BIOHIT HealthCare
Innovating for Health

-CONFIDENTIAL-

Research Project

The Efficacy of Acetium® (Lozenge* and Capsule*) as a Novel Method in Treating Alcohol Dependence. A randomized, double-blind, placebo-controlled trial.

Executed by:

BIOHIT Oyj (Helsinki, Finland);

Research Team:

X Y, X Z, etc.,

---

*Registered Trade Marks of Biohit Oyj (Helsinki, Finland), classified as **Medical Device**.

Background: The majority of people drink alcohol responsibly with no associated harmful effects. However, in many countries, over 20% of people consume alcohol in a way that is potentially or actually harmful to their health and well-being. This leads to huge number of hospital admissions and extremely high costs for the societies, e.g. $220 billion in the US alone.

A proportion of people consuming alcohol at harmful levels will develop alcohol dependence. This condition is characterized by craving; tolerance; a pre-occupation with alcohol; continued drinking in spite of harmful consequences; and the development of a physiological withdrawal syndrome when alcohol is suddenly stopped or consumption markedly reduced. The exact definitions of alcohol dependence (officially recognized as a mental health disorder) are provided by the WHO in their International Classification of Diseases (ICD), and by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Given that many patients are reluctant to reveal the extent of their alcohol problems, carefully validated questionnaires have been designed to facilitate this evaluation, e.g. the Alcohol Use Disorders Identification Test (AUDIT) ranking the subjects into 3 levels of risk; low-, moderate- and strong alcohol dependence.

At the moment, only three pharmaceutical agents (**disulfiram, acamprosate** and **naltrexone**), have been licensed for the maintenance of abstinence and/or relapse prevention in dependent drinkers in the vast majority of countries. Nalmefene has recently been licensed in some countries, for use in people who are drinking at high-risk levels, and who wish to reduce their alcohol consumption but not necessarily abstain.

The **initial step in any treatment of alcohol dependence is withdrawal from alcohol**. Withdrawal management is not a stand-alone process but should be the first phase of a long-term treatment plan. **Psychosocial intervention is the backbone of the treatment for alcohol dependence**. The long-term prognosis for people entering a specialist treatment is comparatively deprived. Over a 10-year period, about one-third have continuing alcohol problems; a third show some improvement and the rest 30% have a good outcome defined as either abstinence or moderate drinking. Accordingly, there is an urgent need for novel pharmacotherapies that would be more effective in the intervention of alcohol dependence.

During the past several years, increasing body of evidence suggests that central and peripheral **acetaldehyde (ACD)** actively participates in the **positive motivational properties** of ethanol. Much of these reward effects of alcohol is suspected to be mediated by **harman** and **norharman** which are condensation products of ACD with biogenic amines in the saliva and in the stomach contents. Both harman and norharman are effective **inhibitors of MAO enzyme**, and as such reinforcing the alcohol- and nicotine dependence

It has been known for several decades that **L-cysteine** (a nonessential amino acid) is able to eliminate the toxicity of ACD by reacting covalently with ACD to form a stable 2-methylthiazolidine-4-carboxylic acid (MTCA). This simple principle was used in the recent innovations of Biohit Acetium® capsule containing 100mg L-cysteine, and Acetium® lozenge (3mg L-cysteine)(Biohit Oyj, Helsinki).

Given the above, it is tempting to speculate that elimination of ACD in the saliva during cigarette smoking by Acetium® lozenge might effectively block (or reduce) the formation of harmans, reduce their high blood levels, and thus alleviate the acetaldehyde-enhanced

nicotine addiction (by reducing MAO-inhibition) among smokers. Indeed, the validity of this hypothesis was recently confirmed in two RCTs, where Acetium® lozenge proved to be a highly effective new tool in assisting smoking quit. **A Europe patent (EP2 197 436 B1) was granted to Acetium® lozenge,** with the main claim of use in reducing tobacco and/or alcohol dependence in an individual who is dependent on tobacco and/or alcohol.

Objective: The present study is **extending this (Biohit patented) concept** from treating the smoking dependence to **treating of alcohol dependence** by the same mechanism (ACD elimination). The objective is to assess whether (in alcohol-dependent subjects) the regular use of slow-release L-cysteine preparations (Acetium® lozenge and Acetium® capsules **as stand-alone or in combination**) concomitantly with alcohol intake, might reduce their alcohol reward effects by interfering with the exposure to high blood levels of harman and norharman arising as condensation products of alcohol-derived ACD and biogenic amines in the saliva and stomach contents.

Specific aims: The null hypothesis of the study implicates that Acetium® lozenges/Acetium® capsule stand-alone or as a combination is not superior to similar placebo combination in maintaining the alcohol abstinence during the 6-month follow-up period. Rejection or not of the null hypothesis is based on comparison of the two strata (Acetium® arms and placebo) against the primary (12-week abstinence) and any of the secondary study endpoints.

Study design: A double-blind, placebo-controlled clinical trial (RCT) testing Acetium® lozenges and Acetium® capsules (**single and in combination**) with similar placebo administration in maintenance of alcohol abstinence in alcohol dependent patients, during a 6-month intervention period.

Methods: This trial is run by an adequately resourced CRO. A cohort of 400 alcohol dependent volunteers will be enrolled by either of two options: 1) in-patient or 2) outpatient setting, both being linked with special clinics of alcohol and addition medicine. Eligible subjects are severely alcohol dependent (AUDIT score >20), who are well motivated to refrain from alcohol abuse, and who give a written consent to participate. After 2 weeks of alcohol withdrawal, the subjects will be randomly allocated to four groups (n=100 in each), receiving either the Acetium® lozenge , Acetium® capsule, the combination of these two, or placebo combination, in a double-blind setting. All subjects must consent for adhering to the treatment regimen: one lozenge with each single alcohol drink, one capsule at 2-hour intervals during a drinking session, and both preparations accordingly. Other pharmaceutical drugs for alcohol dependence are not allowed. All subjects need to fill in a drinking diary on daily basis, and return the diary on weekly basis to the contact clinic. On that occasion, the subjects are tested by breath alcohol test (BAT), AUDIT score, and they will participate in the cognitive behavioral therapy (CBT) as part of the treatment strategy.

The **primary study endpoint** is alcohol abstinence at 12 weeks after withdrawal, used for calculating OR (95%CI) between the Acetium® and placebo study arms. A series of alcohol consumption-related variables are used as the **secondary endpoints**, including the following: 1) the number of monthly drinking days; 2) the number of monthly heavy drinking days (HDD; >60g for M; >40g for F); 3) return to any drinking following abstinence (=relapse); 4) total amount of alcohol consumption; 5) treatment response, i.e., the proportion subjects who decrease their alcohol consumption to low-risk levels or no consumption, as determined from the AUDIT score and Drinking Diary.

The study (n=100 per study arm) is adequately powered (Type II error 0.80, type I error 0.05) to detect a true difference (in 12-week abstinence) of 18% between any of the Acetium® arms compared to the placebo, within the range of 20% abstinence achieved in the placebo and 38% abstinence in any of the Acetium® arms. Within this (20-38%) effect size range, the study power is sensitive to any decrease in this effect size difference, but allows less difference (15%) if the abstinence rate falls between 10% and 25% in the study arms. This effect size range (20-40%) closely coincides with the therapeutic effects reported in large meta-analyses of RCTs.

Study execution and time-table:

The execution of the RCT will be done by an adequately resourced CRO (contract research organisation, which has the overall responsibility of running all the steps of the study from enrolment until study completion. After completion of the 6-month intervention period, the randomization code will be opened, and the data analysed for the primary and secondary endpoints as usual.

At this stage, no exact estimates for the time-table can be given. Because the intervention period is 6 months for all subjects, the crucial determinant of the total time required for completion of the trial is the speed of cohort enrolment. With multiple expert clinics involved, however, that should not be non-proportionate to the total execution time of this RCT.

1.BACKGROUND

1.1.Alcohol misuse, health and societal costs

Approximately 80% of the adult population in the UK consume alcohol (1). The majority of people drink responsibly with no associated harmful effects. However, eg. in England in 2014, 22% of men and 16% of women, amounting to some 10.3 million adults, consumed alcohol in a way that was potentially or actually harmful to their health and well-being)(1). It has been estimated that 5.9% of the adult population in England (8.7% of men and 3.3% of women) are alcohol dependent (2). Based on current population estimates in the UK, this translates to some 3.2 million people, although the figure more frequently cited is 1.6 million (3).

In 2014/2015, there were an estimated 1.1 million alcohol-related hospital admissions in England, representing a 115% increase over 2003/2004 (4,5). A total of 8.697 entirely attributable alcohol-related deaths were registered in the UK during 2014, two-thirds of which were attributed to alcohol-related liver disease (6). However, a considerably higher estimate of 25.332 deaths can be extrapolated from the data provided by Public Health England based on a combination of all deaths relating to alcohol-specific conditions together with those where alcohol was causally implicated in some but not in all cases (7). The estimated annual costs of alcohol misuse to the UK National Health Service (NHS) is £3.5 billion, whereas the overall costs of alcohol-related societal harm approximates to £21 billion per year (8).

In the USA, the proportion of adults consuming alcohol is lower than in the UK at 46.3% (9). The 12-month prevalence of alcohol dependence is estimated to be 3.8% (men 5.4%; women 2.3%) while the estimated lifetime prevalence is 12.5% (men 17.4%; women 8.0%)(10). Alcohol dependence is associated with more than 85.000 deaths per year making it the third leading cause of preventable deaths in the USA (11). The estimated annual cost to the society is more than $220 billion (12).

1.2.Alcohol dependence: definitions, diagnosis and natural history

A proportion of people consuming alcohol at harmful levels will develop alcoho dependence. This condition is characterized by crav§ing; tolerance; a pre-occupation with alcohol; continued drinking in spite of harmful consequences; and the development of a physiological withdrawal syndrome when alcohol is suddenly stopped or consumption

markedly reduced (13). More exact definitions of this condition, which is officially recognized as a mental health disorder, are provided by the World Health Organization in their International Classification of Diseases (ICD)(14), and by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM)(15). The ICD-10 and DSM-IV diagnostic criteria for alcohol dependence have a high diagnostic concordance (16)(**ANNEX 1**).

The diagnosis of alcohol dependence is usually made by reviewing the clinical history. However, this can be inaccurate if the patients are unaware, or reluctant to reveal the extent of their problems with alcohol. Given that this is well recognized, questionnaires have been designed to facilitate this process. The Alcohol Use Disorders Identification Test (AUDIT) (17)(**ANNEX 2**) for example, which was developed as a WHO collaborative initiative (**ANNEX 3**), is designed to identify people who have an alcohol use disorder. A score of ≥8 indicates hazardous/harmful drinking, and a score of >16 indicates alcohol dependence (17).

Harmful alcohol use and alcohol dependence are relatively uncommon before the age of 15 but, thereafter, the prevalence increases abruptly reaching a peak in the early twenties before declining. In one study from the UK, the prevalence of alcohol dependence was 6% among 16–19-year-olds, 8.2% in 20–24-year-olds, 3.6% in 30–34-year-olds, and 2.3% in 50–54-year-olds (18). Thus, substantial remission from alcohol dependence can occur over time, often without any type of intervention (19). However, those who remain dependent in their forties tend to have a more chronic course. Indeed, most studies found that 70–80% of the people entering specialist treatment will relapse in the year after completing treatment, most likely during the first 3 months (20,21). Those who remain abstinent from alcohol for the first year after treatment have a relatively low risk for relapse afterwards (22).

The long-term prognosis for people entering a specialist treatment is comparatively deprived. Over a 10-year period, about one-third have continuing alcohol problems; a third show some improvement and the rest 30% have a good outcome defined as either abstinence or moderate drinking (23). The mortality rate in this population is nearly 4-times higher than the age-adjusted rate for people who are not alcohol dependent. Much of the

excess mortality is accounted for by disorders associated with comorbid tobacco use, including, cardiovascular disease and aero-digestive malignancies (23,24).

2.TREATMENT OF ALCOHOL DEPENDENCE

The severity of alcohol dependence can be assessed using different scores: eg. the Severity of Alcohol Dependence Questionnaire (SADQ)(25) or the extensively validated AUDIT score (17), both providing information that facilitates the clinical management.

2.1.Principles of the treatment

The initial step in any treatment of alcohol dependence is withdrawal from alcohol. In some, but not all instances, medical assistance will be required to **prevent or to treat** the **withdrawal symptoms**; benzodiazepines are the drugs most commonly employed to facilitate this process (13,26,27). Guidelines for expert guidance on the withdrawal process including all aspects of the patient safety and general well-being, have been elaborated eg by the UK National Institute for Health and Care Excellence (NICE)(13,26). People with mild dependence (i.e., SADQ score <15) do not usually need medically-assisted withdrawal, subjects with moderate dependence (SADQ 15–30; AUDIT 16-19) usually do need medical assistance, typically in a community setting (21), whereas people who are severely alcohol dependent (SADQ score >30; AUDIT >20) will require medically-assisted withdrawal, typically in an in-patient or residential setting.

Withdrawal management is not a stand-alone process but should be the first phase of a **long-term treatment plan**. For the majority of subjects who are dependent on alcohol, the most appropriate goal (in terms of alcohol consumption) is a total abstinence. For people with significant psychiatric or physical comorbidity, eg. a depressive disorder or alcohol-related cirrhosis, abstinence should invariably be the goal. Nevertheless, some people will not agree with this advice, preferring a goal of moderation. However, the more severe the level of dependence, the less likely it is that a return to moderate or controlled drinking will be possible (22,28). Thus, where clinicians believe that abstinence is the most appropriate goal, they should strongly advise this course, but should not deny treatment if this advice is not followed (21).

Psychosocial intervention is the backbone of the treatment for alcohol dependence (13). For example in the UK, NICE has provided detailed guidance on the provision of

psychosocial support tailored to reflect the severity of the dependence (13). In the UK, such services are delivered by both the public and non-public providers, and additiona sources of support, such as self-help based interventions, are encouraged. NICE alsc recommends the use of adjuvant pharmacotherapy for people with moderate to severe dependence once they had been successfully withdrawn from alcohol (13). Similarly adjuvant pharmacotherapy is also recommended for people with mild dependence whc have either not responded to initial attempts to attain abstinence or have specifically requested it (13).

Similar approaches to the treatment of alcohol dependence are employed in Europe (29) the USA (30,21,32) and Australia (33). The latest good practice recommendations in France, published by the Societe Francaise d'Alcoologie jointly with the European Federation o Addiction Societies, recommend the use of pharmacological treatments, combined with psychosocial support for relapse prevention in patients with alcohol dependence (29) Likewise, in the USA, the Veterans Administration (VA)(30), National Institute on Alcoho Abuse and Alcoholism (NIAAA)(31) as well as Substance Abuse and Mental Health Services Administration (SAMHSA)(32) all advocate for the management of alcohol dependence the use of adjuvant pharmacotherapy in combination with behavioral intervention or addiction-focused counselling. Finally, the Australian guidelines for the treatment of alcoho problems stipulate that pharmacotherapy should be considered for all alcohol- dependen patients following detoxification – best used in association with psychosocial supports as part of an after-care treatment plan (33).

Before entering into the study design, the efficacy and safety of the current and emerging potential therapeutic agents used in the management of alcohol dependence will be shortly reviewed, so as **to position the planned RCT with Acetium® lozenge into the right context**.

2.2.Licensed pharmacotherapies for the maintenance of abstinence

Disulfiram, **acamprosate** and **naltrexone** are the only pharmaceutical agents licensed for the maintenance of abstinence and/or relapse prevention in dependent drinkers in the vast majority of countries, advocating the use of pharmacotherapy in the management of alcohol dependence, as recently reviewed (34). **Nalmefene** has recently been licensed in

some countries, for use in people who are drinking at high-risk levels who wish to reduce their alcohol consumption but not necessarily abstain (34).

2.2.1.Disulfiram

Disulfiram has been used in clinical practice for over 60 years by now. The oral preparation is licensed for prevention of relapse all over Europe, North America, Australia and parts of Asia. Despite its apparent efficacy when used in compliant and/or supervised subjects, the overall efficacy of disulfiram remains controversial (34).

2.2.1.1.Mode of action

Alcohol is metabolized in the liver by alcohol dehydrogenase (ADH) to acetaldehyde and further into acetic acid by acetaldehyde dehydrogenase (ALDH). Disulfiram is an oral **ALDH-inhibitor** (34). The high levels of acetaldehyde accumulating after alcohol ingestion in drinkers taking disulfiram result in the development of severe symptoms, including flushing, nausea, vomiting, tachycardia, hypotension, dyspnoea, dizziness and headache (34,35). The intensity of the reaction varies with the amount of alcohol, and it can prove even fatal (36,37). The fear of the unpleasant effects provoked by alcohol is believed to be the primary mechanism facilitating abstinence from alcohol (38,39). Disulfiram has also been used in the treatment of cocaine addiction particularly in people with comorbid alcohol-related problems (40,41,42). It inhibits the enzyme dopamine β-hydroxylase, which converts dopamine to norepinephrine (43).

2.2.1.2.Efficacy

Until now, there is no consensus on the optimal trial methodology for assessing the efficacy of disulfiram in treating alcohol dependence (34). A common view persists that disulfiram efficacy cannot be reliably appraised in a double-blind, randomized, clinical trial (RCT) because the psychological fear of provoking an unpleasant disulfiram-alcohol reaction is the key to its effectiveness (34).

A number of systematic reviews and meta-analyses of the available treatment trials have been published (13,42,44,45), with treatment efficacy as the endpoint. The most comprehensive of these (42) included a total of 22 RCTs, published between 1973-2010 and comparing the efficacy of disulfiram to i) no treatment, ii) placebo or iii) other pharmacological treatments, irrespective of blinding or supervision of the medication.

Based on the results of the open-label studies, where compliance was assured by supervision, disulfiram seems to be a safe and efficacious treatment compared to no treatment or to other pharmacological agents (42). However, no evidence of efficacy was found in blinded RCTs or in trials where no supervision was available (42).

2.2.1.3.Safety

A wide variety of side-effects are associated with use of disulfiram: headaches, drowsiness, lethargy, peripheral neuropathy, optic neuritis, hepatotoxicity and even psychosis (37,46,47). In general, the moderately severe side-effect profile can be offset by careful patient selection and supervision (34).

2.2.2.Acamprosate

Acamprosate was introduced into clinical practice some 30 years ago. The oral preparation is licensed for the maintenance of abstinence in alcohol-dependent people in most of Europe, North America, Australia, parts of Asia and Africa, including Japan (34).

2.2.2.1.Mode of action

Acamprosate is the **calcium salt of N-acetyl-homotaurine** (34). Its mechanism of action is unclear, although it has been ascribed to aspects of glutamatergic and/or GABA-ergic neurotransmission. Because of this, acamprosate is frequently referred to as a "functional glutamate antagonist" (48). Recently, however, it has been suggested that acamprosate has no direct neurotransmitter target and that the therapeutic effects associated with its use are due to the co-administered calcium moiety (34,49,50). These findings still await confirmation, but the role of plasma and/or brain levels of calcium as a correlate or mediating factor of the efficacy warrant further exploration (50).

2.2.2.2.Efficacy

The results of a large number of RCTs and meta-analyses have shown that treatment with acamprosate, in conjunction with psychosocial support, significantly increases the likelihood of alcohol-dependent patients to remain completely abstinent from alcohol at 6 months (13,45,51,52,53,54). Mann et al. (51) in their meta-analysis of 17 RCTs (n=4.087 participants), showed that 36.1% of patients receiving acamprosate achieved this endpoint as compared with 23.4% of those receiving placebo. Importantly, the number needed to treat (NNT) to achieve continuous abstinence was 7.8 at 6 months and 7.5 at 12 months

(51). A Cochrane review, including 24 RCTs with 6.915 participants showed a significant beneficial effect of acamprosate on outcome measures other than abstinence (52). Thus the use of acamprosate was associated with 1) a reduction in the return to any drinking, with a NNT of 9; 2) a reduction in the risk of any drinking to 86% of the placebo rate, and 3) an increase in the number of abstinent days by approximately three per month (52).

2.2.2.3.Safety

Acamprosate is not metabolised in the liver, and the drug has no impact on hepatic metabolism or effects on the cytochrome P450 system (34). Thus, it does not interact with alcohol and it is generally safe in patients with impaired hepatic function. However, because it is excreted predominantly by the kidney, precautions should be taken of its use in people with renal insufficiency. Acamprosate is well-tolerated (47), and pharmacovigilance data in 1.5 million patients indicate no serious adverse events (55). The most commonly reported side-effect is diarrhea (51). It does not have addictive potential
and appears safe even if overdosed (48).

2.2.3.Naltrexone

Naltrexone has been used in the management of opioid dependence since 1984 (34). It was first used to treat alcohol dependence in 1994. The oral preparation is licensed for relapse prevention in alcohol-dependent people in several countries of Europe, the USA, Australia and Asia (34).

2.2.3.1.Mode of action

Naltrexone and its active metabolite 6β-naltrexol act as **opioid receptor antagonists** particularly at the μ-opioid receptor. The mechanism of its beneficial effect in the treatment of alcohol dependence is not fully understood (34), but it is believed to reduce the reward effects of alcohol by modulating the dopaminergic mesolimbic pathway (56,57).

2.2.3.2.Efficacy

An increasing number of RCTs have been published to examine the efficacy of naltrexone for the treatment of alcohol dependence (34). These have been analysed in a number of systematic reviews and meta-analyses, using variable inclusion criteria and drinking outcomes but, nevertheless, with comparable results (13,45,53,55,58,59,60). According to these data, among alcohol-dependent people who have been withdrawn from alcohol,

naltrexone, in combination with psychosocial support, has a modest but significant beneficial effect on relapse rates, and in reducing alcohol intake (34).

A Cochrane systematic review and meta-analysis including 40 placebo-controlled RCTs of naltrexone, involving approximately 4.500 participants, showed that treatment with naltrexone significantly reduced the risk of a return to heavy drinking, down to 83% of the placebo rate, with a NNT of 9 (59) Treatment was also associated with 1) a 4% reduction in the number of drinking days; 2) a 3% reduction in the number of heavy drinking days; and 3) a reduction (by 11g) in the amount of alcohol consumed on the drinking days Unfortunately, however, it did not have a significant effect on the return to any drinking (59). The results of a number of other meta-analyses confirm the effects of naltrexone in reducing the risk of a relapse to heavy drinking and the number of drinks consumed or drinking days (58,59,60). Some others found that its use was also associated with a significant, albeit modest effect on the return to any drinking and overall abstinence rates (58,60).

2.2.3.3.Safety

Naltrexone is metabolised in the liver via the enzyme dihydrodiol dehydrogenase predominantly to 6β-naltrexol, and the metabolites are further conjugation with glucuronide (34). As naltrexone is not metabolised via the cytochrome P450 system interactions with drugs metabilised by the liver are likely to be minimal. However, increased plasma naltrexone concentrations have been reported in patients with liver cirrhosis. Naltrexone does not interact with alcohol and does not have addictive potential (34).

The most commonly reported side-effects are nausea, vomiting, dizziness, abdominal pain, reduced appetite, headache and daytime sleepiness. These seem to be dose-dependent and appear to be worse in women (47). Hepatotoxicity has been reported in association with use of naltrexone in doses of >300 mg/day to treat obesity (61). However reviews of the available safety data have confirmed that hepatic toxicity is very unlikely to occur with the standard daily dose of 50 mg (13).

The most important safety consideration in relation to naltrexone is its reaction with opioid drugs. Opioid receptor blockade persists for up to 48–72 h after the last oral dose. Thus, in case of an emergency, non-opioid analgesia would have to be used for pain relief. If

future use of opioids is anticipated, for example, for elective surgery, then naltrexone should be discontinued ahead of time (34).

2.2.4.Nalmefene

Nalmefene is **an opioid system modulator** which is structurally similar to naltrexone but it has a slightly **different receptor profile**. It was first introduced into the treatment of alcohol dependence in the early 1990's (62,63,64). However, a meta-analysis of the three RCTs available at that time using daily doses in the 20–80 mg range, showed that although nalmefene had some beneficial effect on drinking outcomes, none of these was significant (59). Subsequently, the drug was remarketed and licensed, on the basis of a small number of additional industry-sponsored initiatives for use in people who were drinking harmfully and wanted to reduce their alcohol consumption, though not necessarily stop it (65,66,67,68,69). However, this so called "harm reduction" approach to alcohol problems remains highly controversial (34,70). Thus, although several studies have demonstrated that controlled drinking is possible and that moderation-based treatments may be preferred over abstinence-only approaches, the evidence base for using this approach is not strong (34).

Nevertheless, in 2013, nalmefene was approved by the European Medicines Agency (EMA) as a treatment for alcohol dependence in people who **wish to reduce their alcohol consumption** but not necessarily abstain. In November 2014, NICE (71), despite concerns raised by its own Evidence Review Group (72) recommended nalmefene together with psychosocial support, as a treatment option for people drinking at high-risk levels who wished to reduce rather than stop alcohol (34). In France, nalmefene is recommended as the first-line medication for reducing alcohol consumption in people who are alcohol dependent (29). Regulators and advisory bodies in other European countries have not recommended nalmefene for this indication (34).

The drug is not licensed for use in the USA or Australia. Palpaceur et al. (73) have recently undertaken a meta-analysis of the efficacy and safety of nalmefene for the treatment of alcohol dependence. They included all available RCTs of nalmefene, irrespective of publication status, primary outcomes and licensed indications (62–69). Overall, there was some evidence of a beneficial effect of nalmefene on the number of heavy drinking days

per month and on total alcohol consumption, but there were more withdrawals for safety reasons in the nalmefene-treated groups and the findings were not robust. There was no evidence of a beneficial effect of nalmefene on the health outcomes examined. The authors concluded that, at best, nalmefene has limited efficacy in reducing alcohol consumption but they were clearly aware of the limitations of their review and made specific recommendations for future studies (73).

2.2.4.1.Criticism and safety issues

The licensing and subsequent recommendations for the therapeutic use of nalmefene have been widely criticized (34,74,75). The major objections raised include: i) the target population was defined following an unplanned subgroup analysis of the available trials, thus departing from the intention-to-treat principle; ii) the placebo comparator was inappropriate – the efficacy of nalmefene should have been compared with naltrexone which is used off-label for this indication; iii) the supposed advantage conferred by nalmefene on alcohol consumption levels was of questionable clinical relevance; and, iv) no evidence of wider harm reduction was sought or provided in the trials included for review (34,73,74,75).

As nalmefene is an opioid receptor antagonist, the same precautions and guidance provided for naltrexone in relation to opioid usage should apply. The most commonly encountered side-effects are nausea, insomnia, dizziness, vomiting and fatigue (34) However, use of naltrexone has not been associated with evident hepatotoxicity. In addition, naltrexone is considerably more expensive than the other drugs licensed to treat alcohol dependence (34).

2.2.5.Emerging treatment modalities for alcohol dependence

A number of other agents have been proposed and are currently under investigation as potential treatment options for alcohol dependence. These have been presented in detai by Goh et al. in their comprehensive review (34), and a detailed discussion is not relevant in this context. The majority of these emerging drugs already have an established therapeutic profile and are being re-tested in this new indication (34). Of these emerging novel therapies, **baclofen, topiramate** and **metadoxine** are the best known (34). The others with an evidence base include: 1) **gabapentin**: an inhibitor of presynaptic, voltage-gated sodium and calcium channels which is approved for the treatment of epilepsy and

neuropathic pain; 2) **ondansetron**: a serotonin 5-HT3 receptor antagonist which is used to prevent nausea and vomiting in selected clinical situations; 3) **varenicline**: a nicotinic receptor partial agonist which is used for smoking cessation; and, 4) **aripiprazole**: an anti-psychotic which is a partial dopamine agonist. Until now, none of these compounds is licensed for the treatment of alcohol dependence, but they can naturally be used off-label for this purpose (34).

2.3.Predictors of treatment outcomes

The issues related to the outcome of the treatments for alcohol dependence have been addressed in their insightful review by Goh et al. (34). They conclude that the drugs currently available for the treatment of alcohol dependence have **only modest effects,** despite the fact that increasing attention has been focused on optimizing the treatment by identifying people who are more likely to respond (34). These attempts are confounded by 1) the so-called 'placebo effect' and 2) by factors pertaining to adherence and compliance with treatment. In addition, demography, drinking variables and comorbidities need to be considered. Finally, pharmacogenetics is likely to play a more important role as previously realized (34).

2.3.1.Placebo effect

It is a common knowledge that the **placebo effect** can confound efforts to determine treatment effectiveness in clinical trials. The greater the placebo group response, the more difficult it is to demonstrate medication efficacy. The placebo response in trials of drugs for alcohol dependence appears to be even greater than e.g. in trials for depression and schizophrenia (34). Furthermore, more recent studies in alcohol dependence have shown a greater placebo group improvement; an effect which persists even after controlling for several other moderators, including concomitant interventions. Thus, more attempts will need to be made to more effectively isolate alcohol medication effects in the future studies (76,77).

2.3.2.Patient compliance and adherence

The clinical effectiveness of any medication is highly influenced by the degree of patient **compliance** and **adherence** to treatment regimens. Trials of drugs for the treatment of alcohol dependence, not unlike those in the addiction field generally, are characterized by high drop-out rates and generally low levels of compliance with the treatment (43,52,59).

However, incomplete information is available on the factors that affect compliance in this setting (34). Rohsenow et al. (78) reported that compliance with naltrexone was better in those who believed that the medication would help them maintain abstinence. Compliance was not predicted by 1) demographic or pre-treatment alcohol use, 2) commitment to abstinence or 3) perceptions about their own ability to abstain. Supervision or witnessing, which are involved primarily in patients receiving disulfiram are a major determinant of compliance and effectiveness of the therapy (43).

2.3.3.Demography, drinking variables and comorbidities

A number of demographic variables, along with the drinking behavior and potential comorbidities have been explored, and several possible predictors of outcome have been identified, but the results are inconsistent across different studies (34). The most favorable results in people receiving unsupervised disulfiram were in those who were older; more socially stable; impulsive and motivated (35,79). Pooled data from seven placebo-controlled RCTs of acamprosate, involving 1.485 participants, showed that there were no significant relationships between treatment outcomes and gender, the age at onset, the severity of dependence or family history (80). A number of studies have reported that people with a family history of alcohol-related problems are more likely to benefit from naltrexone but other identified predictors such as high levels of craving, early age of onset, concomitant drug misuse and comorbid depression are not as robust (81,82,83).

2.3.4.Pharmacogenetics

The evidence accumulated on the role of pharmacogenetics as a modifier of the response to treatment for alcohol dependence was reviewed recently (34). The discussion is far too detailed to be re-iterated here, however. The authors concluded by stating that to date, no studies have been undertaken to assess the clinical utility of **genotype-guided selection** of medication or dosing strategies (34). Until now, only one study has been published where participants were randomized to treatment with naltrexone or placebo by genotype (84). Unfortunately, the study was not adequately powered to give definitive answers about the feasibility of this approach. The authors are confident in that future studies will ultimately define a range of genetic variations that have clinical value in predicting the response to the drugs used to treat alcohol dependence (34).

Taken together, in far too many countries, individuals with alcohol-use disorders often fail to receive care, particularly evidence-based care. In addition, there is clear evidence that although drug treatment for alcohol dependence is safe and cost-effective, it is substantially underutilized (34). Efforts must be made to overcome the current barriers to treatment which, in large part, reflect reluctance of the doctors to prescribe these medications.

3.ACETALDEHYDE (ACD) AND ALCOHOL DEPENDENCE

Since the discovery of disulfiram as an effective ALDH-inhibitor, used to treat alcoho dependence (38-47), the role of acetaldehyde (ACD) in the effects of ethanol has beer thoroughly investigated on pre-clinical grounds (85). After more than 25 years of intense research, a large number of studies have been published on the **motivational properties** of ACD itself as well as on the role that ethanol-derived ACD plays in the effects of ethanol, as reviewed recently (85).

With respect to the motivational properties of ethanol, these studies were developed following two main strategies: 1) on one hand, were aimed to challenge the suggestion that also ACD may exert motivational properties on its own, while, 2) on the other, with the aid of enzymatic manipulations or ACD inactivation, were aimed to test the hypothesis that ethanol-derived ACD might have a role in **ethanol motivational effects**. Furthermore recent evidence significantly contributed to highlight, as possible mechanisms of action of ACD, its ability to commit either **dopaminergic** and opioidergic transmission as well as to activate the Extracellular signal Regulated Kinase cascade transduction pathway in reward-related brain structures (85). Despite the observation that ACD seems to have inherited the elusive nature of its parent compound (ethanol), the available behavioural and biochemical evidence points to **ACD as a neuroactive molecule**,
capable on its own and as ethanol metabolite, to **exert motivational effects**.

The authors conclude their comprehensive review by stating that current observations support the tenet that the generation of **central** and peripheral **ACD actively participates in the positive motivational properties of ethanol, and raise the possibility that its role can be exploited to devise novel pharmacological approaches that target alcohol abuse related problems (85).** Indeed, this is exactly what Biohit Oyj stipulated several

years ago while summarising their own research on ACD and its elimination in **patent applications** filed in 2008 and approved in 2017 and 2018 in Europe (**EP2 197 436 B1**) and Canada (**No. 2,704,129**), respectively (86,87).

All this evidence elaborated by Biohit Oyj (and others) forms the basis for the formulation of the present study hypothesis, whereby elimination of ACD in the saliva by slow-release L-cysteine (Acetium® lozenge) and from the stomach contents by Acetium® capsules, could have inhibitory effects on ACD-maintained motivationa effects of ethanol, i.e., to be an effective new treatment modality for alcohol dependence (for details, see the following**).**

3.1.Acetaldehyde (ACD), Group 1 human carcinogen (by IARC)

Acetaldehyde (ACD) is the first metabolite of ethanol oxidation (34). It binds to DNA, forming stable DNA adducts that are observed in alcohol consumers. Numerous epidemiological studies in alcohol drinkers with ALDH2 deficiency or low aldehyde dehydrogenase (ADH1B) activity provide the most compelling evidence for the carcinogenicity of acetaldehyde (88). This deficiency results in 1) the accumulation of ACD locally into the saliva during ethanol metabolism and also in 2) markedly increased risk for many upper gastrointestinal tract cancers.

Similarly, it was recently shown that ACD from the tobacco smoke is easily dissolved into the saliva during smoking (89). Thus, toxic aldehydes could mediate the carcinogenic effec of tobacco smoke through saliva to oral cavity and from there further on into the larynx, esophagus, and stomach. Based on firm epidemiological and toxicological documentation, IARC proclaimed (in 2009) ACD as Group I human carcinogen, equivalent to asbestos, formaldehyde and others (90).

3.2.L-cysteine eliminates acetaldehyde in the stomach and in saliva

Cysteine is a non-essential amino acid, which was shown (over 40 years ago) to be capable of eliminating the toxicity of ACD by reacting covalently with it to form a stable 2-methylthiazolidine-4-carboxylic acid (MTCA)(91). MTCA is an inert and non-toxic compound that is eliminated from the body through feces and urine, without being absorbed into the blood circulation. This simple principle was used in the recent innovation

of Biohit Acetium® capsule containing 100mg L-cysteine. **NOTE: Acetium® lozenge and Acetium® capsule are NOT classified as medicines, but as Medical Device.**

In the proof-of-concept study in human, oral administration of Acetium® was confirmed to effectively bind ACD originated from ethanol metabolism in achlorhydric stomach (92).[3] In that setting, the mean ACD level of gastric juice was 2.6-times higher with placebo than with l-cysteine (13 vs. 4.7 μM, $p<0.05$), implicating that L-cysteine can be used to decrease ACD concentration in acid-free stomach during alcohol exposure (92).

Similar results were reported in animal experiments by an Italian group in 2009 (93). In their experiments, male Wistar rats were pretreated intraperitoneally with saline or L-cysteine (10, 20,or 30 mg/kg), before intra-gastric administration of saline, ethanol (1g/kg), or ACD (20 mg/kg). The specificity of L-cysteine effect was assessed using morphine-induced conditioned place preference (cpp)(2.5 mg / kg, i.p.). L-cysteine dose-dependently prevented both ethanol- and ACD-induced cpp, but had no effect on morphine-induced cpp, suggesting that L-cysteine specifically modulates the motivational properties of ethanol (93). The authors concluded that L-cysteine, by binding ethanol-derived ACD would deprive ethanol-induced motivational and rewarding properties thus reducing the liability of alcohol abuse (93).

Already in 2002, this capacity of L-cysteine to bind with ACD led the Biohit research team to examine the concept, whether it would be possible to eliminate alcohol- or cigarette smoke-derived ACD also from the saliva using slow-release L-cysteine buccal tablet (Acetium® lozenge)(94). Indeed, this was shown to be the case in tested volunteers, in whom, up to two-thirds of ACD (after alcohol intake) could be removed from the saliva with a slow-release buccal L-cysteine formulation. This should have important implications e.g. in prevention of upper GI-tract cancers among individuals with high ACD exposure (heavy drinkers, smokers, ALDH2-deficient)(94).

As the logical next step, the company (Biohit Oyj) developed an Acetium® sucking tablet (lozenge) that releases L-cysteine into the oral cavity during smoking and alcohol drinking, and tested this formulation as a potential chemopreventive agent against toxicity of tobacco smoke (95). Seven volunteers smoked five cigarettes, and during every smoking period, sucked a blinded tablet containing 0, 1.25, 2.5, 5, or 10 mg of L-cysteine, followed

by ACD analysis of the saliva at 0-, 5-, and 10-minutes from the start of smoking. L-cysteine reduced highly significantly the salivary ACD. In fact, ACD could be totally inactivated in the saliva during smoking by the sucking tablet containing 5 mg of L-cysteine (95).

3.3.Acetium® lozenge reduces ACD-maintained reward of smoking and assists quit

The idea of testing L-cysteine as potential trigger of smoking quit aroused from subjective reports by smokers who tested Acetium® lozenges for eliminating ACD in the saliva in the smoking context. These emerging subjective reports among smokers suggest that Acetium® lozenges used concomitantly with smoking reduce or even totally eliminate the sensations of smoking-associated pleasure (reward), i.e., the main cause for smoking dependence. The later has been traditionally ascribed to nicotine, the major psychoactive component of tobacco, particularly among adolescents, who seem to be more sensitive to the rewarding effects of nicotine thus leading to nicotine addiction (96,97).

Dependence on smoking, however, is a much more complex issue than just nicotine addiction. Although nicotine is the major psychoactive substance in tobacco, nicotine replacement therapy (NRT) is not highly effective as a treatment for tobacco addiction, particularly in adolescents (98,99). As discussed, ACD is a well-known metabolite of ethanol, which is also present in tobacco smoke in a concentration half that of nicotine (100,101). It has been previously shown that a synergistic interaction exists between nicotine and ACD in self-administration in juvenile but not in adult rats (102). However, the underlying mechanisms are not yet clear. Although ACD has been reported to induce behavioral effects, including reward (85,93), in experimental animals, these are usually only observed following peripheral administration of high doses of drug or following central administration (103). Given the localization of the metabolic enzyme, aldehyde dehydrogenase (ADH) at capillary endothelial junctions, there has been considerable debate as to whether or not ACD can cross the blood brain barrier (BBB)(85).

However, in the elegant experiments, Cao et al. (2007) presented experimental evidence implicating that ACD, a major constituent of tobacco smoke, **enhances behavioral endocrine, and neuronal responses to nicotine** in adolescent and adult rats (104) Although the mechanisms underlying the interaction of nicotine and ACD are still not clearly understood, these data suggest that ACD may influence habituation to stress, possibly via effects on the PVTh (paraventricular nucleus of Thalamus), which is not

protected by the BBB. These experimental data also implicate that other constituents in tobacco and tobacco smoke may also contribute to the effects of nicotine and may, consequently, affect smoking behaviors (104). It is more meaningful to consider not only 'nicotine addiction' but also 'tobacco addiction' by including other tobacco components, including ACD. Assessing the roles of tobacco components other than nicotine should aid in developing more effective smoking cessation therapies. **Because of the fact that smoking dependence and alcohol dependence often occur concurrently in the same subjects, it is feasible to consider that many of the same regulatory mechanisms in the CNS are involved in maintaining the reward (=dependence) to both alcohol and smoking** (85,93).

3.4.Study hypothesis and its scientific basis

3.4.1.Cigarette smoke, acetaldehyde and harmans

In the above cited animal experiments, however, ACD was administered to animals using the iv. or central route (102,103,104). It is known that in concentrations reached in the saliva after cigarette smoke (or alcohol intake), ACD is not absorbed into circulation and thus has no possibility to cross BBB (39,40). This excludes, almost certainly, the possibility of a direct central interaction between cigarette smoke- or alcohol-derived ACD and nicotine, as described in the above animal experiments (104).

This has prompted an exploration for indirect mechanisms behind the suggested contribution of ACD to tobacco and alcohol addiction, first suggested in 2007 by Talhout et al (105). Given that in rodents, ACD induces reinforcing effects acting in concert with nicotine (102,103,104) and ethanol (85,93), these authors hypothesized that **harman** and **salsolinol**, i.e., two condensation products of **ACD and biogenic amines**, may be responsible for these observed reinforcing effects of ACD. In the human, these **beta-carbolines** are known to be synthesized as condensation products of tryptophan and indolealkylamines with aldehydes (106). Accordingly, 1-methyltetrahydro-beta-carboline (**tetrahydroharman**) is formed in the body as the ACD condensate after **alcohol intake**, and its concentration is usually highest at the time of **hang-over**. Its oxidation product, 1-methyl-beta-carboline (**harman**), has also been found in human urine and platelets. They occur in many foods and tobacco smoke, but also appear endogenously in humans (107,108,109).

Norharman and harman are naturally occurring beta-carboline alkaloids exhibiting a wide range of biological, psychopharmacological, and toxicological actions. Harman is formed in cigarette smoke, and among smokers, blood harman levels appear to be 2-10 times higher as compared to non-smokers (105), and markedly elevated also in chronic alcohol users (109). Both harman and salsolinol are potent inhibitors of monoamine oxidase (MAO) enzyme in the CNS of both animals and in man (110,111,112,113). In turn, MAO-inhibitors are known to increase nicotine self-administration and maintain behavioral sensitization to nicotine (105) as well as rewarding sensations associated with alcohol dependence (106,107,108,109). Since harman readily passes the BBB and has sufficient MAO-inhibiting potency, it may contribute to the lower MAO-activity observed in the brain of smokers, as discussed by Talhout et al. in their review (105). This led these authors to speculate that ACD may increase the addictive potential of tobacco products via formation of ACD-biogenic amine adducts (harmans) in cigarette smoke and/or in vivo (105).

3.4.2.Alcohol, acetaldehyde and harmans

Not incidentally, in **chronic alcohol abusers**, the levels of both **harman** and **norharman** are **significantly higher** than among non-alcoholics (109). This is the case with smokers as well, shown to have 2-10 times higher blood harman levels than non-smokers (105). This emphasizes the similarities in the central reward mechanisms (MAO-inhibition) contributing to maintenance of alcohol dependence (17,19,96) and smoking dependence (86,87,89,91,93).

The effects of harman and norharman as mediators of alcohol reward (i.e., the ACD-reinforced effects) have been studied to some extent since the late 1980's both in animal experiments and in chronic alcohol users (85,93,103,106-110,114). The literature is far too extensive to be covered here in any detail, but the key observations substantiating the concept on **ACD** as an active agent **mediating the positive motivational properties of alcohol** are included. These data are raising the possibility of **targeting alcohol dependence-related problems by interfering with the actions of ACD by its effective elimination in the saliva and gastric contents during alcohol intake** (85).

Based on the hypothesis that beta-carbolines are involved in the pathogenesis of **alcohol-related mood disturbance**, harman and norharman levels were assayed in the blood plasma of alcoholics and correlated to the Hamilton Depression (HAM-D) scores after 3

and 5 weeks post-admission (115). Tobacco smoking was co-evaluated since it is known to influence beta-carboline levels (105). After a 3-week period, plasma harman but not norharman was increased in depressed alcoholics and positively related to the HAM-D sum-score ($r = 0.47$; $p<0.04$) and to tobacco smoking ($r=0.56$; $p<0.02$). Since no correlation between depression and smoking was found, these data could account for the higher incidence of **depressive symptoms in withdrawn** alcoholics with increased harman levels. Also the partial correlations support this hypothesis (115).

In the search for mechanisms specific for alcoholism, it has become evident that beta-carbolines (e.g. harman and norharman) are compounds that may act on brain reward systems, thereby mediating an increase in voluntary ethanol (ETOH) drinking in experimental animals (85,93,103,105,109). In 1996, Rommelspacher et al. (116) analyzed relationships between these compounds and clinical variables (e.g., family history personality data, and affect) in alcoholics and to trace the time course of blood concentrations in subjects abstaining from alcohol for at least 6 months. Non-alcoholics were investigated during sober and ETOH-loading conditions (1 g ETOH/kg body weight). Importantly, the levels of harman were elevated in the chronically intoxicated alcoholics and correlated with the scores on the self-rating depression (SDS) and the self-rating anxiety (SAS) scales. The group of alcoholics with at least one alcoholic parent had higher levels than the group without such a history. Levels remained elevated for 6 months.

Norharman levels were only slightly elevated on the day of admission. They were correlated to high harm avoidance and SDS scores. A family history of alcoholism and the severity of alcoholism as assessed by the number of ICD-10 criteria fulfilled were correlated with norharman levels. Long-term observation revealed elevated levels of norharman after 3 months of abstinence, but not after 6 months. The association of harman levels with anxiety and depression demonstrated in the present study suggests that alcoholics with high harman levels **use alcoholic beverages as self-medication** in an attempt to overcome possible anxiogenic/depressiogenic actions of harman (116). Norharman levels are less strongly associated with these mood states, but significantly correlated to harm avoidance tendencies. It has been suggested that the activity of the indolergic neurons is relatively high in individuals with a high harm avoidance score.

In their classical study of 1991, Rommelspacher et al. (109) measured the levels of aromatic beta-carbolines (norharman and harman) in the blood plasma of alcoholics and non-alcoholics, testing the hypothesis that the condensation products of neurotransmitters with aldehydes are involved in the pathogenesis of alcoholism. The identity of the extracted compounds was confirmed by various elution conditions of the high performance liquid chromatography (HPLC), newly developed radioreceptor assays, and the mass spectrum of norharman. The levels of norharman and harman in non-alcoholics were unchanged after a load with ethanol (1g/kg body weight). The **norharman** levels of the **alcoholics** were **significantly higher** than those of the non-alcoholic controls (99.5±26.6 pg/ml vs. 26.9±10.7 pg/ml; $p<0.001$) and did not change significantly during a 3-week detoxication period (109). In the subgroup of alcoholics with delirium or hallucinosis, a slight increase of norharman during detoxication could be detected while in alcoholics with vegetative withdrawal symptoms, norharman levels dropped slightly over time ($p=0.07$). No difference was found with respect to harman between non-alcoholics and alcoholics. These results suggest **disturbed regulatory processes** in the formation and/or metabolism of norharman in alcoholics.

On the basis of these data, it is tempting to speculate, that elimination of ACD in the saliva after cigarette smoking and in the context of alcohol intake, using L-cysteine sucking tablets (lozenges)(95), might effectively block (or reduce) the 1) formation of ACD-biogenic amine condensates (beta-carbolines), 2) reduce their elevated blood levels, and by so doing, 3) might alleviate the ACD-associated nicotine and alcohol dependence (by reducing MAO-inhibition) among smokers and alcohol addicts.

Until now, this **patented concept** (86,87) has been **tested only among smokers**, but not among alcohol-dependents. The study hypothesis was based on the assumption that regular use of Acetium® lozenges concomitantly with smoking will trigger withdraw from cigarette smoking. Indeed, this concept was shown to be correct in two recent RCTs in Finland (published in 2016-2017)(117,118), where Acetium® lozenge proved to be significantly more effective than placebo in assisting the smokers to quit. In the first RCT a cohort of 423 cigarette smokers were randomly allocated to intervention (n=212) and placebo arms (n=211). Smoking-related data were recorded by questionnaires, together with nicotine dependence testing by Fagerström scale. The participants used a smoking diary to record the daily number of cigarettes, test lozenges and sensations of smoking.

The data were analyzed separately for point prevalence of abstinence (PPA) and prolonged abstinence (PA) endpoints. Altogether, 110 study participants completed the trial per protocol (PP), 234 had minor violations (mITT), and the rest (n=79) were lost to follow-up. During the 6-month trial, 65 participants quit smoking; 38 (17.9%) in the intervention arm and 27 (12.8%) in the placebo arm [OR=1.48; 95%CI 0.87-2.54; p=0.143]. Success in the PP group was better (42.9% vs. 31.1%, respectively; OR=1.65, 95% CI=0.75-3.62; p=0.205) than in the mITT group: 13.5% vs. 7.4% (p=0.128). The authors concluded that the efficacy of Acetium lozenge remained to be formally confirmed because the study was not adequately powered (117).

These promising data prompted us to confirm the results in an adequately-powered study testing the concept that effective elimination of ACD in the saliva by slow-release L- cysteine (Acetium® lozenge, Biohit Oyj, Helsinki), would assist in smoking cessation by reducing ACD-enhanced nicotine addiction (118). In this second RCT with a similar study design, a cohort of 1,998 cigarette smokers were randomly allocated to intervention (n=996) and placebo arms (n=1,002). As before (117), the results were analysed separately for PPA and PA endpoints (118). Altogether, 753 study subjects completed the trial per protocol (PP), 944 with violations (mITT), and the rest (n=301) were lost to follow-up (LTF). During the 6-month intervention, 331 subjects stopped smoking; 181 (18.2%) in the intervention arm and 150 (15.0%) in the placebo arm (OR=1.43; 95%CI=1.09-1.88); p=0.010). In the PP group 170 (45.3%) quitted smoking in the intervention arm compared to 134 (35.4%) in the placebo arm (OR=1.51, 95%CI=1.12-2.02; p=0.006). In multivariate (Poisson regression) model, **decreased level of smoking pleasure** (scale 1-10) (p=0.010) and "**smoking sensations changed**" (Y/N) were powerful independent predictors of the quit events (Incidence Rate Ratio, IRR=12.01; 95%CI=1.5-95.6). This second (adequately powered) RCT confirmed Acetium® lozenge to be an effective means to aid smoking quit (118). This represents a major breakthrough in the development of smoking intervention methods because slow-release L-cysteine is non-toxic, with no side-effects or limitations of use, and importantly, completely nicotine-free.

3.4.3.Study hypothesis

The present study is extending the idea confirmed in these two recent clinical trials (117,118) and presented in the two Biohit patents (86,87). **This study is designed to assess whether, in alcohol-dependent subjects, the regular use of slow-release L- cysteine preparations (Acetium® lozenge and Acetium® capsules stand-alone and in combination) concomitantly with alcohol intake, might reduce their alcohol reward effects by interfering with the high blood levels of harman and norharman (109) arising as the condensation products of alcohol-derived ACD and biogenic amines in the saliva and stomach contents (86,87,105).**

4.STUDY DESIGN

This double-blind, placebo-controlled trial is designed to test the efficacy of intervention by i) **Acetium® lozenges** (used concomitantly with alcohol intake), by ii) **Acetium® capsules** (taken at 2-hour intervals during the whole drinking session), and iii) **the combination of the two** in reaching **alcohol withdrawal** as compared with similarly administered placebo preparations. Two optional approaches in the enrolment of the study subjects can be used, as reported in numerous RCTs for alcohol dependence: **1) in-patient** (residential) setting, or **2) outpatient** setting.

In option 1): A cohort of 400 alcohol dependent subjects (confirmed by **AUDIT scale: ≥20**) will be enrolled by the participating **clinics of alcohol and addiction medicine**, where these subjects are being normally treated in an in-patient or residential setting (13,29-33). This is important, because 1) the initial step in the treatment of alcohol dependence is withdrawal from alcohol, 2) **psychosocial intervention** (behavioural intervention or addiction-focused counselling) is **the backbone** of the treatment for alcohol dependence (13), and 3) the use of pharmacological treatments, combined with psychosocial support for relapse prevention is generally recommended for these patients (29).

In option 2): the cohort of 400 **outpatient volunteers** can be enrolled, who agree to **abstinent for at least 2 weeks prior** to randomization to the placebo or **three Acetium arms**. Cognitive behavioural therapy will be provided on weekly basis during the entire period of intervention by the contact clinic (of alcohol and addiction medicine). Self-

reported drinking or abstinence shall be controlled by determinations of breath alcohol concentration and by daily alcohol diary, returned on weekly basis.

All subjects will be requested to fill in a questionnaire (AUDIT score) recoding their current alcohol consumption practices to establish the level of alcohol dependence. The subjects will be administered an alcohol drinking diary on daily basis, submitted to the study monitors on weekly basis (on the occasion of their cognitive therapy), for recording the compliance of each subject with the study protocol, as well as all eventual changes and relapses of daily drinking. The intervention is continued for 6 months (24 weeks), when the study endpoints will be assessed.

4.1.Aims of the study

The single most important goal of this study is to establish whether Acetium® lozenge Acetium® capsule, and both combined are effective in increasing and maintaining the alcohol abstinence among alcohol dependent subjects. The null hypothesis of the study implicates that Acetium® lozenges/Acetium® capsule (stand-alone or in combination) is not superior to placebo in maintaining (and triggering) the alcohol withdrawal during the 6-month follow-up period. Rejection or not of the null hypothesis is based on comparison of the four strata (three Acetium® arms and placebo) against the primary (12-week abstinence) and any of the secondary study endpoints (Section 4.4.3). Albeit measuring slightly different aspects of alcohol dependence, a recent meta-analysis recommends using both the primary and secondary endpoints in analysing the results of RCTs for alcohol dependence (119).

In addition to these univariate primary and secondary endpoints, the study also attempts to estimate the role of Acetium® lozenge/capsule and their combination as an independent covariate of alcohol withdrawal in multivariate (Cox) proportional hazards (HR) regression model, controlled for potential confounders (age, sex, smoking, alcohol amount, others). Another aim is to assess whether these longitudinal data on Acetium® intervention in alcohol dependence can be modelled using the newly described statistical technique competing risks regression (120,121). In this alcohol dependence intervention trial, the competing risks events (to be observed during Acetium® intervention) are: i) **no effect** (=alcohol drinking continues unchanged as compared with the baseline), ii) **withdrawal** (=abstinence from alcohol drinking since the withdrawal date with or without

grace period), iii) **relapse** (=abstinence for a period but relapse afterwards), and iv) **reduction** of alcohol drinking (=number of drinking days, heavy drinking days, reduced at study endpoint).(more details in Section 4.5.1.).

4.2.Patients

This intervention trial is conducted in collaboration between **Biohit Oyj** (Helsinki, Finland) and **a CRO company** (XY)(City Z, W country)(hereafter called "the Partners"). The study is organised and monitored exclusively by XY, supervised by a steering committee consisting of the members from both research Partners. The CRO (XY) is completely responsible for identifying and contracting the in-patient clinics, if **option 1** will be used, as well as inviting and enrolling the outpatient volunteers, if **option 2** is being selected as the mode of study execution (73,119).

A cohort of 400 clinically verified alcohol dependents (AUDIT score ≥20) (both genders, no age limit), will be enrolled by using **OPTION 1** (in-patient setting) or **OPTION 2** (outpatient setting). Eligible subjects must be alcohol abusers who are motivated to refrain from alcoho drinking, and who give a written consent to participate. The subjects will be randomly allocated to four groups (n=100 in each), receiving either 1) Acetium® lozenge, 2) Acetium® capsule, 3) lozenge/capsule combination, or 4) placebo (lozenges, capsules, both), in a double-blind setting, where both the examiners and the test subjects are blinded to the test substances. All subjects must consent (for entire study period) to receive also **cognitive behavioural therapy** on regular basis as scheduled by the referral clinic of alcohol and addiction medicine, because psychosocial therapy is an essential part of treatment for alcohol dependence.

The following subjects should be considered non-eligible: 1) those who refuse to sign written consent, 2) those who are not motivated to refrain from drinking, 3) those who do not commit themselves for accepting the psychosocial intervention.

4.3.Methods

4.3.1.Baseline data

Before enrolment in the cohort, all subjects are requested to sign a written concept, after having been explained (both verbal and written), i) the details of the study and ii) the commitment requested from each subject for the successful completion of this 6-month

intervention study. Before study onset, each subject will be requested to fill in a simple questionnaire (**The WHO Alcohol Use Disorders Identification Test (AUDIT)** for screening risk drinking) recoding their current alcohol drinking practices (**ANNEX 2)** Another version of this questionnaire also includes a couple of supplementary questions that are not a part of the AUDIT score, but provide useful additional information about the subject's drinking practices and its associated risks (**ANNEX 3).**

4.3.2.Alcohol dependence intervention by Acetium® combination and placebo

The patients consenting to participate in the trial will be randomised into four groups of equal size (three Acetium arms and controls) using the random number seed for a cohort of 400 alcohol dependent subjects. This intervention trial will be conducted using a double-blind setting, where both the examiners and the test subjects are blinded to the test substances (Acetium lozenge and capsules; placebo lozenge and capsules). All subjects receive written instructions explaining the study design as well as the daily practice to be followed in usage of the test substances (Acetium®- or placebo stand-alone and in combination) on the occasion of every single daily alcohol drink or drinking session.

Following the randomization, all participants will receive their numbered packages of the test substances (Acetium® lozenge & Acetium® capsules; placebo lozenge & placebo capsules), equalling the **need of one week** (+10% extra), calculated on the basis of their reported drinking frequency at baseline. New lot of the test substances will be delivered on **weekly basis** on the occasion of the subject's visit in the clinic for i) return of the drinking diary, and ii) admission for the psychosocial therapy.

All subjects are instructed to strictly adhere to the drug administration protocol. Most importantly, they should not neglect taking: 1) **one** (test/placebo) **lozenge** concomitantly with **each single alcohol drink** consumed, and 2) **one** (test/placebo) **capsule** at **2-hour intervals** during the continued drinking session, or 3) both the lozenge and the capsule (combination arm). This is **essential** to ensure the proper function of Acetium® lozenges (i.e., to eliminate alcohol-derived ACD in the saliva), and Acetium® capsules (to eliminate alcohol-derived ACD in the stomach contents) in the context of single alcohol drinks and continuous alcohol intake (session), respectively.

4.3.3.Follow-up data

For accurate monitoring of the drinking practices and their eventual changes, all study subjects will be administered a drinking diary (**ANNEX 4**), to be filled on daily basis, recording the daily numbers and types of alcohol drinks consumed. In addition, the reported alcohol abstinence (and amount of daily drinking) will be monitored on weekly basis by the use of AUDIT score and alcohol breath test in the contact clinic, upon the subject's attendance in the cognitive therapy, return of the diaries, and obtain the new lot of test preparations. **On that occasion, the number of reported drinks will be matched to the consumed test substances, to control for the compliance in the protocol**.

4.3.3.1.Drinking diary

The smoking diary (**ANNEX 4**) will provide valuable information about the drinking practices of each participant, and is also intended to assist in the preparation to withdrawal The format of the drinking diary is standardized and originally developed and continuously used by the NHS in the UK. In addition to recording the alcohol consumption on daily and weekly basis, the diary helps categorizing the level of the risk associated with each level of daily alcohol drinking. Any changes to a lower category should be an important step in the path to alcohol withdrawal.

These weekly alcohol diaries must be returned to the study monitor on weekly basis, on the occasion when the study subject is attending the contact clinic to deliver the diary, to receive the cognitive therapy as well as to be tested for AUDIT score and breath test. The latter is important to confirm the subject's compliance with the study protocol. One additional means to do this is to match the consumed test substances with the weekly diary.

4.3.3.2.Breath alcohol test (BAT)

Breath alcohol test (BAT) is the simple means to control the level of alcohol in the blood When alcohol is consumed, it goes into the stomach and further to the small intestine, from where its absorption into the blood takes place. Via circulation, alcohol is distributed to all body tissues, lungs included. Upon breathing, alcohol is exhaled, and the BAT measures how much alcohol is in the air breathed out. The BAT device uses that measurement to estimate how much alcohol is in the blood. That number is known as BAC

(blood alcohol content). Measurable levels are found as soon as 15 minutes after drinking, and BAC is usually highest about an hour after you drink.

When the body weight, amount and type of drinks as well as the start and stop times of the drinking session are known, the formula can calculate the BAC levels at each time point until BAC zero. In the clinical visit, the BAT measurement will be correlated with the data reported in the diary, which is a simple means to control the compliance of the study subject in the intervention protocol. Any observed discrepancy needs to be carefully addressed in the accompanying therapy session.

4.3.4.Cognitive behavioural therapy (CBT)

Psychosocial intervention is **the backbone of the treatment** for alcohol dependence (13) For example in the UK, NICE has provided detailed guidance on the provision of psychosocial support tailored to reflect the severity of the dependence (13). In the UK such services are delivered by both the public and non-public providers, and additiona sources of support, such as self-help based interventions, are encouraged. NICE alsc recommends the use of adjuvant pharmacotherapy for people with moderate to severe dependence once they had been successfully withdrawn from alcohol (13).

The modes and efficacy of the cognitive behavioural therapy (CBT) have been addressed in several comprehensive reviews from different countries, e.g. by McHugh et al. 2010 (122) Because of the fact that the details and practices of CBT vary from clinics to clinics and by country, it is impossible to enter into any details in this context. CBT for substance use disorders (SUDs) has demonstrated efficacy as both a **monotherapy** and as part of **combination treatment strategies**. Although CBT for substance abuse is characterized by heterogeneous treatment elements - such as operant learning strategies, cognitive and motivational elements, and skills building interventions - across protocols, several core elements emerge that focus on overcoming the powerfully reinforcing effects of psychoactive substances, alcohol included (122).

According to McHugh et al. (122), CBT for substance use disorders captures a broad range of behavioural treatments including those targeting operant learning processes, motivational barriers to improvement, and traditional variety of other cognitive-behavioural interventions. Overall, these interventions have demonstrated efficacy in

controlled trials and may be combined with each other or with pharmacotherapy to provide more robust outcomes (122). Despite this heterogeneity, core elements emerge based in a conceptual model of SUDs as disorders characterized by learning processes and driven by the strongly reinforcing effects of substances of abuse. Particular challenges to the field include the determination of the most effective combination treatment strategies and improving the dissemination of CBT to service provision settings (122). Novel treatment strategies including more scalable modalities (such as computer-based programs) and combination strategies to improve rates or speed of treatment response (such as DCS; d-cycloserine) may aid in the transportability of treatments outside of research settings (122).

In the present trial, the CBT will be instituted following the practices adopted by the local contact clinics. The sessions will be repeated on weekly basis during the entire intervention period, thus comprising an essential element of **the combination treatment strategy** where the efficacy of Acetium® lozenge, Acetium® capsule and their combination is being tested as the **adjuvant pharmacotherapy** for subjects with severe alcohol dependence (13).

4.4.Study endpoints

4.4.1.Study compliance

Because of the study design (double-blind, placebo-controlled trial), the study endpoints can only be assessed at the stage when the randomization is unveiled. This is planned to take place after completion of the 6-month intervention period by all those compliant subjects (PP, mITT) who are not lost to follow-up or censored for other reasons.

Because of the relative complexity of the study setting (multi-centre, combination treatment, in-patient or outpatient), it can be anticipated (119) that the number of subjects lost to follow-up (**LTF**), those not completely adherent to the study protocol, as well as those interrupting the intervention for other reasons, will not be negligible in both study arms, it is clear that the final analyses must be run separately for two groups: 1) **Per Protocol (PP**), and 2) **Modified intention-to-treat (mITT)**. The former include all subjects (in both arms) who have been compliant with the intervention protocol, without any major violations in i) taking the test substances (lozenges, capsules), and ii) in recording all the follow-up data (Section 4.3.3). The latter (mITT) category includes all those subjects who

were not necessarily fully compliant with the protocol, but who completed the follow-up and of whom, the study endpoints can be reliably recorded.

4.4.2.Primary endpoint

The primary outcome is **abstinence at least 12 weeks** after randomization. As mentionec above, randomization shall take place **after at least 2 weeks of withdrawal as the baseline** (Section 4). There are two main reasons for maintaining the **12-week abstinence** as the primary endpoint (119). First, abstinence is the **most appropriate** and commonly reported **outcome** for severely dependent drinkers (119,123,124). Second, completely abstaining from alcohol has been shown to **improve cognitive function** (123,124) and **quality of life** (125,126,127). This endpoint is also quite clear-cut to define (Y/N) and confirm by the i) drinking diaries, ii) BAT, and iii) CBT by the contact clinics running the follow-up visits.

4.4.3.Secondary endpoints

There is **no consensus** about the **most useful secondary endpoints**, however, and highly variable secondary endpoints have been used in different RCTs and meta-analyses (73,119) In some RCTs, different **health-related** outcomes have been used even as the primary outcomes, such as: 1) mortality, 2) accidents (including motor vehicle crashes) or injuries, 3) quality of life or functioning, and 4) somatic complications of alcoholism (73). Their arguments were that such outcomes have been used in previous systematic reviews (128) and these reflect the expected clinical benefits of treatment of alcohol dependence (73).

In the same review, the authors classified secondary outcomes into three categories: alcohol consumption outcomes, biological outcomes, and treatment safety outcomes (73) The **alcohol consumption** outcomes were 1) monthly number of HDDs (heavy drinking days), defined as days with alcohol consumption of 60g or more for males and 40g or more for females, 2) total alcohol consumption, 3) response (i.e., patients are decreasing their consumption to low-risk levels or no consumption, 4) complete abstinence, 5) total Drinker Inventory of Consequences (DrInC) score, 6) Clinical Global Impression–Severity score, and 7) Alcohol Dependence Scale score (73).

In another authoritative review, the following secondary outcomes were considered: (1) amount of alcohol consumption, 2) drinking frequency, 3) intervention compliance, 4) adverse events, and 5) withdrawal from study (119). Depending on the length of follow-up reported, the endpoints for each outcome can be categorized into short-term (12 - 20 weeks), intermediate-term (20 -36 weeks), and long-term (>36 weeks)(119).

Given that the 1) present intervention trial is of relatively short duration (6 months), 2) the main focus is to assess the efficacy of the novel treatment combination (Acetium lozenge & Acetium capsule) combined with the CBT, the use of the health-related outcomes listed above (73) do not seem the most appropriate, because i) many of the events (mortality, accidents, somatic complications) do not necessarily accumulate in amounts sufficient to be counted as secondary endpoints. Some others (changes in quality of life or functioning) might be complicated to verify as such. On the other hand, more interesting (and more straightforward to record) are the **alcohol consumption-related outcomes** listed by the same authors (73). In the other review (119), some of the listed study outcomes are clearly the items related to study compliance (PP, mITT, LTF), which need to be taken care in the final analysis of the data as "study compliance" (34,43,52,59,78), and are NOT suitable as secondary endpoints.

By taking into account the design of the present intervention trial, the **most appropriate secondary endpoints** are those related to **alcohol consumption** at the end of the 6-month follow-up (study conclusion). Accordingly, **the secondary endpoints** used in analysis of the trial data include the following: **1)** the number of monthly drinking days; **2)** the number of monthly heavy drinking days (HDD; >60g for M; >40g for F); **3)** return to any drinking following abstinence (=relapse); **4)** total amount of alcohol consumption; **5)** treatment response, i.e., the proportion subjects who decrease their alcohol consumption to low-risk levels or no consumption, as determined from the AUDIT score (Annex 2) and Drinking Diary (Annex 3).

Together with the primary endpoint (12-week abstinence), this intervention trial is appropriately designed to give us the answers to the set study aims, including any of the selected secondary endpoints (Section 4.1.).

4.5.Statistical analysis

All statistical analyses will be performed using the SPSS 25.0.0.2 for Windows (IBM, NY, USA) and STATA/SE 15.1 software (STATA Corp., Texas, USA). The descriptive statistics will be conducted according to routine procedures. Frequency tables will be analyzed using the $\chi 2$-test, with the likelihood ratio (LR) or Fisher's exact test for categorical variables. Differences in the means of continuous variables are analyzed using non-parametric (Mann-Whitney or Kruskal-Wallis) test for two- and multiple independent samples, respectively.

There are different ways to assess the primary (and secondary) endpoints of the study. The most straightforward is to calculate the risk estimates (OR) for the 12-week abstinence in the three test (Acetium®) arms versus the placebo arm, using conventional univariate regression models, where the results are expressed as crude OR (odds ratio), and their 95% confidence intervals (95% CI).

As to some of the secondary endpoints, e.g. relapse (=return to any drinking), a different approach can be used. Using the relapse as the event, the effect of Acetium® arms versus placebo can be modelled by the regression techniques based on count variables, i.e. Poisson regression. In that case, relapse is expressed as events per person time (months) at risk, and the four arms are compared using the incidence rate ratio (IRR) statistics. When applied to panel type of data (Panel Poisson; weekly diaries as time variable), the covariates reflecting intra-subject variation (at FU visits=weekly diaries) can be adequately controlled which is a definite advantage in this type of longitudinal setting. A similar type of approach based on panel data, i.e., generalized estimating equation (GEE) modelling, can be used to estimate the effect of Acetium® therapy on persistence of the relapse/abstinence, using the abstinence (yes/no) recorded at each follow-up visit as the dependent variable.

4.5.1.Modelling of alcohol dependence intervention by competing-risks regression

In addition to these conventional techniques of data analysis, a new approach to model the complex process of alcohol abstinence can be attempted in this trial. This type of intervention trial is more complex than merely having a single outcome, abstinence or not as a dichotomous outcome. In this alcohol dependence intervention trial, t he competing risks events (to be observed during Acetium® intervention) are: i) no effect (=alcoho drinking continues unchanged as compared with the baseline), ii) withdrawal (=abstinence

from alcohol drinking since the withdrawal date with no relapse, iii) relapse (=abstinence for a period but relapse afterwards), and iv) reduction of alcohol drinking (=number of drinking days, heavy drinking days, reduced at study endpoint.

Thus, another method for modeling these complex data can be used, by taking into account the fact that i) the longitudinal data be utilized in full, ii) dependence of the repeated measurements at follow-up visits (and diary) be taken into account, and iii) the multiple-outcome dependent variable (no change, abstinence, relapse, reduction) be treated in a single statistical model. All these prerequisites are met by **the competing- risks regression** (120,121), which will be used to model the impact of Acetium® intervention (and other covariates) on the competing risks outcomes of this trial. In simple terms, competing-risks regression generates hazard for (failure) events of interest, while simultaneously keeping the subjects who experience competing events still "at risk" so that they can be adequately counted as not a chance of failing (120,121). Different from the usual Cox regression models producing HR (hazard ratio), this technique reports exponential coefficients known as sub-hazard ratios (SHR).

4.5.2.Power analysis

Due to the fact that several optional tools are available for statistical analysis of these data, also the power of the study can (and needs to) be analysed differently, following the algorithms specified for each of these statistical techniques. In the simplest approach (univariate logistic regression for calculating OR for 12-week abstinence), the power can be calculated using the **two-sample proportion test**, comparing proportion of abstinence in the three Acetium® arms and the placebo arm. The study (n=100 per study arm) is adequately powered (Type II error 0.80, type I error 0.05) to detect a true difference of 18% between any of the Acetium® arms and the placebo arm, within the range of 20% abstinence achieved in the placebo and 38% abstinence in any of the Acetium® arms. Within this (20-38%) effect size range, the study power is sensitive to any decrease in this effect size difference, but allows less difference (15%), if the abstinence rate falls between 10% and 25% in the two arms. As determined from the recent meta-analysis of a large number of RCTs, the efficacy of the combination therapy (CBT + pharmacotherapy) significantly increased the proportion of completely abstinent subjects at 6 months, the effect size varying in the range of 40% and 20% for therapy and placebo, respectively (119). For the secondary endpoints, different power calculations need to be done, which are

different to predict, because of meagre data to be used as the reference in these calculations.

5.STUDY EXECUTION AND TIME TABLE

For execution of this type of intervention trial, three options are available: 1) to hire a CRO (contract research organisation) to set up and monitor the whole study; 2) to find suitable clinics, which would be willing to conduct the study on the basis of research collaboration, and 3) to set up and monitor the whole study by their own research staff. The last option is immediately ruled out, because of the currently limited resources of the company's research department and the lack of necessary expertise needed in administering the CBT on weekly basis. The same applies to option 2) which would also necessitate a significant input by the company staff.

This leaves option 1), i.e., to hire an adequately resourced CRO, as the only realistic alternative to conduct this trial. A cohort of 400 volunteers with severe alcohol dependence needs to be enrolled, using either i) an in-patient or ii) an outpatient setting. Both necessitates an involvement of an expert clinic of alcohol and addition medicine, where these subjects will be treated by CBT on weekly basis, in addition to the usual weekly monitoring of the follow-up items (diary, BAT, AUDIT score). From all subjects, a written consent is needed. The first necessary step in alcohol withdrawal, two weeks before randomization. This cohort of 400 volunteers will be randomised to the three test and placebo arms in a double-blind fashion. The use of the intervention regimen (Acetium lozenges & capsules; placebo lozenge & capsules) will be instructed before start of the study. Adherence to the regimen is followed on weekly basis by the contact clinic, where the study subjects will obtain the new lot of the test remedies, against the completely filled drinking diaries, allowing the follow-up of their consumption. The intervention will be continued for 6 months. After completion of the intervention period, the randomization code will be opened, and the data analysed for the primary and secondary endpoints, as usual.

At this stage, no exact estimates for the time-table can be given. Given that the intervention period is 6 months for all subjects, the crucial determinant of the total time required for completion of the trial is the speed of cohort enrolment. With multiple clinics involved however, that should not be non-proportionate to the total execution period of the study.

6.REFERENCES

1.Health & Social Care Information Centre. Health Survey for England, 2014. Leeds: Health & Social Care Information Centre, 2015. Available at: http://www.hscic.gov.uk/catalogue/PUB19295/HSE2014-ch8-adult-alc-con. pdf

2.Health & Social Care Information Centre. Adult Psychiatric Morbidity Survey, 2007. Leeds: Health & Social Care Information Centre, 2009. Available at http://www.hscic.gov.uk/pubs/psychiatricmorbidity07

3.Public Health England. Alcohol Treatment in England 2013-14. London: Public Health England, 2014. Available at http://www.nta.nhs.uk/uploads/adult-alcohol-statistics-2013-14-commentary.pdf

4.Public Health England. Liver Disease Profiles. London: Public Health England, 2015. Available at http://www.fingertips.phe.org.uk/profile/liverdisease/data#page/0

5.Health & Social Care Information Centre. Statistics on Alcohol, England 2016. Leeds: Health & Social Care Information Centre, 2016. Available at http://www.content.digital.nhs.uk/catalogue/PUB20999/alc-eng-2016-rep.pdf

6.Office for National Statistics. Alcohol-Related Deaths in the United Kingdom, Registered in 2014. Newport: Office for National Statistics, 2016. Available at http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/ alcoholrelateddeathsintheunitedkingdom/ registeredin2014

7.Public Health England. Local Alcohol Profiles for England. London: Public Health England, 2015. Available at http://www.fingertips.phe.org.uk/profile/local-alcohol-profiles/data#page/0

8.House of Commons Health Committee. Government's Alcohol Strategy. London: The Stationary Office Ltd, 2012. Available at http://www.publications.parliament.uk/pa/cm201213/cmselect/cmhealth/132/132.pdf

9.Teesson M, Baillie A, Lynskey M, et al. Substance use, dependence and treatment seeking in the United States and Australia: a cross-national comparison. Drug Alcohol Depend 2006;81:149–55.

10.Hasin DS, Stinson FS, Ogburn E, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry 2007;64:830–42.

11.Mokdad AH, Marks JS, Stroup DF, et al. Actual causes of death in the United States, 2000. JAMA 2004;291:1238–45.

12.Bouchery EE, Harwood HJ, Sacks JJ, et al. Economic costs of excessive alcohol consumption in the U.S., 2006. Am J Prev Med 2011;41:516–24.

13.National Institute for Health and Care Excellence. Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. CG115. London: National Institute for Health and Care Excellence, 2011. Available at http://www.nice.org.uk/guidance/cg115

14.World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization, 1992.

15.American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. Washington, DC: American Psychiatric Association, 1994.

16.Grant BF. ICD-10 and proposed DSM-IV harmful use of alcohol/alcohol abuse and dependence, United-States 1988: a nosological comparison. Alcohol Clin Exp Res 1993;17:1093–101.

17.Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. Addiction 1993;88:791–804.

18.Drummond DC, Oyefeso N, Phillips T, et al. Alcohol Needs Assessment Research Project: The 2004 National Alcohol Needs Assessment for England. London: Department of Health, 2005.

19.Dawson DA, Grant BF, Stinson FS, et al. Recovery from DSM-IV alcohol dependence: United States, 2001-2002. Addiction 2005;100:281–92.

20.Hunt WA, Barnett LW, Branch LG. Relapse rates in addiction programs. J Clin Psychol 1971;27:445–56.

21.Raistrick D, Heather N, Godfrey C. Review of the Effectiveness of Treatment for Alcohol Problems. London: National Treatment Agency for Substance Misuse, 2006.

22.Schuckit MA. Alcohol-use disorders. Lancet 2009;373:492–501.

23.Edwards G, Brown D, Oppenheimer E, et al. Long term outcome for patients with drinking problems: the search for predictors. Br J Addict 1988;83:917–27.

24.Marshall EJ, Edwards G, Taylor C. Mortality in men with drinking problems: a 20-year follow-up. Addiction 1994;89:1293–8.

25.Stockwell T, Murphy D, Hodgson R. The severity of alcohol dependence questionnaire: its use, reliability and validity. Br J Addict 1983;78:145–55.

26.National Institute for Health and Care Excellence. Alcohol-Use Disorders: Diagnosis and Management of Physical Complications. CG100. London: National Institute for Health and Care Excellence, 2010. Available at http://www.nice.org.uk/guidance/cg100

27.Morgan MY. Acute alcohol toxicity and withdrawal in the emergency room and medical admissions unit. Clin Med 2015;15:486–9.

28.Edwards G, Gross MM. Alcohol dependence: provisional description of a clinical syndrome. Br Med J 1976;1:1058–61.

29.Rolland B, Paille F, Gillet C, et al. Pharmacotherapy for Alcohol Dependence: the 2015 Recommendations of the French Alcohol Society, Issued in Partnership with the European Federation of Addiction Societies. CNS Neurosci Ther 2016; 22: 25–37.

30.U.S.Department of Veterans Affairs; U.S. Department of Defense.VA/DoD Clinical Practice Guideline for Management of Substance Use Disorders (SUD), 2009. Available online at http://www.healthquality.va.gov/guidelines/MH/sud/sud_full_601f.pdf

31.Pettinati HM, Weiss RD, Miller WR, et al. Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence. COMBINE Monograph Series, Volume 2. DHHS Publication No. (NIH) 04–5289. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism, 2004.

32.Center for Substance Abuse and Treatment. Incorporating Alcohol Pharmacotherapies into Medical Practice (Treatment improvement protocol (TIP); no. 49). Rockville, MD: Substance Abuse and Mental Health Services Administration (SAMHSA), 2009.

33.Haber P, Lintzeris N, Proude E, et al. on behalf of the Australian Government Department of Health and Ageing. Guidelines for the Treatment of Alcohol Problems. Sydney: University of Sydney, 2009. Available at http://www.health.gov.au/internet/main/nsf//AustAlctreatguidelines% 202009.pdf

34.Goh ET, Morgan MY. Review article: pharmacotherapy for alcohol dependence – the why, the what and the wherefore. Aliment Pharmacol Ther 2017;45:865–82.

35.Fuller RK, Branchey L, Brightwell DR,et al. Disulfiram treatment of alcoholism. A veterans administration cooperative study. JAMA 1986;256:1449–55.

36.van Ieperen L. Sudden death during disulfiram-ethanol reaction. S Afr Med J 1984;66:165.

37.Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. Drug Saf 1999;20:427–35.

38.Krampe H, Ehrenreich H. Supervised disulfiram as adjunct to psychotherapy in alcoholism treatment. Curr Pharm Des 2010;16:2076–90.

39.Skinner M, Coudert M, Berlin I, et al. Effect of the threat of a disulfiram-ethanol reaction on cue reactivity in alcoholics. Drug Alcohol Depend 2010;112:239–46.

40.Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F. Disulfiram therapy in patients abusing cocaine and alcohol. Am J Psychiatry 1993;150:675–6.

41.Carroll KM, Nich C, Ball SA, et al. One-year follow-up of disulfiram and psychotherapy for cocainealcohol users: sustained effects of treatment. Addiction 2000;95:1335–49.

42.Skinner MD, Lahmek P, Pham H, Aubin HJ. Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. PLoS ONE 2014;9:e87366.

43.Gaval-Cruz M, Weinshenker D. Mechanisms of disulfiram-induced cocaine abstinence: antabuse and cocaine relapse. Mol Interv 2009;9:175–87.

44.Jørgensen CH, Pedersen B, Tønnesen H. The efficacy of disulfiram for the treatment of alcohol use disorder. Alcohol Clin Exp Res 2011;35:1749–58.

45.Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and metaanalysis. JAMA 2014;311:1889–900.

46.Malcolm R, Olive MF, Lechner W. The safety of disulfiram for the treatment of alcohol and cocaine dependence in randomized clinical trials: guidance for clinical practice. Expert Opin Drug Saf 2008;7:459–72.

47.Sinclair JM, Chambers SE, Shiles CJ, Baldwin DS. Safety and tolerability of pharmacological treatment of alcohol dependence: comprehensive review of evidence. Drug Saf 2016;39:627–45.

48.Kalk NJ, Lingford-Hughes AR. The clinical pharmacology of acamprosate. Br J Clin Pharmacol 2014;77:315–23.

49.Spanagel R, Vengeliene V, Jandeleit B, et al. Acamprosate produces its anti-relapse effects via calcium. Neuropsychopharmacology 2014;39:783–91.

50.Kufahl PR, Watterson LR, Olive MF. The development of acamprosate as a treatment against alcohol relapse. Expert Opin Drug Discov 2014;9:1355–69.

51.Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcoholdependent individuals: results of a meta-analysis. Alcohol Clin Exp Res 2004;28:51–63.

52.Rösner S, Hackl-Herrwerth A, Leucht S, et al. Acamprosate for alcohol dependence. Cochrane Database Syst Rev 2010;9:CD004332.

53.Donoghue K, Elzerbi C, Saunders R, et al. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, Europe versus the rest of the world: a meta-analysis. Addiction 2015;110:920–30.

54.Plosker GL. Acamprosate: a review of its use in alcohol dependence. Drugs 2015;75:1255–68.

55.Mason BJ. Acamprosate and naltrexone treatment for alcohol dependence: an evidence-based risk-benefits assessment. Eur Neuropsychopharmacol 2003;13:469–75.

56.Drobes DJ, Anton RF, Thomas SE, et al. Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. Alcohol Clin Exp Res 2004;28:1362–70.

57.Anton RF. Naltrexone for the management of alcohol dependence. N Engl J Med 2008;359:715–21.

58.Roozen HG, de Waart R, van der Windt DA, et al. A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. Eur Neuropsychopharmacol 2006;16:311–23.

59.Rösner S, Hackl-Herrwerth A, Leucht S, et al. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2010;12:CD001867.

60.Jarosz J, Miernik K, Wazchal M, Walczak J, Krumpl G. Naltrexone (50 mg) plus psychotherapy in alcohol-dependent patients: a meta-analysis of randomized controlled trials. Am J Drug Alcohol Abuse 2013;39:144–60.

61.Mitchell JE, Morley JE, Levine AS, et al. High-dose naltrexone therapy and dietary counseling for obesity. Biol Psychiatry 1987;22:35–42.

62.Mason BJ, Ritvo EC, Morgan RO, et al. A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. Alcohol Clin Exp Res 1994;8:1162–7.

63.Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Arch Gen Psych 1999;56:719–24.

64.Anton RF, Pettinati H, Zweben A, et al. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol 2004;24:421–8.

65.Karhuvaara S, Simojoki K, Virta A, et al. Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. Alcohol Clin Exp Res 2007; 31: 1179–87.

66.Gual A, He Y, Torup L, et al. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. Eur Neuropsychopharmacol 2013;23:1432–42.

67.Mann K, Bladstr€om A, Torup L, Gual A, van den Brink W. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biol Psychiatry 2013;73:706–13.

68.van den Brink W, Aubin HJ, Bladström A, et al. Efficacy of as-needed nalmefene in alcoholdependent patients with at least a high drinking risk level: results from a subgroup analysis of two randomized controlled 6-month studies. Alcohol Alcohol 2013;48: 570–8.

69.van den Brink W, Sørensen P, Torup L, et al. Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: a 1-year, randomized controlled study. J Psychopharmacol 2014;28:733–44.

70.Marlatt GA, Witkiewitz K. Harm reduction approaches to alcohol use: health promotion, prevention, and treatment. Addict Behav 2002;27:867–86.

71.National Institute for Health and Care Excellence. Nalmefene for Reducing Alcohol Consumption in People with Alcohol Dependence: Evaluation Report. TA325. London: National Institute for Health and Care Excellence, 2014. Available at http://www.nice.org.uk/guidance/ta325

72.Stevenson M, Pandor A, Stevens JW, et al. Nalmefene for reducing alcohol consumption in people with alcohol dependence: an evidence review group perspective of a NICE single technology appraisal. Pharmacoeconomics 2015;33:833–47.

73.Palpacuer C, Laviolle B, Boussageon R, et al. Risks and benefits of nalmefene in the treatment of adult alcohol dependence: a systematic literature review and meta-analysis of published and unpublished double-blind randomized controlled trials. PLoS Med 2015;12:e1001924.

74.Fitzgerald N, Angus K, Elders A, et al. Weak evidence on nalmefene creates dilemmas for clinicians and poses questions for regulators and researchers. Addiction 2016;111:1477–87.

75.Naudet F, Palpacuer C, Boussageon R, Laviolle B. Evaluation in alcohol use disorders - insights from the nalmefene experience. BMC Med 2016;14:119–27.

76.Litten RZ, Castle IJ, Falk D, et al. The placebo effect in clinical trials for alcohol dependence: an exploratory analysis of 51 naltrexone and acamprosate studies. Alcohol Clin Exp Res 2013;37:2128–37.

77.Del Re AC, Maisel N, Blodgett JC, Wilbourne P, Finney JW. Placebo group improvement in trials of pharmacotherapies for alcohol use disorders: a multivariate meta-analysis examining change over time. J Clin Psychopharmacol 2013;33:649–57.

78.Rohsenow DJ, Colby SM, Monti PM, et al. Predictors of compliance with naltrexone among alcoholics. Alcohol Clin Exp Res 2000;24:1542–9.

79.Baekeland F, Lundwall L, Kissin B, Shanahan T. Correlates of outcome in disulfiram treatment of alcoholism. J Nerv Ment Dis 1971;153:1–9.

80.Verheul R, Lehert P, Geerlings PJ, Koeter MW, van den Brink W. Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients. Psychopharmacology 2005;178:167–73.

81.Volpicelli JR, Clay KL, Watson NT, O'Brien CP. Naltrexone in the treatment of alcoholism: predicting response to naltrexone. J Clin Psychiatry 1995;56(Suppl 7): 39–44.

82.Monterosso JR, Flannery BA, Pettinati HM, et al. Predicting treatment response to naltrexone: the influence of craving and family history. Am J Addict 2001;10:258–68.

83.Rubio G, Ponce G, Rodriguez-Jimenez R, et al. Clinical predictors of response to naltrexone in alcoholic patients: who benefits most from treatment with naltrexone? Alcohol Alcohol 2005;40:227–33.

84.Oslin DW, Leong SH, Lynch KG, et al. Naltrexone vs placebo for the treatment of alcohol dependence: a randomized clinical trial. JAMA Psychiatry 2015;75:430–7.

85.Peana AT, Acquas E. Behavioural and biochemical evidence of the role of acetaldehyde in the motivational effects of ethanol. Front Behav Neurosci 2013;7:861-9.

86.Biohit Oyj European Patent Specification EP 2 197 436 B1

87.Biohit Oyj, Canadian Patent No. 2,704,129

88.Salaspuro M. Acetaldehyde as a common denominator and cumulative carcinogen in digestive tract cancers. Scand J Gastroenterol 2009;24:1–15.

89.Salaspuro V, Salaspuro M. Synergistic effect of alcohol drinking and smoking on in vivo acetaldehyde concentration in saliva. Int J Cancer 2004;111:480-3.

90.Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens-Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009;10(11):1033-34.

91.Sprince H, Parker C, Smith CJ, Gonzales L. Protective action of ascorbic acid and sulfur compounds against acetaldehyde toxicity: implications in alcoholism and smoking. Agents Actions 1975;5:164–73.

92.38.Linderborg K, Marvola T, Marvola M, Salaspuro M, Färkkilä M, Väkeväinen S. Reducing carcinogenic acetaldehyde exposure in the achlorhydric stomach with cysteine. Alcohol Clin Exp Res 2011;35:516–22.

93.Peana AT, Assaretti AR, Muggironi G, Enrico P, Diana M. Reduction of ethanol-derived acetaldehyde induced motivational properties by L-cysteine. Alcohol Clin Exp Res 2009;33:43–48.

94.Salaspuro V, Hietala J, Kaihovaara P, Pihlajarinne L, Marvola M, Salaspuro M. Removal of acetaldehyde from saliva by a slow-release buccal tablet of L-cysteine. Int J Cancer 2002;97:361–64.

95.Salaspuro VJ, Hietala JM, Marvola ML, Salaspuro MP. Eliminating carcinogenic acetaldehyde by cysteine from saliva during smoking. Cancer Epidemiol Biomarkers Prev 2006;15:146-9.

96.Benowitz NL. Nicotine addiction. N Engl J Med 2010; 362:2295–303.

97.Abstinent Smokers' Nicotinic Receptors Take More Than a Month to Normalize. http://www.drugabuse.gov/news-events/nida-notes/2009/10/abstinent-smokers-nicotinic-receptors-take-more-than-month-to-normalize.

98.Guide to quitting smoking. American Cancer Society. http://www.cancer.org/docroot/ped/content/ped_10_13x_guide_for_quitting_smoking.

99.Fiore MC, Jaén CR, Baker TB, et al (2008). Clinical practice guideline: treating tobacco use and dependence: 2008 update. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service. http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf.

100.Hoffmann D, Hecht S. Advances in tobacco carcinogenesis. In: Cooper CS, Grover P, editors. Handbook of experimental pharmacology. Heidelberg: Springer Verlag; 1990; pp. 63–102.

101.Hoffmann D, Hoffmann I. The changing cigarette, 1950–1995. J Toxicol Environ Health 1997;50:307–64.

102.Belluzzi JD, Wang R, Leslie FM. Acetaldehyde enhances acquisition of nicotine self-administration in adolescent rats. Neuropsychopharmacol 2005;30:705–12.

103.Quertemont E, Tambour S, Tirelli E. The role of acetaldehyde in the neurobehavioral effects of ethanol: a comprehensive review of animal studies. Prog Neurobiol 2005;75:247–74.

104.Cao J, Belluzzi JD, Loughlin SE, Keyler DE, Pentel PR, Leslie FM. Acetaldehyde, a major constituent of tobacco smoke, enhances behavioral, endocrine, and neuronal responses to nicotine in adolescent and adult rats. Neuropsychopharmacol 2007;32:2025-35.

105.Talhout R, Opperhuizen A, van Amsterdam JG. Role of acetaldehyde in tobacco smoke addiction. Eur Neuropsychopharmacol 2007;17:627-36.

106.Airaksinen MM, Kari I. Beta-carbolines, psychoactive compounds in the mammalian body. Part I: Occurrence, origin and metabolism. Med Biol 1981;59:21-34.

107.Herraiz T, Guillén H, Arán VJ. Oxidative metabolism of the bioactive and naturally occurring beta-carboline alkaloids, norharman and harman, by human cytochrome P450 enzymes. Chem Res Toxicol 2008;21:2172-80.

108.Tsuchiya H, Ohtani S, Yamada K, Tajima K, Sato M. Formation of tetrahydro-beta-carbolines in human saliva. Biochem Pharmacol 1995;50:2109-12.

109.Rommelspacher H, Schmidt LG, May T. Plasma norharman (beta-carboline) levels are elevated in chronic alcoholics. Alcohol Clin Exp Res 1991;15:553-9.

110.Abu GH, Lalies MD, Nutt DJ, Hudson AL. The modulatory action of harmane on serotonergic neurotransmission in rat brain. Brain Res 2015;9;1597:57-64.

111.Goodwin AK, Lantz-McPeak SM, Robinson BL, Law CD, Ali SF, Ferguson SA. Effects of adolescent treatment with nicotine, harmane, or norharmane in male Sprague-Dawley rats. Neurotoxicol Teratol 2015;47:25-35.

112.Smith TT, Schaff MB, Rupprecht LE, Schassburger RL, Buffalari DM, Murphy SE, et al. Effects of MAO inhibition and a combination of minor alkaloids, beta-carbolines, and acetaldehyde on nicotine self-administration in adult male rats. Drug Alcohol Depend 2015;155:243-52.

113.Arnold MM, Loughlin SE, Belluzzi JD, Leslie FM. Reinforcing and neural activating effects of norharmane, a non-nicotine tobacco constituent, alone and in combination with nicotine. Neuropharmacol 2014;85:293-304.

114.Callaway JC, Airaksinen MM, Salmela KS, Salaspuro M. Formation of tetrahydroharman (1-methyl-1,2,3,4-tetrahydro-beta-carboline) by Helicobacter pylori in the presence of ethanol and tryptamine. Life Sci 1996;58:1817-21.

115.Kiefer F, Krodel A, Jahn H, Wolf K, Barocka A. Harman and norharman plasma levels in weaned alcoholics: correlations with depression and tobacco smoking. Addict Biol 2000;5:437-41.

116.Rommelspacher H, Dufeu P, Schmidt LG. Harman and norharman in alcoholism: correlations with psychopathology and long-term changes. Alcohol Clin Exp Res 1996;20:3-8.

117.Syrjänen K, Salminen J, Aresvuo U, Hendolin P, Paloheimo L, Eklund C, Salaspuro M, Suovaniemi O. Elimination of cigarette smoke-derived acetaldehyde in saliva by slow-release L-cysteine lozenge is an effective new method to assist smoking cessation. A randomised, double-blind, placebo-controlled intervention. Anticancer Res 2016;36:2297-306.

118.Syrjänen K, Eronen K, Hendolin P, Paloheimo L, Eklund C, Bäckström A, Suovaniemi O. Slow-release L-cysteine (Acetium®) lozenge is an effective new method in smoking cessation. A randomized, double-blind, placebo-controlled intervention. Anticancer Res 2017;37:3639-48.

119.Cheng HY, Elbers RG, Higgins JPT, Taylor A, MacArthur GJ, McGuinness L, Dawson S, López-López JA, Cowlishaw S, Hickman M, Kessler D. Therapeutic interventions for alcohol dependence in non-inpatient settings: a systematic review and network meta-analysis (protocol). System Rev 2017;6:77-85. DOI 10.1186/s13643-017-0462-2

120.Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-507.

121.Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: Competing risks and multi-state models. Stat Med 2007;26:2389-98.

122.McHugh RK, Hearon BA, Otto MW. Cognitive-behavioral therapy for substance use disorders. Psychiatr Clin North Am 2010;33:511–25.

123.Kühn S, Charlet K, Schubert F, Kiefer F, Zimmermann P, Heinz A, et al. Plasticity of hippocampal subfield volume cornu ammonis 2+3 over the course of withdrawal in patients with alcohol dependence. JAMA Psychiatry. 2014;71:806–11.

124.Rosenbloom MJ, Rohlfing T, O'Reilly AW, Sassoon SA, Pfefferbaum A, Sullivan EV. Improvement in memory and static balance with abstinence in alcoholic men and women: selective relations with change in brain structure. Psychiatry Res 2007;155:91–102.

125.Foster JH, Powell JE, Marshall EJ, Peters TJ. Quality of life in alcohol dependent subjects - a review. Qual Life Res 1999;8:255–61.

126.Johnson BA, Ait-Daoud N, Akhtar FZ, Ma JZ. Oral topiramate reduces the consequences of drinking and improves the quality of life of alcoholdependent individuals: a randomized controlled trial. Arch Gen Psychiatry.
2004;61(9):905–12. doi:10.1001/archpsyc.61.9.905.

127.Morgan MY, Landron F, Lehert P. Improvement in quality of life after treatment for alcohol dependence with acamprosate and psychosocial support. Alcoholism Clin Exp Res 2004;28:64–77.

128.Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 2014;311:1889–1900.

ANNEX 1. Diagnostic criteria of alcohol dependence according to ICD-10 and DSM-IV

Table 1 | Comparisons between the ICD and DSM diagnostic criteria for alcohol dependence

Criterion	ICD-10*	Criterion	DSM-IV*
1	Strong desire or sense of compulsion to use the substance	N/A	N/A
2	Impaired capacity to control use as evidenced by the substance often being taken in larger amounts or over a longer period than intended or by a persistent desire or unsuccessful efforts to control use	3	Persistent desire or one or more unsuccessful efforts to cut down or control drinking
		4	Drinking in larger amounts or over a longer period than the person intended
3	Physiological withdrawal	2	Physiological withdrawal
4	Tolerance	1	Tolerance
5	Pre-occupation with substance use as manifested by important interests being given up or reduced or a great deal of time spent in activities necessary to obtain, take or recover from the effects of the substance	5	Important social, occupational or recreational activities given up or reduced because of drinking
		6	A great deal of time spent in activities necessary to obtain, to use or to recover from the effects of drinking
6	Persistent substance use despite clear evidence of harmful consequences	7	Continued drinking despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by drinking

ICD-10, international classification of diseases, 10th Edition[14]; DSM-IV, diagnostic and statistical manual of mental disorders, 4th Edition;[15] N/A, Not Applicable

* In both the ICD-10 and the DSM-IV criteria, a diagnosis of alcohol dependence is made if three or more of the criteria are present together at some time during the previous 12 months

ANNEX 2. **AUDIT questionnaire: screen for alcohol misuse***

Please circle the answer that is correct for you

1. How often do you have a drink containing alcohol?

Never
Monthly or less
2 4 times a month
2 3 times a week
4 or more times a week

2. How many standard drinks containing alcohol do you have on a typical day when drinking?

1 or 2
3 or 4
5 or 6
7 to 9
10 or more

3. How often do you have six or more drinks on one occasion?

Never
Less than monthly
Monthly
Weekly
Daily or almost daily

4. During the past year, how often have you found that you were not able to stop drinking once you had started?

Never
Less than monthly
Monthly
Weekly
Daily or almost daily

5. During the past year, how often have you failed to do what was normally expected of you because of drinking?

Never
Less than monthly
Monthly
Weekly
Daily or almost daily

6. During the past year, how often have you needed a drink in the morning to get yourself going after a heavy drinking session?

Never
Less than monthly
Monthly
Weekly
Daily or almost daily

7. During the past year, how often have you had a feeling of guilt or remorse after drinking?

Never
Less than monthly
Monthly
Weekly
Daily or almost daily

8. During the past year, have you been unable to remember what happened the night before because you had been drinking?

Never
Less than monthly
Monthly
Weekly
Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?

No
Yes, but not in the past year
Yes, during the past year

10. Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested you cut down?

No
Yes, but not in the past year
Yes, during the past year

Scoring the audit

Scores for each question range from 0 to 4, with the first response for each question (eg. never) scoring 0, the second (eg. less than monthly) scoring 1, the third (eg. monthly) scoring 2, the fourth (eg. weekly) scoring 3, and the last response (eg. daily or almost daily) scoring 4. For questions 9 and 10, which only have three responses, the scoring is 0, 2 and 4 (from left to right).

A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

---

*Saunders JB, Aasland OG, Babor TF *et al*. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption — II. Addiction 1993,88:791–803 (17).

ANNEX 3. The WHO Alcohol Use Disorders Identification Test (AUDIT) for screening risk drinking

Introduction

Because alcohol use can affect health and interfere with certain medications and treatments, it is important that we ask you some questions about your use of alcohol. Your answers will remain confidential, so please be as accurate as possible. Try to answer the questions in terms of **'standard drinks'**. Please ask for clarification if required.

AUDIT Questions Please tick the response that best fits your drinking.

						Score	Sub totals
	Never	*Monthly or less*	*2 - 4 times a month*	*2 - 3 times a week*	*4 or more times a week*		
1. How often do you have a drink containing alcohol?	☐ Go to Qs 9 & 10	☐	☐	☐	☐		
	1 or 2	*3 or 4*	*5 or 6*	*7 to 9*	*10 or more*		
2. How many standard drinks do you have on a typical day when you are drinking?	☐	☐	☐	☐	☐		
	Never	*Less than monthly*	*Monthly*	*Weekly*	*Daily or almost daily*		
3. How often do you have six or more standard drinks on one occasion ?	☐	☐	☐	☐	☐		
4. How often during the last year have you found that you were not able to stop drinking once you had started?	☐	☐	☐	☐	☐		
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	☐	☐	☐	☐	☐		
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	☐	☐	☐	☐	☐		
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	☐	☐	☐	☐	☐		
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	☐	☐	☐	☐	☐		
	No		*Yes, but not in the last year*		*Yes, during the last year*		
9. Have you or someone else been injured because of your drinking?	☐		☐		☐		
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	☐		☐		☐		
						TOTAL	

Supplementary Questions

	No	*Probably Not*	*Unsure*	*Possibly*	*Definitely*
Do you think you presently have a problem with drinking?	☐	☐	☐	☐	☐
	Very easy	*Fairly easy*	*Neither difficult nor easy*	*Fairly difficult*	*Very difficult*
In the next 3 months, how difficult would you find it to cut down or stop drinking?	☐	☐	☐	☐	☐

D0718 - 8/09 - P1 of 2

How to score and interpret the AUDIT

The World Health Organization's Alcohol Use Disorders Identification Test (AUDIT) is a very reliable and simple screening tool which is sensitive to early detection of risky and high risk (or hazardous and harmful) drinking. It has three questions on alcohol consumption (**1 to 3**), three questions on drinking behaviour and dependence (**4 to 6**) and four questions on the consequences or problems related to drinking (**7 to 10**).

The **Supplementary Questions** do not belong to the AUDIT and are **not** scored. They provide useful clinical information associated with the client's perception of whether they have an alcohol problem and their confidence that change is possible in the short-term. They act as an indication of the degree of intervention required and provide a link to counselling or brief intervention following feedback of the AUDIT score to the client.

Scoring the AUDIT

- The columns in the AUDIT are scored from left to right.
- **Questions 1 to 8** are scored on a five-point scale from **0, 1, 2, 3,** and **4**.
- **Questions 9 & 10** are scored on a three -point scale from **0, 2** and **4**.
- Record the score for each question in the **"score"** column on the right, including a zero for questions **2 to 8** if 'skipped'.
- Record a total score in the **"TOTAL"** box at the bottom of the column. The maximum score is 40.

Consumption score

Add up **questions 1 to 3** and place this sub-score in the adjacent single box in the far right column (maximum score possible = 12). A score of 6 or 7 may indicate a risk of alcohol-related harm, even if this is also the total score for the AUDIT (e.g. consumption could be over the recommended weekly intake of 28 for men and 14 for females in the absence of scoring on any other questions). Drinking may also take place in dangerous situations (e.g. driving, fishing/boating). Scores of 6 to 7 may also indicate potential harm for those groups more susceptible to the effects of alcohol, such as young people, women, the elderly, people with mental health problems and people on medication. Further inquiry may reveal the necessity for harm reduction advice.

Dependence score

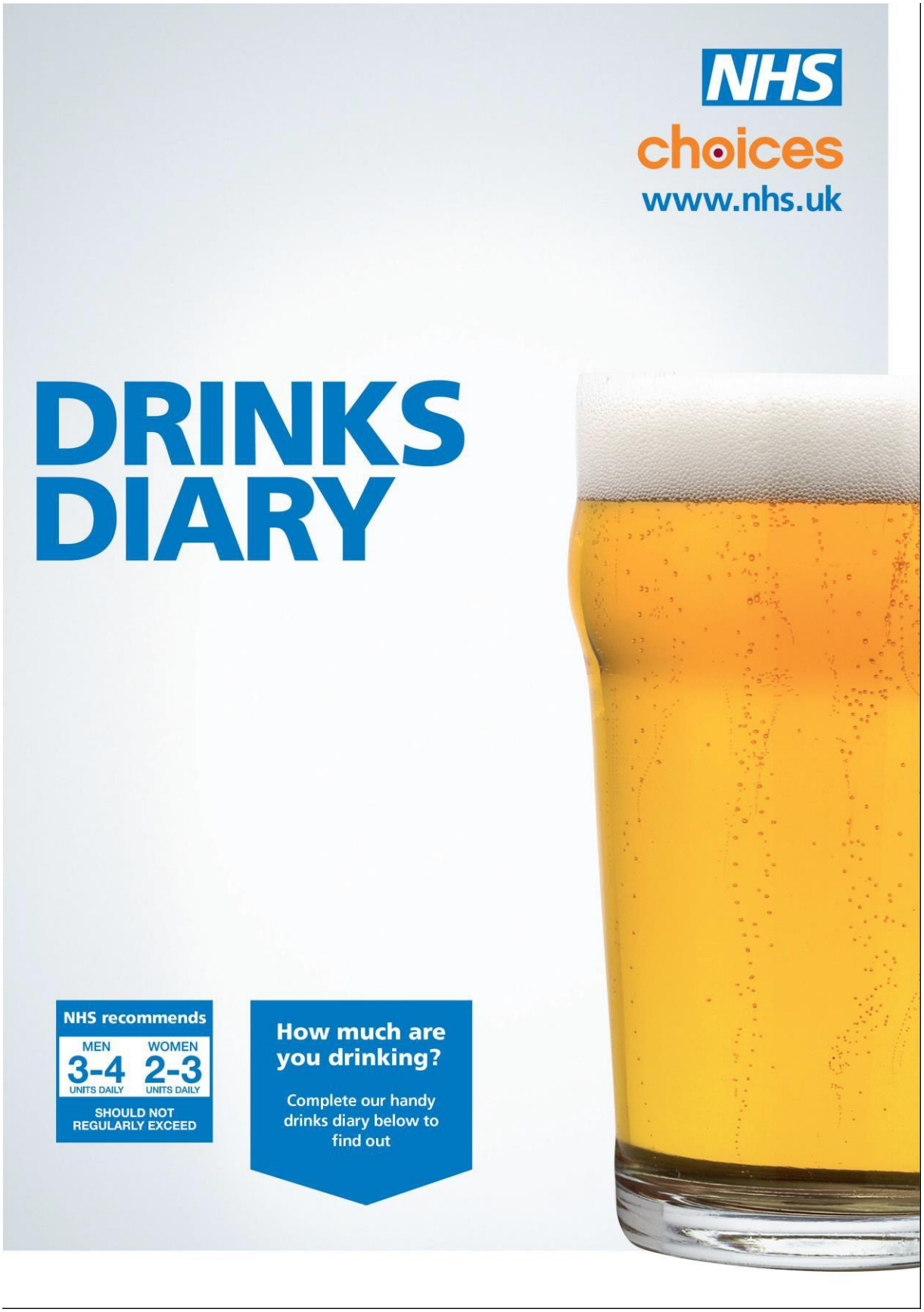
Add up **questions 4 to 6** and place this sub-score in the adjacent single box in the far right column (maximum score possible = 12). In addition to the total AUDIT score, a secondary 'dependence' score of 4 or more as a subtotal of questions 4 to 6, suggests the possibility of alcohol dependence (and therefore the need for more intensive intervention if further assessment confirms dependence).

Alcohol-related problems score

Any scoring on **questions 7 to 10** warrants further investigation to determine whether the problem is of current concern and requires intervention.

AUDIT Total score	*Dependence score*	*Risk level*	*Possible Interventions*
0 - 7	below 4	**Low-risk**	• Use 'Right Mix' materials to reinforce low-risk drinking, particularly for those who previously had alcohol problems or whose circumstances may change. • Harm reduction advice may be appropriate for those in susceptible groups (see 'Consumption Score' above).
8 - 15	below 4	**Risky** or **hazardous level.** Moderate risk of harm. May include some clients currently experiencing harm (especially those who have minimised their reported intake and problems).	• Brief Intervention - feedback of AUDIT and harm reduction advice may be sufficient Ideally also: - setting goals and limits - a motivational interview - self-monitoring of drinking - use of "The Right Mix" self-help guide
	4 or more	Assess for dependency	• Counselling may be required.
16 - 19	below 4	**High-risk** or **harmful level.** Drinking that will eventually result in harm, if not already doing so. May be dependent.	• Brief Intervention (all components) is a minimum requirement. • Assessment for more intensive intervention. • Counselling using CBT principles and motivational interviewing in individual sessions and/or in groups. • Follow-up and referral where necessary.
	4 or more	Assess for dependence	
20 or more	below 4	**High-risk** Definite harm, also likely to be alcohol dependent. Assess for dependence.	• Further assessement preferably including family and significant others. • More intensive counselling and/or group program. • Consider referral to medical or specialist services for withdrawal management.
	4 or more	**Almost certainly dependent.** Assess for dependency.	• Pharmacotherapy to manage cravings. • Relapse prevention, longer-term follow-up and support.

ANNEX 4. THE DRINKING DIARY



How much are you drinking? Keep a drinks diary for a week to find out

Follow these three easy steps:

1. Fill out the diary using the basic alcohol units information below, or download a full drinks tracker at **www.nhs.uk/alcohol**. If you're not sure about the units in a drink, try and choose one below that seems close to it rather than miss it out altogether
2. Add up the units for each day and write the total in the last column
3. Finally, divide your total for the week by seven to give you an average units per day

Drinks and units

You can always work out the number of units in any drink for yourself. You simply multiply the volume (in ml) by the ABV [in %] and divide by 1,000. **For example, 125 (ml of red wine) x 12 (% ABV) / 1,000 = 1.5 units.**

*Gin, rum, vodka, whisky, tequila, sambuca. Large (35ml) single measures of spirits are 1.4 units.

Drinks diary

Day	Type of drink	Number of drinks	Units	Total units for day
Example	Pint of lower-strength lager Single small vodka and coke	1 1	2 1	3
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				
Sunday				
			Total	
			Daily average	

If do you find you are over the recommended limits (no more than 3-4 units a day on a regular basis for men; and no more than 2-3 units a day for women), you may well want to start cutting back.

Which category are you?

Now look at the average units per day and the total for the week that you wrote down and compare it with the categories below. If the last week was not typical, you may want to consider whether you are really sitting in the right category.

Liver problems, reduced fertility, high blood pressure, increased risk of various cancers and heart attack are some of the numerous harmful effects of regularly drinking above recommended levels.

Which category fits you best?

1 Lower risk

- **As a man, you don't drink more than 3-4 units a day on a regular basis**
- **As a woman, you don't drink more than 2-3 units a day on a regular basis**

Lower-risk drinking means that you have a low risk of causing yourself future harm.

2 Increasing risk

- **As a man, you drink more than 3-4 units a day on a regular basis**
- **As a woman, you drink more than 2-3 units a day on a regular basis**

Drinking at this level substantially increases the risk of alcohol damaging your health.

3 Higher risk

- **As a man, you regularly drink more than 8 units a day, or more than 50 units a week**
- **As a woman, you regularly drink more than 6 units a day, or more than 35 units a week**

If you're in this group, you're at an even higher risk of damaging your health compared to increasing risk drinkers. Your body may well have suffered damage already, even if you're not yet aware of it.

Next steps

Visit the alcohol pages in Live Well **www.nhs.uk/alcohol** to read about the health risks of drinking too much, get tips on cutting down, and get help and support.

www.nhs.uk/alcohol