526$), level of education ($P = 0.082$) or living situation ($P = 0.219$). No differences were found between the two groups regarding age at first use of alcohol ($P = 0.452$), and at first misuse of alcohol ($P = 0.806$), duration of drinking habit ($P = 0.882$) and the duration in years of alcoholism ($P = 0.506$). No differences emerged, either, for the presence of a psychiatric diagnosis ($P = 0.533$) or problematic social adjustment ($P = 0.364$). FHA-AUD patients showed a higher concomitant use of cocaine ($P = 0.000$), benzodiazepines ($P = 0.000$), cannabis ($P = 0.000$) and hallucinogens ($P = 0.011$). They consumed a higher amount of alcohol at the beginning of their dependence history ($P = 0.003$), and reach a higher maximum level of alcohol consumption ($P = 0.016$). There is a trend towards more severe physical complications in FHA-alcoholic patients ($P = 0.056$).

Table 2 shows the most significant correlates of former heroin use in AUD patients. Concomitant use of cocaine and cannabis is the strongest correlate of being a former heroin alcoholic. Moreover, being older at the time of present treatment is positively correlated with past heroin use. In other words, former heroin AUD patients are rather typical of the older generation of AUD patients, showing a concomitant use of cocaine and cannabinoids (chi-square = 75.01; df = 3; $P < 0.001$).

Table 3 shows the heroin dependence history of 60 FHA-AUD patients at treatment entry. FHA-AUD patients reported their age at first continuous use of heroin to be 22.12 ± 8.2. Of these 60 patients, 88.3% reached the 'revolving door phase' (Stage 3) and showed a dependence length of 9.38 years ± 5.5. The development of addiction may be considered to consist of three stages: 1-acute (immediate) drug effects (Honeymoon Stage); 2-transition from recreational use to patterns of use consistent with addiction (Increasing Dose Stage);

Table 1. Univariate association between past use of heroin in AUD patients and sociodemographic characteristics, psychiatric comorbidity, social adjustment and drug addiction history

	FHA-AUD patients $N = 60$	NFHA-AUD patients $N = 388$	Chi/T	*P*
Age (mean ± SD)	43.38 ± 6.3	44.13 ± 10	0.55	0.580
Sex (male)	50 (83.3)	228 (74.2)	2.32	0.127
Civil status (single)	37 (64.9)	197 (57.4)	1.12	0.289
Unemployed	29 (48.3)	157 (40.5)	2.23	0.526
High educational level (>8 years)	29 (48.3)	142 (36.6)	3.03	0.082
Living alone	21 (35.0)	106 (27.3)	1.50	0.219
Concomitant use of Cocaine	45 (75.0)	99 (25.5)	58.34	0.000
Concomitant use of BZD	15 (25.9)	21 (5.6)	27.37	0.000
Concomitant use of THC	39 (65.0)	67 (17.3)	65.30	0.000
Concomitant use of hallucinogens	4 (7.0)	6 (1.6)	6.44	0.011
Diagnosis				
Chronic psychosis	1 (1.7)	10 (2.6)		
Recurrent depression	1 (1.7)	23 (5.9)		
Bipolar spectrum	15 (25.0)	111 (28.6)		
Anxiety disorders	2 (3.3)	17 (4.4)		
Absence of dual diagnosis	41 (68.3)	227 (58.5)	3.15	0.533
Age at first use of alcohol	15.17 ± 4.8	15.70 ± 5.1	0.75	0.452
Age at first misuse of alcohol	24.27 ± 6.4	24.02 ± 7.2	−0.24	0.806
Drinking duration	28.22 ± 8.2	28.44 ± 10.6	0.14	0.882
Alcoholism duration	19.15 ± 8.6	20.12 ± 10.7	0.66	0.506
Initial alcohol Units/daily	9.78 ± 9.1	7.02 ± 7.5	−2.95[a]	0.003
Max alcohol Units/daily	25.13 ± 11.6	21.55 ± 10.1	−2.40[a]	0.016
Severe physical complications	16 (26.7)	64 (16.5)	3.66	0.056
Problematic social adjustment	28 (46.7)	157 (40.5)	0.82	0.364

[a]Mann–Whitney *z*-test.

BZD, benzodiazepines; THC, cannabinoids.

Table 2. Most significant correlates of 60 former users of heroin from among 448 AUD patients applying for treatment

Predictors	Step	Odds ratio	Min	Max	*P*
Age	3	1.05	1.01	1.08	0.006
Concomitant use of cocaine	2	5.70	2.64	12.33	0.000
Concomitant use of cannabinoids	1	4.97	2.36	10.46	0.000

Statistics: chi-square =75.01, df = 3, $P < 001$; correctly classified: **90.0%**.

Table 3. Heroin dependence history of 60 former heroin-dependent AUD patients at treatment entry

	FHA-AUD patients *N* = 60
Heroin dependence history	
Age at continuous use of heroin (M ± SD) (range)	22.12 ± 8.2 (13–49)
Stage 3 reached[a] (*N* (%))	53 (88.3)
Heroin dependence length (M ± SD) (range) in years	9.38 ± 5.5 (1–21)
Age when heroin use stopped (*N* (%))	34.09 ± 7.2 (26–48)
Heroin free for almost 2 years (*N* (%))	36 (60.0)
Treatment history	
Age at alcohol treatment request (M ± SD) (range)	43.38 ± 6.3 (22–58)
Past opioid agonist treatment (*N* (%))	18 (30.5)
AOT length (in years) (M ± SD) (range)	5.30 ± 4.0 (1–12)
Age at last AOT (in years) (M ± SD) (range)	33.92 ± 8.1 (25–50)
Blocking doses (at least 80 mg of methadone and 16 mg of buprenorphine) not reached (*N* (%))	34 (56.6)

[a]Stage 3 is defined as the 'revolving door phase' of heroin dependence, which identifies the last stage of the illness.

and 3-end-stage addiction, which is characterized by an overwhelming desire to obtain the drug, a diminished ability to control drug-seeking and reduced pleasure from biological rewards (Revolving Door Stage) (Kalivas and Volkow, 2005).

The mean age for stopping heroin use was 34.09 ± 7.2; 60% stayed free of heroin for at least 2 years. Considering their treatment history, FHA-AUD patients set their age at the moment when alcohol treatment was requested at 43.38 ± 6.3, corresponding to a mean of about 9 years after they had stopped heroin use. In the past, only 30.5% had been enrolled in an opioid agonist treatment and those had spent a mean of 5.30 ± 4.0 years in AOT with only 56.6% reaching 'blocking dosages' of opioid medications. They were 33.92 ± 8.1 years old at their last AOT.

According to Dole and Nyswander's theory the methadone blocking dosage is the dosage that blocks the patient's abnormal reactions to heroin and permits him/her to live as a normal citizen in the community. Generally this dosage is above 60 mg/day—in our experience at least 80 mg/day of methadone or 16 mg/day of buprenorphine (Dole *et al.*, 1966; Pacini *et al.*, 2010a; Maremmani *et al.*, 2011).

DISCUSSION

During the 2004–2007 period, the prevalence of FHA-AUD patients varied between 10.5 and 15.1%.

FHA-AUD patients show a greater concomitant use of cocaine, benzodiazepines, cannabinoid and hallucinogens than NFHA-AUD patients. Their alcohol use is characterized by a higher number of alcohol units/daily at the beginning of AUD. FHA-AUD patients show a concomitant use of cocaine and cannabinoids. They are distinguished by a significant heroin dependence history. Only 30.5% of FHA had enrolled in an AOT, and of these patients only 56.6% reached blocking dosages.

Being older and abusing cocaine and cannabinoids are correlates of past heroin use. Being older is not surprising because, if alcohol is considered as a negative outcome or a consequence of incorrect opioid treatment, we expected that time will elapse before patients request treatment for alcohol-related problems.

Moreover, the addiction history of these patients is complicated by polyabuse. The presence of polyabuse, especially in heroin-addicted patients, can reflect an unsatisfactory treatment outcome (Lubrano *et al.*, 2002; Maremmani *et al.*, 2007; Somers and O'Connor, 2012), polyabuse being an attempt to satisfy the heightened tolerance to opiates by taking a range of substances providing an alternative rewarding effect (Maremmani and Shinderman, 1999). This possibility is also supported by the positive outcomes achieved when AOTs with over-standard dosages are adopted (Peles *et al.*, 2005, 2006). Another assumption, although not mutually exclusive with the previous one, considers the subsequent use of cocaine in FHA patients as an attempt to augment or optimize the baseline energy level and resolve the hypophoria derived from the long-term use of heroin (and other sedatives) (Maremmani *et al.*, 2008).

In the present study, FHA-AUD patients showed a greater number of alcohol units per day and reached a higher maximum consumption of alcohol than NFHA-AUD patients at the beginning of AUD. An observation of this kind was first made by Ceccanti and Vitali (Ceccanti and Vitali, 2009). One possible explanation for greater alcohol consumption in FHA-AUD patients is related to the need for a cross-acting substance (alcohol specifically, but benzodiazepines could be involved as well) to compensate for the lack of heroin/opioid availability (Maremmani and Shinderman, 1999). Indeed, patients treated with low dosages of methadone show a stronger craving alcohol as well as for heroin (Lubrano *et al.*, 2002). We observed the need for high doses of methadone in heroin-addicted patients who are prone to concomitant alcohol or benzodiazepine abuse (Maremmani *et al.*, 2007).

Looking now at the heroin dependence history of our sample, more than two-thirds of our sample reached the latest stage of heroin dependence (the 'revolving door' phase). In spite of this, only one-third had ever enrolled in an AOT programme and, of these, slightly more than half reached blocking dosages. As previously mentioned, reaching blocking dosage and long-term staying in treatment (but also, performing all the phases of treatment—induction, stabilization, maintenance and reduction of medication under medical supervision) are critical to the success of an AOT programme (Dole, 1999; Maremmani *et al.*, 2003b, 2011; Fareed *et al.*, 2009; Maremmani and Pacini, 2009a,b; Pacini *et al.*, 2010a). Unfortunately, dosages below recommended levels have been highlighted in one-third of methadone facilities in the USA (Pollack and D'Aunno, 2008). It appears that our FHA-AUD patients often had not received an optimized AOT programme, and ceased using heroin only to become an AUD patients, so that an apparent remission was actually a switch of addiction. Omitting or interrupting an effective treatment for heroin dependence may favour substituting a surrogate. A premature removal of agonist drugs, and the preference for drug-free regimens are examples of interventions that may directly favour, or fail to

counter, a switching evolution of heroin dependence towards alcoholism (Pacini *et al.*, 2005).

The prevalence of alcohol use during AOT is put at about one-third (Chen *et al.*, 2011), though ranging from 5 to 50% (Rittmannsberger *et al.*, 2000; Backmund *et al.*, 2003). Nevertheless, there are few studies of emerging alcohol use in former heroin-dependent patients, despite the consensus that a percentage of heroin-dependent patients can develop alcoholism or serious drinking problems heroin addiction (Simpson and Sells, 1974; Belenko, 1979; Rounsaville *et al.*, 1982; Lehman *et al.*, 1990; Ottomanelli, 1999; Gossop *et al.*, 2006; Ryder *et al.*, 2009; Blagov and Kurgak, 2011).

A connection between alcohol and opiate receptors is recognized (Gianoulakis, 1993; Froehlich and Li, 1994; Gianoulakis and de Waele, 1994; Gianoulakis *et al.*, 1996; Herz, 1997), and naltrexone and nalmefene have been approved for the treatment of alcoholism; they take advantage of antagonist action on opioid mu-receptors, which in its turn has the effect of reducing the alcohol reward effect (Volpicelli *et al.*, 1995; Rosner *et al.*, 2010; Hillemacher, 2011).

At present, there is a lack of apparent interest in agonist opioid medications, despite the fact that the literature shows that encouraging results in the treatment of specific behaviour patterns in populations of AUD patients have been reported after treatment with agonist opioids. Regarding AUD treatment during AOT, both methadone and buprenorphine were able to reduce alcohol use, but greater effectiveness was found with higher doses of buprenorphine compared with higher doses of methadone (32 and 200 mg/day, respectively) (Nava *et al.*, 2008). Overall, high doses of methadone (over 100 mg/day) have been previously appeared necessary to reduce abuse of alcohol (Maxwell and Shinderman, 1999). In line with these findings, methadone dosage was correlated with craving for alcohol in heroin-dependent patients; patients treated with low dosages of methadone showing stronger cravings for both heroin and alcohol (Lubrano *et al.*, 2002). In addition, the prevalence of alcohol in naltrexone maintained heroin-dependent patients is quite high (Maremmani *et al.*, 2003a). In a sample of non-alcoholic heroin-addicted patients, short-term methadone administration was associated with alcohol reduction, though individual cases required the dosage of the opioid to be raised to very high levels (methadone, for instance, to 400 mg daily) (Caputo *et al.*, 2002).

Dihydrocodeine and buprenorphine have shown promising results in AUD patients without any previous use of opiates (Ulmer *et al.*, 2007, 2009, 2012). Anecdotally, we too found low-dose buprenorphine to be effective in treating former heroin-dependent AUD patients (Piz *et al.*, 2011; Maremmani *et al.*, 2014).

CONCLUSIONS

The prevalence of FHA-AUD patients is not negligible. This specific cluster of AUD patients, not alcohol-dependent during heroin use, seems to have been inadequately treated for their heroin dependence, and tends to develop a more severe form of AUD. For these patients we propose a reconsideration of low dose or 'soft' AOT as therapy worth further investigation.

CONFLICT OF INTEREST STATEMENT

None declared.

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