Pharmacotherapy for alcohol-dependence: the 2015 recommendations of the French Alcohol Society, issued in partnership with the European Federation of Addiction Societies

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Short Running Title: French Recommendations on Alcohol Dependence

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ABSTRACT

BACKGROUND: The latest French good practice recommendations (GPRs) for the screening, prevention, and treatment of alcohol misuse were recently published in partnership with the European Federation of Addiction Societies (EUFAS). This article aims to synthesize the GPRs focused on the pharmacotherapy of alcohol dependence.

METHODS: A four-member European steering committee defined the questions that were addressed to an 18-member multi-professional working group (WG). The WG developed the GPRs based on a systematic, hierarchical and structured literature search and submitted the document to two review processes involving 37 French members from multiple disciplines and 5 non-French EUFAS members. The final GPRs were graded A, B, or C, or expert consensus (EC) using a reference recommendation grading system.

RESULTS:

- The treatment of alcohol dependence consists of either 1) alcohol detoxification / abstinence maintenance programs or 2) drinking reduction programs.
- The therapeutic objective is the result of a decision made jointly by the physician and the patient.
- Benzodiazepines (BZDs) are the first-line medication for detoxification (GRADE A).
- BZD dosing should be guided by regular clinical monitoring (GRADE B).
- Residential detoxification is more appropriate for patients with a history of seizures, delirium tremens, unstable psychiatric comorbidity, or another associated substance use disorder (GRADE B).
- BZDs are only justified beyond a one-week period in the case of persistent withdrawal symptoms, withdrawal events or associated BZD dependence (GRADE B).
- BZDs should not be continued for more than four weeks (GRADE C).
- The dosing and duration of thiamine (vitamin B1) during detoxification should be adapted to nutritional status (EC).
- Medications for relapse prevention should be automatically associated with adapted psychosocial support (GRADE A).
- Acamprosate and naltrexone are the first-line options for relapse prevention (GRADE A).
- Disulfiram can be proposed as second-line treatment in patients who are correctly informed and adequately supervised (EC).
- Medications for reducing alcohol consumption are only indicated in dependent individuals (EC).
- Nalmefene is indicated as a first-line treatment for reducing alcohol consumption (GRADE A).
- The second-line prescription of baclofen, up to 300 mg/d, to prevent relapse or reduce drinking should be carried out according to the “temporary recommendation for use” (TRU) issued by the French Health Agency (EC).
- Abstinence is recommended throughout pregnancy (EC).
- If medically-assisted withdrawal is necessary during pregnancy, BZD use is recommended (GRADE B).
- No medication other than those for alcohol withdrawal should be initiated in pregnant or breastfeeding women (EC).
- In a stabilized pregnant patient taking medication to support abstinence, the continuation of the drug should be considered on a case-by-case basis, weighing the benefit/risk ratio. Only disulfiram should be always stopped, given the unknown risks of the antabuse effect on the fetus (EC).
- First-line treatments to help maintain abstinence or reduce drinking are off-label for people under 18 years of age and should thus be considered on a case-by-case basis after the repeated failure of psychosocial measures alone (EC).
- Short-half-life BZDs should be preferred for the detoxification of elderly patients (GRADE B).
- The initial doses of BZDs should be reduced by 30 to 50% in elderly patients (EC).
- In patients with chronic alcohol-related physical disorders, the goal of abstinence is recommended (EC)
- Any antidepressant or anxiolytic medication should be introduced after a psychiatric reassessment after 2-4 weeks of alcohol abstinence or low-risk use (GRADE B).
- A smoking cessation program should be offered to any smokers involved in an alcohol treatment program (GRADE B).

DISCLAIMER: The French guidelines are based on the both the available evidence and national aspects of clinical practice. They do not constitute inflexible treatment recommendations.

KEYWORDS

Guidelines,

Pharmacotherapy,

Alcoholism,

Alcohol,

France,

Primary Care,

Addiction Medicine

1. INTRODUCTION

Alcohol dependence is usually defined as the most severe stage of alcohol use disorders (AUDs)(1), and it defines the clinical boundary beyond which the use of pharmacological treatments is officially indicated (2). Recently, new treatment strategies and medications have been developed to treat alcohol dependence. Drinking reduction programs have been increasingly proposed as an alternative of detoxification and subsequent abstinence maintenance among patients with alcohol dependence. Such programs aim to target the patients for whom the classical abstinence-based treatment strategies are unappealing or unattainable (3) and thus to reduce the important treatment gap observed among patients with AUDs (4). These new concepts have been developed worldwide, and a new medication, nalmefene, has been recently introduced in Europe as a pharmacological support for drinking reduction programs (5). Because practices are evolving, national guidelines must frame and integrate the new treatment concepts, taking into account both the international evidence and the local care system and medical culture.

In France, two former national guideline documents date back to 1999 and 2001 (6,7). They essentially emphasized the classic alcohol dependence treatment program based on assisted detoxification and abstinence maintenance (8). Moreover, the French addiction care system has evolved considerably since 2001, and the birth of addiction medicine as a holistic and individualized discipline has led to the implementation of specific multiaddiction treatment facilities that now integrate the French territory and aim to provide a more standardized care (9). More importantly, a recent development in the field specific to France has been the spread and the official regulation of the off-label use of high-dose baclofen for alcohol dependence, abstinence maintenance and drinking reduction (10).

For these reasons, it was necessary to develop new, updated, and methodologically rigorous good practice recommendations (GPRs) for French clinicians that encompass recent national and international developments pertaining to the treatment of alcohol misuse. The purpose of these new GPRs was to integrate the features of the French health system and local specificities and to meet the

international requirements for high quality standards, including full ethical and methodological transparency and international scientific peer-review. Therefore, the *Société Française d'Alcoologie* (SFA), i.e., the French Alcohol Society, appealed to the European Federation of Addiction Societies (EUFAS) to support the development of new French guidelines. This support consisted of 1) participating in the entire drafting process of the GPRs as external observers and transparency advisors and 2) having the GPR document peer-reviewed by non-French European members of the EUFAS.

The final GPRs were published online in French and in English and made accessible for free on the SFA Website (11,12). Overall, the GPRs are not restricted to alcohol dependence but embrace the much wider spectrum of alcohol misuse. This choice was made to emphasize the key role of primary care settings in the screening, detection, and treatment of any stage of alcohol misuse, including alcohol dependence (13). The aim of this article is to provide a synthesis of the French GPRs with a narrower focus on pharmacotherapy. As previously mentioned, alcohol dependence is the only stage of alcohol misuse in which pharmacotherapy is indicated. Therefore, only a portion of the French GPRs - i.e., the recommendations related to the therapeutic aspects of alcohol dependence and the specific management of medications in that context - is described herein.

2. METHODS

The committees and groups involved in the GPR-writing process were selected according to the methodological guidelines of the *Haute Autorité de Santé* (HAS), i.e., the French National Authority for Health (14). The HAS is an official French regulatory institution that aims to "*bring together under a single roof a number of activities designed to improve the quality of patient care and to guarantee equity within the health care system*" (15).

A four-member steering committee was created in July 2013 (see a list of the participants in the acknowledgment section). The steering committee issued a list of 19 questions related to alcohol misuse. The steering committee then gathered an 18-member multidisciplinary and multiprofessional working group (WG). The WG performed an initial systematic review of the literature with the aim of providing recommendations regarding the 19 questions issued by the steering committee. Based on the literature review performed by the WG and the subsequent expert discussion among its members, the WG drafted the first version of the GPR document and graded each recommendation using the HAS grading grid (see Table 1) (14).

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The initial draft of the GPRs was submitted to a first peer-review group comprising 37 French general practitioners, addiction specialists, addiction researchers, nurses, midwifes, and members of patient associations. After the first round of peer review, the WG revised the recommendation document. The revised draft was then submitted to a second peer-review group comprised of 5 non-French members of the EUFAS. The final version was published online on the SFA's website in both French and English (11,12). In the present article, we selected the recommendations related to the management of pharmacotherapy regarding AUDs. From the 19 initial questions about the GPRs, we selected the recommendations referring to 6 questions pertaining to medication prescription and treatment objectives (See Table 2).

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3. RESULTS

3.1 What are the objectives of the therapeutic intervention?

The short version of the recommendations issued in response to this question is listed in Table 3.

It has been stated that the therapeutic interventions for patients with alcohol dependence should primarily aim to improve the subject's quality of life (EC). In practice, this implies reducing alcohol-induced harms, i.e., those that affect the subject's physical and mental health, interpersonal, social and professional adaptation, or legal situation. Such changes, however, require the subject to abandon harmful drinking patterns, which implies a protracted modification of alcohol use with the goal of either abstinence or a significant reduction in consumption (16,17). Consequently, the GPRs considered that therapeutic interventions for alcohol misuse, including alcohol dependence, should aim for abstinence or moderation (EC).

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Subjects with severe alcohol dependence, the misuse of multiple associated substances or severe psychiatric comorbidities are less likely to return to stable, low-risk alcohol use than are subjects who do not exhibit such features (18–20). Furthermore, the alcohol use outcome is substantially improved when the treatment goal is based on the informed decision of the service user (21,22). Such patient information also corresponds to current ethical requirements regarding the patient-physician relationship (23). Consequently, the objectives of therapeutic intervention for subjects with alcohol dependence should first rely on the informed decision of the service user (GRADE B).

The severity of the alcohol dependence should also be taken into consideration. It has thus been recommended in the GPRs that abstinence should be the goal for subjects with severe alcohol dependence and/or dependence with significant psychiatric or physical comorbidity (EC). If the service

user is unable or unwilling to reach a goal of abstinence, a drinking reduction program aimed at harm reduction can be implemented, although the patient should be regularly encouraged to abstain (EC). For subjects with mild dependence, no significant comorbidities and good social support, a moderate level of drinking is a suitable goal unless the patient prefers abstinence (EC).

In any case, any significant reduction in the average alcohol use, such as the proportion of heavy drinking, should be encouraged (GRADE A) because such reductions help reduce the overall risks and harms induced by alcohol.

3.2 How should intervention be planned?

Therapeutic interventions should be planned according to the consumption goal (i.e., abstinence or moderation). However, consumption goals may fluctuate from one period to another and between a goal of reducing alcohol use or abstaining and can vary either way. The motivation to change can be volatile.

Regarding the abstinence goal, the therapeutic intervention can usually be separated into two phases: 1) assisted alcohol withdrawal and 2) abstinence maintenance (or relapse prevention). These two phases should be distinguished, notably because they have different monitoring and therapeutic purposes and may require specific pharmacotherapy.

For patients seeking moderation rather than abstinence, an assisted alcohol withdrawal period is not necessarily warranted. In this case, there is no clear distinction between the moderation period and the relapse prevention period because the two goals are generally combined (EC).

3.3 How should treatment with a goal of detoxification be conducted?

Alcohol withdrawal consists of the immediate cessation of alcohol consumption. Alcohol withdrawal can be accidental, imposed by circumstances, or planned with a therapeutic aim. In patients with alcohol dependence, alcohol withdrawal may trigger an alcohol withdrawal syndrome (AWS) starting a few hours after the last alcohol intake and continuing for a few days. AWS can consist of numerous types of symptoms to varying degrees (24): 1) subjective disorders, i.e., anxiety, agitation, irritability, insomnia, and nightmares; 2) gastrointestinal disorders, i.e., anorexia, nausea, vomiting, and diarrhea; and 3) autonomic disorders, i.e., sweat, tremor, tachycardia, and hypertension. Complications of AWS include delirium, hallucinations, or seizures. The main risk factors for AWS complications include a high level of daily drinking, previous episodes of AWS, associated substance use disorders, and associated physical comorbidities (25). The intensity of AWS can vary. Approximately 95% of alcohol withdrawal situations are free of severe complications (26). However, complications can be serious and sometimes even life-threatening (24). AWS thus requires specific prevention, intervention and supervision efforts.

Detoxification is defined as the medical procedure for rapidly and safely achieving an alcohol-free state in a subject with alcohol dependence. The recommendations issued in the GPR document concerning the overall management of alcohol detoxification can be viewed in Table 4. Alcohol detoxification can take place on an outpatient or residential basis. Residential detoxification is safer (24), whereas outpatient detoxification is less expensive (27). Outpatient detoxification is not recommended in patients with communication difficulties, a history of seizures, unstable psychiatric comorbidities or high-dose polydrug use, especially daily, historical or high-dose benzodiazepine (BZD) addiction (EC). Residential treatment should also be recommended on a case-by-case basis considering specific circumstances, such as the extent of the withdrawal syndrome, the failure of repeated outpatient detoxification attempts, severe or unstable comorbidity, age-related frailty,

pressing demands from the subject's family, limited social support, a precarious social situation, or pregnancy (EC). In other situations, outpatient detoxification is preferable (EC).

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Alcohol detoxification may require preventive or therapeutic medications for AWS. BZDs have demonstrated good efficacy for preventing and treating AWS symptoms and complications (28) and have been the quasi-ubiquitous treatment for AWS prevention in France since the release of the French guidelines for the management of alcohol detoxification (7). Consequently, BZDs are the recommended medication for AWS (GRADE A). However, because AWS occurs in only a little more than half of alcohol-dependent patients (29), medications are not necessary for every patient (GRADE C). The symptom-adjusted prescription of BZDs is both safe and more strategy for the patient (30) and should be prioritized, although it is more easily applicable in residential settings, where the patient can be assessed several times a day (GRADE C). A symptom-adjusted treatment strategy may be supported by withdrawal symptom evaluation scales, such as the Clinical Institute Withdrawal Assessment for Alcohol – revised scale (CIWA-Ar scale; 24), or the Cushman score (32), the use of which is extremely widespread in France. When such monitoring conditions are not met, preventive BZD treatment should be implemented (EC).

The use of long half-life BZDs is considered globally safe and is recommended (EC). Short half-life BZDs (such as oxazepam) have not demonstrated enhanced safety in this situation, and the clearance of oxazepam was found to be severely reduced among subjects with alcoholic liver disease (33). In the event of concerns about BZD use (e.g., chronic respiratory failure, decompensated liver cirrhosis with ascites, jaundice or prothrombin time <50%, obesity, advanced patient age) and the risk of withdrawal syndrome, residential detoxification is strongly recommended (EC). In such cases, BZDs can be administered according to a symptom-triggered protocol only in the event of patent signs of withdrawal and after the re-assessment of each dose (EC). In the event of severe withdrawal

symptoms or withdrawal events, treatment with BZDs should not be continued for more than four weeks, including the dose reduction phase (GRADE C).

Thiamine (vitamin B1) is considered both a preventive and curative treatment for Wernicke's encephalopathy, which can occur at any stage among individuals with an AUD, including during alcohol withdrawal (34). Because there is currently no clear evidence regarding how to use thiamine among alcohol-dependent individuals (34), the systematic initiation of a thiamine prescription is recommended, although the treatment dose and duration should be adapted to the subject's underlying nutritional status (EC).

3.4 How can relapse be prevented?

If abstinence has been chosen as an objective, the aim of the treatment is to maintain abstinence, i.e., prevent relapse (see 3.1). When the treatment goal is abstinence, the therapeutic regimen usually includes an initial provision for alcohol detoxification. Relapse prevention corresponds to the therapeutic phase that follows alcohol withdrawal. In the past, relapse was defined as having the first drink after detoxification. More recently, relapse has been defined by the resumption of high-level use (greater than or equal to 5 units/day on a single occasion for males aged under 65 years; greater than or equal to 4 units/day for males over 65 years of age and for females)(35). It should be noted that these levels were defined by the US Food and Drug Administration, which defines a unit as 14 grams of alcohol, whereas a standard unit in France corresponds to 10 grams (36).

The GRP recommendations regarding relapse prevention are listed in Table 5.

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In subjects with alcohol dependence, pharmacological treatments can be used to support abstinence. Medications for relapse prevention should be combined with adapted psychosocial support for

patients with alcohol dependence (GRADE A). Enhanced psychosocial support may increase motivation and thus compliance with medications, which, in turn, improves therapeutic efficacy (EC).

Both acamprosate and naltrexone have been demonstrated to be efficacious for relapse prevention (37–39), and they display a globally good level of tolerability (37). Therefore, either medication can be used as a first-line treatment to support relapse prevention (GRADE A). Acamprosate has been found to be slightly more efficacious for maintaining abstinence, while naltrexone appears to be slightly more efficacious for reducing heavy drinking and craving (38). These features can help professionals decide which drug to prescribe, depending on the patient's situation.

Disulfiram has also demonstrated satisfactory efficacy for preventing relapse (40,41). It is worth mentioning that the drug's specific mode of action implies that double-blind designs are not adequate (41). Moreover, disulfiram is associated with potentially harmful adverse drug reactions and safety issues (42). This drug requires close medical supervision and safety surveillance. It is thus recommended that disulfiram be proposed as second-line treatment for patients who are motivated to sustain abstinence and are adequately informed about the risk of the antabuse effect and adequately supervised (EC).

In France, high-dose baclofen (HDB), i.e., up to 300 mg/d, has become a widespread off-label medication for alcohol dependence (10). Both general practitioners and addiction specialists can prescribe HDB, either for abstinence maintenance or drinking reduction (43,44). Although a recent clinical trial found that HDB had a significant effect on abstinence maintenance (45), the sample size of that trial was small, and the results of two clinical trials with larger samples are still being awaited (46,47). Moreover, HDB is known to induce frequent neuropsychiatric adverse drug reactions, such as sedation, dizziness, insomnia, and tinnitus (48–50). More rarely, seizures, manic symptoms, and baclofen withdrawal syndromes have been associated with HDB (51–53).

In 2014, baclofen was officially authorized by the French Health Agency as a second-line prescription for preventing relapse among alcohol-dependent patients at doses up to 300 mg/d (54). This

authorization consists of a specific measure called a “temporary recommendation for use” (TRU) and is thus associated with a specific supervision procedure. The TRU will be applied until the results of the two aforementioned trials become available. In case of demonstrated efficacy, the TRU can be changed to an official labeling. Otherwise, the measure will be removed, and HDB will no longer benefit from any regulatory efforts to frame prescriptions and monitoring practices. The French GPRs have thus followed the TRU measure and have stated that HDB can be prescribed as a second-line treatment for abstinence maintenance at doses up to 300 mg/d only if the different criteria of the national regulatory measure are met.

3.5 How should treatment aimed at reducing drinking be conducted?

In France, recommendations suggest that alcohol consumption be limited to below at-risk use, i.e., fewer than 21 standard drinks (sd; 10 g of alcohol per sd) per week for males and fewer than 14 sd per week for females and fewer than 4 sd on each drinking occasion (EC). However, in certain circumstances, any use of alcohol is considered a risky behavior, e.g., during childhood or pregnancy, when driving an automobile or operating a machine, or in subjects with specific physical disorders or medical diseases. Thus, the ideal objective of drinking reduction programs should be personalized according to the patient’s needs.

However, any reduction in alcohol use can have a significant impact on health. It has been demonstrated an exponential relationship between alcohol use and the risk of death (55), and reductions in consumption have a greater impact when the level of initial consumption is higher. For example, a reduction of 36 grams of alcohol per day was calculated as reducing the risk of death by three times more in a drinker who consumes 96 g/day than in a drinker who consumes 60 g/day (56).

Therefore, several recommendations have been issued on how to conduct a drinking reduction treatment (see Table 6).

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It is recommended that consumption below the at-risk levels be targeted insofar as possible, although any lasting reduction in consumption should be considered a positive result and a possible initial step towards a greater reduction (EC).

The reduction of alcohol consumption can be directly proposed to patients with mild dependence or to patients with a more severe disorder who do not wish or are not yet able to attempt abstinence (EC).

Until early 2010, psychosocial interventions were the only therapeutic strategies available for alcohol treatment. Since then, medicinal strategies have become available. The psychosocial interventions recommended for reducing alcohol use among patients with alcohol dependence are motivational interventions and cognitive behavioral programs, notably behavioral self-control training (57). The most important therapeutic element appears to be daily self-monitoring of consumption (57), which should be routinely used across drinking reduction programs (GRADE A).

Pharmacological treatments that support drinking reduction have only been evaluated in individuals with alcohol dependence and are thus recommended only for that population (EC). Nalmefene is the first medicinal product to demonstrate efficacy for reducing alcohol consumption in subjects with alcohol dependence (58), and it is also the first drug to receive regulatory labeling in France for the indication of reducing drinking in alcohol-dependent individuals. Although naltrexone is normally indicated for the prevention of relapse after withdrawal (see 3.4), some data indicate that it may have efficacy for reducing alcohol use (59). As indicated in part 3.4, the prescription of HBD to reduce alcohol use among alcohol-dependent patients has been authorized by the TRU measure since March 2014 at doses up to 300 mg/d until further data are available.

Consequently, nalmefene is recommended as the first-line medication for reducing alcohol consumption in subjects with alcohol dependence (GRADE A). The use of HDB to treat alcohol use

among alcohol-dependent patients should be considered a second-line option, and its prescription should strictly follow the criteria of the TRU measure (EC).

3.6 How treatment should be managed in specific populations: pregnant women, adolescents, the elderly, and individuals with somatic or psychiatric comorbidities or multiple-substance use

Table 7 lists the main recommendations for managing treatment in specific populations.

Given the lack of any current international consensus on alcohol toxicity thresholds for embryos or fetuses, abstinence throughout pregnancy is recommended for pregnant women, including pregnant women with alcohol dependence (EC). Pregnancy in a woman who misuses alcohol is a medical priority and requires the cessation of all alcohol use as soon as possible, regardless of the term during which the intervention takes place (EC). The patient must be managed by a multidisciplinary community/hospital team (EC). If medically assisted withdrawal is necessary during pregnancy, short-term use of BZDs is currently considered safe for the dyad (60,61) and is therefore recommended (GRADE B).

No medical treatments designed to help maintain abstinence or achieve a reduction in alcohol use have been properly evaluated in pregnant or breastfeeding women with alcohol dependence. It is therefore recommended that no treatments other than those for alcohol withdrawal be initiated in pregnant or breastfeeding women (EC). In the event that a pregnancy occurs in a patient who is obviously stabilized by pharmacological treatment, the continuation of treatment should be considered on a case-by-case basis by weighing the benefit/risk ratio (EC). Treatment with disulfiram is an exception to this recommendation; it is preferable to discontinue disulfiram treatment in particular because the risks of the antabuse effect on the fetus are unknown (EC). In other cases, the decision must be pragmatic and reached after a multidisciplinary consultation involving at least the patient's own doctor, the addiction specialist, the obstetrician and the regional pharmacovigilance center (EC).

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In adolescence, alcohol dependence is commonly associated with severe psychiatric disorders and family problems (62). Therefore, any adolescent under the age of 16 years with alcohol dependence should undergo a pediatric psychiatric assessment (GRADE C). Because the overall prognosis is less favorable in such situations (63), abstinence is often the preferred goal (GRADE C). However, given that it is sometimes difficult to get these young patients to agree to abstain, it may be necessary to establish a goal of drinking reduction as part of a harm-reduction strategy (EC). Given the absence of specific data regarding the use of medication for alcohol dependence in adolescents, first-line treatments to help maintain abstinence or reduce drinking do not have marketing authorization in France or elsewhere for subjects under the age of 18 years. Off-label use of medication is recommended on a case-by-case basis and only for severe misuse after the repeated failure of psychosocial measures alone (EC).

In elderly patients with alcohol dependence, especially those who vulnerable because of physical disability, heavy medication use, or cognitive impairment, it is preferable to conduct the detoxification process in a hospital setting to control or more easily prevent serious complications, i.e., delirium tremens, convulsions, falls, and intracerebral hematomas (EC). In addition, it is essential to ensure good hydration in these subjects, who frequently have cardiovascular problems and a precarious fluid-electrolyte balance (EC). The onset of withdrawal syndrome may be delayed in elderly patients compared to younger ones. Given the pharmacokinetic and pharmacodynamics modifications observed in this population, particular caution is required when prescribing BZDs (EC).

BZDs remain the treatment of choice for the elderly; however, in contrast with the recommendations for younger adult populations, short half-life BZDs reduce the risk of accumulation (64,65) and the resulting adverse events, such as sedation and falls, in the elderly (66). Therefore, short half-life BZDs are preferred for elderly patients (GRADE B). Initial doses must be reduced by 30 to 50% (EC).

Medicinal treatment to reduce alcohol use or prevent relapse among the elderly is no different than the recommendations for younger patients. Social and environmental management that aims to combat isolation is particularly important (GRADE B) because it is a major cause of alcohol misuse in the elderly (67). For patients living at home, meal delivery, home-help services and community nurse visits can support abstinence maintenance (EC). Such visits are also a way of alerting medical and social services in the event of difficulties. For patients living in an institution, improving their living environment, engaging them in support groups and breaking their solitude are also invaluable (EC).

Patients with both alcohol dependence and alcohol-related physical complications should be offered coordinated care that includes an addiction specialist, the concerned specialist(s) and the patient's general practitioner (EC). Given the absence of clear data regarding the existence of a toxicity threshold in patients with liver cirrhosis, pancreatitis, cognitive disorders, ataxia or peripheral neuropathy, alcoholic cardiomyopathy, alcohol-related cancer or other chronic somatic complications related to alcohol, abstinence is recommended in these situations (EC). If the patient is unwilling to stop drinking, intermediate objectives to reduce his/her alcohol use may be established with the aim of limiting damage, but the final goal remains total abstinence (EC).

In patients with liver cirrhosis, baclofen, at a dose of 30 mg/d, has demonstrated encouraging results in cirrhosis patients (68). To date, higher dosages have not been assessed in this population, and severe liver failure is a contraindication for the use of baclofen according to the TRU. When alcohol detoxification is required in subjects with alcohol liver disease, oxazepam should not be considered safer in this population (see part 3.3). In the case of decompensated liver cirrhosis with ascites, jaundice or prothrombin time <50%, residential detoxification is strongly recommended (EC). In similar cases, the use of naltrexone for abstinence maintenance is contraindicated. In contrast, acamprosate has a good global safety profile, and the absence of liver metabolism and of pharmacokinetic

interactions with alcohol could represent an advantage in the treatment of alcohol dependent patients affected by end-stage alcoholic liver disease; however, no trials with repeated administrations of acamprosate in these patients have been performed. In cases of less-severe alcoholic liver diseases, including compensated cirrhosis, naltrexone treatment is possible as long as monthly laboratory tests (prothrombin time, transaminases) are performed.

Some patients with alcoholic liver cirrhosis may need a liver transplantation (69), after which some of these subjects do appear able to resume stable low-risk alcohol use (70); however, in light of the current absence of sufficient ongoing data and given the significant impact of resumed misuse on the transplanted organ (69, 71), continued abstinence should be maintained insofar as possible (EC).

The cognitive disorders induced by alcohol are often reversible after detoxification, but their persistence has a negative impact on treatment compliance and living conditions (72). Consequently, if an alcohol-induced cognitive disorder is suspected or diagnosed, particularly in conjunction with alcoholic liver disease or nutritional deficiencies, the management of the detoxification and post-detoxification period in a residential setting is preferable to outpatient management for obtaining protracted abstinence (EC).

Depressive symptoms are often observed in patients presenting non-stabilized alcohol misuse. In the majority of cases, these symptoms quickly disappear after detoxification or a significant reduction in alcohol use (73,74). A diagnosis of major depressive episode and the introduction of an antidepressant should only be considered after the alcohol misuse is in remission, i.e., abstinence or low-risk use for 2 to 4 weeks (GRADE B). At the present time, no particular antidepressant treatment has shown superiority over the others in patients with alcohol dependence (75); thus, no particular drug should thus be globally preferred (GRADE A). Severe symptoms of depression may indicate a need for medically managed detoxification in a residential setting (EC). Alcohol misuse frequently causes symptoms of anxiety, which are sometimes severe. In this case, too, symptoms disappear or often

improve after detoxification or a marked reduction in alcohol use (74). As with depression symptoms, long-term pharmacological treatments of the anxiety should only be considered after a psychiatric reassessment of the patient in a remission state, i.e., after the patient has abstained or been drinking at a low-risk level for 2 to 4 weeks (GRADE B).

The presence of concomitant addictive disorders always requires a global management program that incorporates all substances, including tobacco. In the event of medically managed detoxification, quitting smoking at the same time reduces risk of a subsequent alcohol relapse (76). A smoking cessation approach is therefore recommended, and pharmacological assistance should be systematically offered to smokers when they are giving up alcohol in either a hospital or an outpatient setting (GRADE B).

4. DISCUSSION

The aim of the present article was to synthesize the portions of the 2015 French GPRs that pertain to the pharmacotherapy of alcohol dependence. As indicated above, a nation's guidelines are not a mere literature review of the evidence; they should also integrate the nation's care system and medical habits. They may also propose recommendations in areas where no evidence is currently available. Consequently, the guidelines issued in different countries can vary on several points, despite a basis in the same literature. Thus, a comparison of the French GPRs with other national guidelines is warranted. For instance, a very illustrative example of transnational differences is the determination of low-risk thresholds, which are highly variable among countries (36).

Regarding pharmacotherapy, France has developed some prescribing particularities over time. Diazepam has been by far the most widely used BZD for alcohol detoxification. In many other countries, the use of chlordiazepoxide is also very common. For example, both diazepam and chlordiazepoxide are recommended as first-line detoxification treatments in the National Institute for

Clinical Excellency (NICE) guidelines, i.e., the English recommendations (77). In some other countries, such as Australia, chlordiazepoxide is not labeled, and diazepam is thus the only first-line recommendation (78). In France, chlordiazepoxide has been labeled for anxiety but not for alcohol detoxification, and it is not routinely used for this indication in clinical practice. For this reason, only diazepam has been recommended in the GPRs. It is noteworthy that BZDs have not shown a clear superiority to some anticonvulsants (i.e., carbamazepine) in the management of alcohol withdrawal (28). The recommendation of BZDs as first-line pharmacotherapy is therefore based on widespread consensus rather than on clear evidence. Moreover, the choice not to recommend short half-life BZDs for the management of detoxification in patients with liver disease can appear confusing, because this use is frequent in practice and was mentioned by previous expert statements (79, 80). However, these previous statements were completely empirical, and the scientific comparisons between using short or long half-life BZDs for alcohol detoxification actually appear both scarce and contradictory (33, 81). Consequently, after a long debate, the working group decided not to clearly recommend short half-life BZDs in this case. It is also warranted to mention sodium oxybate, which has been found efficacious notably for the prevention of AWS (82), and is labeled in Italy and Austria for both preventing AWS and maintenance abstinence. Nevertheless, sodium oxybate is currently not labeled in France and was thus not directly discussed in the GPRs.

For the indication of abstinence maintenance, disulfiram is recommended in the French GPRs as a second-line treatment for patients who have experienced a previous failure of naltrexone or acamprosate. This is essentially because of concerns about the safety of the drug. The same recommendation can also be found in the NICE guidelines (77) but not in the Australian guidelines, which allow the first-line prescription of disulfiram with certain precautions (78).

Undoubtedly, the most recent French prescribing particularity has been the off-label use of HDB. This practice initially derived from a single-case patient-physician account (83) whose story was widely disbursed in the media (10). In France, HBD is used equally for drinking reduction and abstinence

maintenance (44). This prescribing practice has also been noted in French-speaking border countries, such as Belgium and Switzerland (84,85). Moreover, the use of HDB has also been reported in non-French-speaking countries, such as Germany, where the first positive results were found for HDB in abstinence maintenance (45). Nevertheless, France is currently the only country where HDB prescriptions have been regulated by the national drug agency. HDB is mentioned in the Australian guidelines, and the last-resort utilization of HDB has been reported by Australian researchers in case series (86). In Italy, baclofen has a long history of use among some teams, but essentially at low doses (87). In contrast, baclofen does not seem to be used for alcohol dependence in the UK, and the NICE does not even mention the drug. If the recent large-sample clinical trials that have been conducted in France provide significant results (46,47), European labeling might be bestowed upon HDB. This could homogenize the HDB prescription practices, which are currently very heterogeneous among European countries.

It is worth noting that despite its off-label status, baclofen was one of the first medications to be used for drinking reduction in France before the commercial availability of nalmefene. In fact, the publication of the new French GPRs was warranted in part because of the emergence of this new treatment concept. Studies of patient preferences have highlighted that drinking reduction should be offered as an additional treatment option for alcohol-dependent subjects (88), and the recent clinical trials of nalmefene have provided further evidence that a pharmacological treatment could support drinking reduction in subjects with alcohol dependence who drink heavily (58, 89–92). However, several aspects of the pharmacotherapy of drinking reduction and controlled drinking remain to be clarified. In practice, switches in drinking patterns can be observed in all directions. Only a few of these changes have been investigated in clinical trials; thus, many situations have been poorly codified. For example, it is unclear whether patients with alcohol dependence who decide to attempt to resume low-risk drinking after a period of abstinence can benefit from pharmacological support. No drug is currently indicated in such situations, and there is currently no empirical evidence that such an approach is sensible for patients.

Despite the consideration of the French national care system and clinical practices in the drafting of the GPRs, external (non-French) participation was also important for the transparency and quality of the GPRs. This was the role served by the EUFAS members who were on the steering committee or who participate in the document's review process. This involvement should be viewed as one of the first benefits of the EUFAS' mission, which includes the promotion of cross-European interaction with regard to clinical practices (93). The next step could consist of elaborating homogenous European GPRs, but such a project could also come up against very heterogeneous local practices and regulations.

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REFERENCES

1. Laramee P, Kusel J, Leonard S, Aubin HJ, François C, Daeppen JB. The economic burden of alcohol dependence in Europe. *Alcohol Alcohol* 2013; **48**(3):259-69.

2. European Medicines Agency. Guideline on the development of medicinal products for the treatment of alcohol dependence. 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf (Accessed 01/09/15).

3. Marlatt GA, Witkiewitz K. Harm reduction approaches to alcohol use: health promotion, prevention, and treatment. *Addict Behav* 2002; **27**(6):867-86.

4. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. *Bull World Health Organ* 2004; **82**(11):858-66.

5. Aubin HJ, Daeppen JB. Emerging pharmacotherapies for alcohol dependence: A systematic review focusing on reduction in consumption. *Drug Alcohol Depend* 2013; **133**(1):15-29.

6. Haute Autorité de Santé, Société Française d'Alcoologie. Conférence de consensus 7 et 8 mars 2001: modalités de l'accompagnement du sujet alcoolodépendant après un sevrage. http://www.has-sante.fr/portail/upload/docs/application/pdf/alcool2.pdf (Accessed 01/09/15).

7. Haute Autorité de Santé, Société Française d'Alcoologie. Conférence de consensus du 17 mars 1999: Objectifs, indications et modalités du sevrage du patient alcoolodépendant. http://www.has-sante.fr/portail/upload/docs/application/pdf/alccol2.pdf (Accessed 01/09/15).

8. Rolland B, Laprevote V, Geoffroy PA, Guardia D, Schwan R, Cottencin O. Abstinence dans l'alcoolodépendance : approche critique et actualisée des recommandations nationales de 2001. *Presse Med* 2013; **42**(1):19-25.

9. Cottencin O, Harbonnier J, Guardia D, Rolland B, Danel T. The System of Medical Treatment for Addiction in France. *Int J Ment Health* 2014; **43**(3):19-26.

10. Rolland B, Bordet R, Cottencin O. Alcohol-dependence: the current French craze for baclofen. *Addiction* 2012; **107**(4):848-9.

11. Société Française d'Alcoologie. Alcohol misuse: screening, diagnosis and treatment. 2015. http://www.sfalcoologie.asso.fr/download/SFA-GPR-AlcoholMisuse.pdf?PHPSESSID=9da9bde13d18fec259c6001837efa055 (Accessed 01/09/15).

12. Société Française d'Alcoologie. Mésusage de l'alcool: dépistage, diagnostic et traitement. Recommandations de bonne pratique. *Alcoologie et Addictologie* 2015;**37**(1):5-84. http://www.sfalcoologie.asso.fr/download/RBP2014-SFA-Mesusage-AA.pdf (Accessed 01/09/15).

13. Rolland B, Mann K, Paille F, Aubin H-J. The New French Guidelines on Alcohol Misuse: An Initiative for Strengthening Cross-European Interplay. *Addiction* 2015; **110**(8):1362-3.

14. Haute Autorité de Santé. Practice Guidelines: "Clinical practice guidelines" method. 2011. http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-07/guideline_by_cpg_method_-_quick_methodology_guide_-_4_pages.pdf (Accessed 01/09/15).

15. Haute Autorité de Santé. About HAS. http://www.has-sante.fr/portail/jcms/r_1455134/fr/about-has. (Accessed 01/09/15).

16. Gastfriend DR, Garbutt JC, Pettinati HM, Forman RF. Reduction in heavy drinking as a treatment outcome in alcohol dependence. *J Subst Abuse Treat* 2007; **33**(1):71-80.

17. Luquiens A, Aubin H-J. Patient preferences and perspectives regarding reducing alcohol consumption: role of nalmefene. *Patient Prefer Adherence* 2014; **8**:1347-52.

18. Vaillant GE. A 60-year follow-up of alcoholic men. *Addiction* 2003; **98**(8):1043-51.

19. Gual A, Bravo F, Lligoña A, Colom J. Treatment for alcohol dependence in Catalonia: health outcomes and stability of drinking patterns over 20 years in 850 patients. *Alcohol Alcohol* 2009; **44**(4):409-15.

20. Subbaraman MS, Witbrodt J. Differences between abstinent and non-abstinent individuals in recovery from alcohol use disorders. *Addict Behav* 2014; **39**(12):1730-5.

21. Al-Otaiba Z, Worden BL, McCrady BS, Epstein EE. Accounting for self-selected drinking goals in the assessment of treatment outcome. *Psychol Addict Behav* 2008; **22**(3):439-43.

22. Adamson SJ, Heather N, Morton V, Raistrick D. Initial preference for drinking goal in the treatment of alcohol problems: II. Treatment outcomes. *Alcohol Alcohol* 2010; **45**(2):136-42.

23. World Health Organization. Empowering patients. 2012. http://www.euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/sections/news/2012/4/empowering-patients (Accessed 01/09/15).

24. Hall W, Zador D. The alcohol withdrawal syndrome. *Lancet* 1997;**349**(9069):1897-900.

25. Maldonado JR, Sher Y, Ashouri JF, Hills-Evans K, Swendsen H, Lolak S, et al. The « Prediction of Alcohol Withdrawal Severity Scale » (PAWSS): systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol* 2014; **48**(4):375-90.

26. Schuckit MA. Alcohol-use disorders. *Lancet* 2009; **373**(9662):492-501.

27. Hayashida M, Alterman AI, McLellan AT, O'Brien CP, Purtill JJ, Volpicelli JR, et al. Comparative effectiveness and costs of inpatient and outpatient detoxification of patients with mild-to-moderate alcohol withdrawal syndrome. *N Engl J Med* 1989; **320**(6):358-65.

28. Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. *Cochrane Database Syst Rev* 2010; (3):CD005063.

29. Rehm J, Allamani A, Aubin HJ, et al. People with alcohol use disorders in specialized care in eight different European countries. *Alcohol Alcohol* 2015; **50**(3):310-8.

30. Daeppen JB, Gache P, Landry U, et al. Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. *Arch Intern Med* 2002; **162**(10):1117-21.

31. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict* 1989; **84**(11):1353-7.

32. Cushman P, Forbes R, Lerner W, Stewart M. Alcohol withdrawal syndromes: clinical management with lofexidine. *Alcohol Clin Exp Res* 1985; **9**(2):103-8.

33. Sonne J, Andreasen PB, Loft S, Døssing M, Andreasen F. Glucuronidation of oxazepam is not spared in patients with hepatic encephalopathy. *Hepatol* 1990; **11**(6):951-6.

34. Latt N, Dore G. Thiamine in the treatment of Wernicke encephalopathy in patients with alcohol use disorders. *Intern Med J* 2014; **44**(9):911-5.

35. US Department of Helath & Human Services, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism. Helping patients who drink too much. A clinican's guide. 2005. http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf (Accessed 01/09/15).

36. Furtwaengler NAFF, de Visser RO. Lack of international consensus in low-risk drinking guidelines. *Drug Alcohol Rev* 2013; **32**(1):11-8.

37. Bouza C, Angeles M, Magro A, Muñoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction* 2004; **99**(7):811-28.

38. Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction* 2013; **108**(2):275-93.

39. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* 2014; **311**(18):1889-900.

40. Jørgensen CH, Pedersen B, Tønnesen H. The efficacy of disulfiram for the treatment of alcohol use disorder. *Alcohol Clin Exp Res* 2011; **35**(10):1749-58.

41. Skinner MD, Lahmek P, Pham H, Aubin H-J. Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. *PloS One* 2014; **9**(2):e87366.

42. Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Saf* 1999; **20**(5):427-35.

43. Dupouy J, Fournier JP, Jouanjus E, et al. Baclofen for alcohol dependence in France: Incidence of treated patients and prescription patterns-A cohort study. *Eur Neuropsychopharmacol* 2014; **24**(2):192-9.

44. Rolland B, Paille F, Fleury B, Cottencin O, Benyamina A, Aubin HJ. Off-Label Baclofen Prescribing Practices among French Alcohol Specialists: Results of a National Online Survey. *PloS One* 2014; **9**(6):e98062.

45. Müller CA, Geisel O, Pelz P, et al. High-dose baclofen for the treatment of alcohol dependence (BACLAD study): A randomized, placebo-controlled trial. *Eur Neuropsychopharmacol* 2015; **25**(8):1167-77.

46. BACLOVILLE study (NCT01604330). Baclofen for the Treatment of Alcohol Drinkers - Full Text View - ClinicalTrials.gov. 2012. http://clinicaltrials.gov/ct2/show/NCT01604330 (Accessed 01/09/15).

47. ALPADIR study (NCT01738282). Efficacy and Safety of Baclofen for Maintenance of Abstinence in Alcohol Dependent Patients - Full Text View - ClinicalTrials.gov. http://clinicaltrials.gov/show/NCT01738282 (Accessed 01/09/15).

48. Auffret M, Rolland B, Deheul S, et al. Severe tinnitus induced by off-label baclofen. *Ann Pharmacother* 2014; **48**(5):656-9.

49. Rigal L, Legay Hoang L, Alexandre-Dubroeucq C, Pinot J, Le Jeunne C, Jaury P. Tolerability of High-dose Baclofen in the Treatment of Patients with Alcohol Disorders: A Retrospective Study. *Alcohol Alcohol* 2015; **50**(5):551-7

50. Rolland B, Labreuche J, Duhamel A, et al. Baclofen for alcohol dependence: Relationships between baclofen and alcohol dosing and the occurrence of major sedation. Eur Neuropsychopharmacol 2015; doi: 10.1016/j.euroneuro.2015.05.008.

51. Rolland B, Deheul S, Danel T, Bordet R, Cottencin O. A Case of De novo Seizures Following a Probable Interaction of High-Dose Baclofen with Alcohol. *Alcohol Alcohol* 2012; **47**(5):577-80.

52. Geoffroy PA, Auffret M, Deheul S, Bordet R, Cottencin O, Rolland B. Baclofen-Induced Manic Symptoms: Case Report and Systematic Review. *Psychosomatics* 2014; **55**(4):326-32.

53. Rolland B, Jaillette E, Carton L, et al. Assessing alcohol versus baclofen withdrawal syndrome in patients treated with baclofen for alcohol use disorder. *J Clin Psychopharmacol* 2014; **34**(1):153-6.

54. Agence Française du Médicament et des produits de santé. Recommandation temporaire d'utilisation (RTU) pour le baclofène - Point d'information 2014. http://ansm.sante.fr/S-informer/Actualite/Une-recommandation-temporaire-d-utilisation-RTU-est-accordee-pour-le-baclofene-Point-d-information (Accessed 01/09/15).

55. Rehm J, Greenfield TK, Rogers JD. Average volume of alcohol consumption, patterns of drinking, and all-cause mortality: results from the US National Alcohol Survey. *Am J Epidemiol* 2001; **153**(1):64-71.

56. Rehm J, Roerecke M. Reduction of drinking in problem drinkers and all-cause mortality. *Alcohol Alcohol* 2013; **48**(4):509-13.

57. Michie S, Whittington C, Hamoudi Z, Zarnani F, Tober G, West R. Identification of behaviour change techniques to reduce excessive alcohol consumption. *Addiction* 2012; **107**(8):1431-40.

58. Mann K, Bladström 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**(8):706-13.

59. Rösner S, Leucht S, Lehert P, Soyka M. Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. *J Psychopharmacol* 2008; **22**(1):11-23.

60. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol* 1994; **8**(6):461-75.

61. Wikner BN, Stiller C-O, Bergman U, Asker C, Källén B. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. *Pharmacoepidemiol Drug Saf* 2007; **16**(11):1203-10.

62. Kuperman S, Chan G, Kramer JR, et al. Relationship of age of first drink to child behavioral problems and family psychopathology. *Alcohol Clin Exp Res* 2005; **29**(10):1869-76.

63. Grant JD, Scherrer JF, Lynskey MT, et al. Adolescent alcohol use is a risk factor for adult alcohol and drug dependence: evidence from a twin design. *Psychol Med* 2006; **36**(1):109-18.

64. Salzman C, Shader RI, Greenblatt DJ, Harmatz JS. Long v short half-life benzodiazepines in the elderly. Kinetics and clinical effects of diazepam and oxazepam. *Arch Gen Psychiatry* 1983; **40**(3):293-7.

65. Wilkinson GR. The effects of liver disease and aging on the disposition of diazepam, chlordiazepoxide, oxazepam and lorazepam in man. *Acta Psychiatr Scand* 1978; (**274**):56-74.

66. Ballokova A, Peel NM, Fialova D, Scott IA, Gray LC, Hubbard RE. Use of benzodiazepines and association with falls in older people admitted to hospital: a prospective cohort study. *Drugs Aging* 2014; **31**(4):299-310.

67. Blazer DG, Wu L-T. The epidemiology of at-risk and binge drinking among middle-aged and elderly community adults: National Survey on Drug Use and Health. *Am J Psychiatry* 2009; **166**(10):1162-9.

68. Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007; **370**(9603):1915-22.

69. DiMartini A, Dew MA, Day N, et al. Trajectories of alcohol consumption following liver transplantation. *Am J Transplant* 2010; **10**(10):2305-12.

70. Lucey MR. Liver transplantation in patients with alcoholic liver disease. *Liver Transplant* 2011; **17**(7):751-9.

71. Dumortier J, Dharancy S, Cannesson A, et al. Recurrent Alcoholic Cirrhosis In Severe Alcoholic Relapse After Liver Transplantation: A Frequent and Serious Complication. *Am J Gastroenterol* 2015; **110**(8):1160-6.

72. Sullivan EV, Rosenbloom MJ, Lim KO, Pfefferbaum A. Longitudinal changes in cognition, gait, and balance in abstinent and relapsed alcoholic men: relationships to changes in brain structure. *Neuropsychology* 2000; **14**(2):178-88.

73. Davidson KM. Diagnosis of depression in alcohol dependence: changes in prevalence with drinking status. *Br J Psychiatry* 1995; **166**(2):199-204.

74. Liappas J, Paparrigopoulos T, Tzavellas E, Christodoulou G. Impact of alcohol detoxification on anxiety and depressive symptoms. *Drug Alcohol Depend* 2002; **68**(2):215-20.

75. Torrens M, Fonseca F, Mateu G, Farré M. Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. Drug Alcohol Depend 2005; 78(1):1-22.

76. Joseph AM, Willenbring ML, Nugent SM, Nelson DB. A randomized trial of concurrent versus delayed smoking intervention for patients in alcohol dependence treatment. *J Stud Alcohol* 2004; **65**(6):681-91.

77. National Institute for Health and Clinical Excellence. Alcohol use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. 2011. http://www.nice.org.uk/nicemedia/live/13337/53191/53191.pdf (Accessed 01/09/15).

78. Australian Governement. Department of Health and Ageing. Guidelines for the Treatment of Alcohol Problems. 2009. http://www.health.gov.au/internet/ministers/publishing.nsf/Content/76AE6384CE9A3830CA2576BF003073F8/$File/DEZEM_Alcohol%20Guide_FA.pdf (Accessed 01/09/15).

79. Peppers MP. Benzodiazepines for alcohol withdrawal in the elderly and in patients with liver disease. *Pharmacotherapy* 1996; **16**:49-57.

80. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *JAMA* 1997; **278**: 144-151.

81. Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet* 1981; **6**(2):89-105.

82. Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. *Cochrane Database Syst Rev* 2010; (2):CD006266.

83. Ameisen O. Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: a self-case report of a physician. *Alcohol Alcohol* 2005; **40**(2):147-50.

84. Gache P. [Baclofen: the new miracle cure for alcoholism?] Le baclofène sera-t-il le nouveau médicament miracle de l'alcoolisme? *Rev Med Suisse* 2011; **7**(302):1458-61.

85. Dom G. Why Belgian alcohol patients are treated differently than their French counterparts. *Acta Clin Belg* 2012; **67**(5):315-6.

86. Pastor A, Jones DML, Currie J. High-dose baclofen for treatment-resistant alcohol dependence. J Clin Psychopharmacol 2012; 32(2):266-8.

87. Mirijello A, Caputo F, Vassallo G, et al. GABAB agonists for the treatment of Alcohol Use Disorder. *Curr Pharm Des* 2015; **21**(23):3367-72.

88. Heather N, Adamson SJ, Raistrick D, Slegg GP. Initial preference for drinking goal in the treatment of alcohol problems: I. Baseline differences between abstinence and non-abstinence groups. *Alcohol Alcohol* 2010; **45**(2):128-35.

89. Gual A, He Y, Torup L, van den Brink W, Mann K, ESENSE 2 Study Group. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. *Eur Neuropsychopharmacol* 2013; **23**(11):1432-42.

90. van den Brink W, Aubin H-J, Bladström A, Torup L, Gual A, Mann K. Efficacy of as-needed nalmefene in alcohol-dependent 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**(5):570-8.

91. Aubin HJ, Reimer J, Nutt DJ, et al. Clinical relevance of as-needed treatment with nalmefene in alcohol-dependent patients. *Eur Addict Res* 2015; **21**(3):160-8.

92. François C, Rahhali N, Chalem Y, Sørensen P, Luquiens A, Aubin HJ. The Effects of as-Needed Nalmefene on Patient-Reported Outcomes and Quality of Life in Relation to a Reduction in Alcohol Consumption in Alcohol-Dependent Patients. *PloS One* 2015; **10**(6):e0129289.

93. Mann KF. Why should we need a European Federation of Addiction Societies? *Addiction* 2008; **103**(1):6-8.

TYPE OF STUDIES ON WHICH THE RECOMMENDATION IS BASED	GRADE OF RECOMMENDATION
RECOMMENDATION BASED ON ESTABLISHED SCIENTIFIC EVIDENCE i.e., based on studies with a high level of evidence (**LEVEL OF EVIDENCE 1**): - randomised comparative trials with high power and no major biases - meta-analysis of randomised comparative trials - decision analysis based on properly conducted studies	**A**
RECOMMENDATION BASED ON SCIENTIFIC ASSUMPTION i.e., based on studies with an intermediate level of evidence (**LEVEL OF EVIDENCE 2**): - randomized comparative trials with low power - properly conducted non-randomized comparative studies - cohort studies	**B**
RECOMMENDATION BASED ON WEAK LEVEL OF EVIDENCE i.e., based on studies with an low level of evidence - **LEVEL OF EVIDENCE 3**: case-control study - **LEVEL OF EVIDENCE 4**: retrospective studies, case series, or comparative studies with major biais	**C**
RECOMMENDATION BASED ON EXPERT CONSENSUS If no studies are available, the recommendations are based on a consensus between working group experts, after consulting the review group. The absence of classification does not mean that the recommendations are not relevant and useful. However, this should prompt additional studies.	**EC**

TABLE 1. Recommendation grading according to the *Haute Autorité de Santé*, i.e., the French High Autorithy for Health [X]

#	RECOMMENDATION	GRADE
6.1	Therapeutic intervention aims for a change in alcohol use: abstinence or moderation	EC
6.2	The goal of treatment should be set with the service user	B
6.3	Abstinence is the appropriate goal for severe alcohol dependence, and/or dependence with significant psychiatric or physical comorbidity (e.g., depression or alcohol-related liver disease). If the service user is unwilling to reach a goal of abstinence, a supported harm reduction program of care should be considered	EC
6.4	For mild dependence without significant comorbidities and with adequate social support, the treatment objective can be a moderate level of drinking unless the service user prefers abstinence or there are other reasons for advising abstinence	EC
6.5	The goal for moderation should ideally aim not to exceed 21 standard units of alcohol (i.e., 210 g of alcohol) per week for males and 14 standard units of alcohol (i.e., 140 g of alcohol) per week for females	EC
	However, any significant reduction in average alcohol use, as in the proportion of days with excessive use, is liable to provide substantial benefit to the individual	A

TABLE 2 **Recommendations issued on the objectives of therapeutic intervention (QUESTION 6 of the RCPs)**
Each recommendation was graded from A to C using the methodological tool published by the Haute Autorité de Santé (HAS), i.e., the French High Autorithy for Health [X], according to the level of evidence of the studies on which the recommendation was based (see Table 1). EC= 'expert consensus', i.e., recommendations issued on consensual expert opinion, when no study was available; RCPs= 'recommendations for clinical practice'.

#	RECOMMENDATION	GRADE
7.12	Benzodiazepines (BZDs) are the first-line medication for alcohol withdrawal syndrome	A
	Using benzodiazepines with long half-life should be preferred	EC
7.13	The indication for and tailoring of BZD treatment should be guided by regular and rigorous clinical surveillance, which may be supported by withdrawal symptom evaluation scales (CIWA-Ar scale or Cushman score)	B
7.15	In the event of contraindication to BZDs (e.g., chronic respiratory failure, decompensated liver cirrhosis with ascites, jaundice or Prothrombin time <50%, obesity, elderly patients), and a risk of withdrawal syndrome, residential detox is strongly recommended	EC
	BZDs should be administered according to an symptom-triggered protocol, only in the event of patent signs of withdrawal and after re-assessment of each dose	EC
	BZDs with a short half-life (such as oxazepam) have not demonstrated better safety in this situation, and their half-life may be prolonged in the event of liver failure	B
7.16	Symptom-adjusted prescription of BZDs applies more to residential detoxification. Residential detox is appropriate for patients with difficulty in communicating, history of seizures, unstable psychiatric comorbidity or other associated addiction	B
7.17	BZDs are only justified beyond a one-week period in the case of persistent withdrawal! symptoms, withdrawal events or associated BZD dependence	B
7.18	In the event of severe withdrawal symptoms or withdrawal events, treatment with BZDs should not be continued for more than four weeks, including the dose reduction phase	C
7.19	Routine prescription of thiamine (vitamin B1) should be adapted to nutritional status	EC
11.1	Residential detox is indicated in the following cases: delirium (mental confusion and/or hallucinations) or epileptic seizures at the time of evaluation; history of delirium or epileptic seizures; high-dose multiple drug use, notably concomitant BZD dependence	EC
	Residential treatment should also be envisaged on a case-by-case basis under certain circumstances: extent of withdrawal syndrome, failure of repeated outpatient detoxification, severe or unstable comorbidity, age-related frailty, pressing demand from family, limited social support, precarious social situation, pregnancy	
11.2	Outpatient detoxification should be preferred apart from the indications for residential detoxification	EC
11.3	In the majority of cases, detoxification does not require pharmacological treatment, provided thorough and repeated clinical evaluations take place before and during the detoxification process	B

	When such monitoring conditions are not met, preventive BZD treatment should be implemented	**EC**
11.4	Unless disproportionate depressive symptoms are observed, the initiation of an antidepressant treatment is not indicated during the detox procedure	**EC**

TABLE 3 **Recommendations issued on the overall management of alcohol detoxification (i.e., Questions 7 and 11 of the RCPs)**

Each recommendation was graded from A to C using the methodological tool published by the Haute Autorité de Santé (HAS), i.e., the French High Autorithy for Health [X], according to the level of evidence of the studies on which the recommendation was based (see Table 1). EC= 'expert consensus', i.e., recommendations issued on consensual expert opinion, when no study was available; RCPs= 'recommendations for clinical practice'.

#	RECOMMENDATION	GRADE
12.4	Medications for relapse prevention should be automatically associated with adapted psychosocial support in patients with alcohol-dependence	**A**
12.5	Increased compliance with medications improves therapeutic efficacy	**EC**
12.6	Acamprosate or naltrexone are the first-line treatment for supporting relapse prevention	**A**
12.7	Disulfiram can be proposed as second-line treatment in patients motivated to sustain abstinence, correctly informed of the risk of the antabuse effect, and adequately supervised	**EC**
12.8	The second-line prescription of baclofen for preventing relapse among alcohol-dependent patients has been authorized by a "temporary recommendation for use" (TRU) up to the dose of 300 mg/d, and requires the online reporting of patients' follow-up on the TRU portal. Doses should be increased and decreased slowly according to efficacy and tolerability	**EC**

TABLE 4 **Recommendations issued on the management of relapse prevention (QUESTIONS 7 & 11 of the RCP document)**

Each recommendation was graded from A to C using the methodological tool published by the Haute Autorité de Santé (HAS), i.e., the French High Autorithy for Health [X], according to the level of evidence of the studies on which the recommendation was based (see Table 1). EC= 'expert consensus', i.e., recommendations issued on consensual expert opinion, when no study was available; RCP= recommendations for clinical practice.

#	RECOMMENDATION	GRADE
10.1	Reducing consumption can be directly proposed to patients with mild dependence, or to patients with a more severe disorder who do not wish or are not yet able to attempt abstinence	EC
10.2	It is recommended that consumption below the at-risk levels be targeted insofar as possible, although any lasting reduction in consumption should be accepted as a positive result, and may be an initial step towards a greater reduction	EC
10.3	Self-assessment of daily alcohol consumptions should be used in psychosocial support for drinking reduction	A
10.4	Medications for reducing alcohol consumption are only indicated in dependent individuals	EC
10.5	Nalmefene is indicated as a first-line treatment for reducing alcohol consumption in dependent individuals	A
10.6	The second-line prescription of baclofen for reducing alcohol use among alcohol-dependent patients has been authorized by a “temporary recommendation for use” (TRU) up to the dose of 300 mg/d, and requires the online reporting of patients’ follow-up on the TRU portal	EC

TABLE 5. Recommendations issued on the conduction of a drinking reduction strategy (QUESTIONS 7 &10)
Each recommendation was graded from A to C using the methodological tool published by the Haute Autorité de Santé (HAS), i.e., the French High Autorithy for Health [X], according to the level of evidence of the studies on which the recommendation was based (see Table 1). EC= ‘expert consensus’, i.e., recommendations issued on consensual expert opinion, when no study was available

#	RECOMMENDATION	GRADE
16.2	Abstinence throughout pregnancy is recommended for any pregnant women	EC
16.4	If medically-assisted withdrawal is necessary during pregnancy, using BZDs is recommended	B
16.5a	No treatments other than those for alcohol withdrawal should be initiated in pregnant or breastfeeding women	EC
16.5b	In the event of a pregnancy occurring in a patient obviously stabilized by a medication for supporting abstinence, the continuation of the drug should be considered on a case-by-case basis, weighing up the benefit/risk ratio.	EC
16.5c	Disulfiram is an exception, and it should be always stopped during pregnancy, to the unknown risks on the fetus of the antabuse effect	EC
16.7a	Any adolescent with alcohol dependence under the age of 16 should undergo a pediatric psychiatric assessment	C
16.7b	In the case of alcohol dependence occurring under the age of 16, the objective of abstinence should be preferred	EC
16.7c	First-line treatments to help maintain abstinence or reduce drinking are off-label, and should thus be considered on a case-by-case basis, after repeated failure of psychosocial measures alone.	EC
16.8a	In elderly patients with alcohol-dependence, it is preferable to conduct the detoxification process in a hospital setting	EC
16.8b	Short half-life benzodiazepines should be preferred for detoxification in elderly patients	B
16.8c	Initial doses of benzodiazepines should be reduced by 30 to 50% in elderly patients	EC
16.8d	Psychosocial support should be particularly emphasized in elderly patients with alcohol dependence	B
16.10	In patients with chronic alcohol-related physical disorders, a goal of abstinence is recommended	EC
16.11	Antidepressants or anxiolytic medication should be introduced only after reassessment of the psychiatric state, after 2-4 weeks of alcohol abstinence or low-risk use	B
16.12	It is recommended that a smoking cessation approach be encouraged and that pharmacological assistance be systematically offered to smokers when they are giving up alcohol, in either a hospital or an outpatient setting (GRADE B)	B

TABLE 6 **Recommendations issued on the management of treatment for alcohol dependence in specific population, i.e., pregnant women, children and adolescents, elderly subjects, comorbid alcohol-related physical conditions, comorbid psychiatric and substance use disorders (QUESTIONS 16 of the RCPs)**

Each recommendation was graded from A to C using the methodological tool published by the Haute Autorité de Santé (HAS), i.e., the French High Autorithy for Health [X], according to the level of evidence of the studies on which the recommendation was based (see Table 1). EC**=** 'expert consensus', i.e., recommendations issued on consensual expert opinion, when no study was available; RCPs= recommendations for clinical practice.