NEC NUTRIMENTUM ET CURAE

Nutr Cur 2024; 03(Special 1): e150
DOI: 10.57625/nec.2024.57

Treatment of alcohol use disorder: position paper of the Società Italiana di Alcologia (SIA)

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ABSTRACT

Alcohol use disorder (AUD) is frequent globally and is responsible for more than 5% of the global burden of disease and mortality. Despite this, less than 10% of people with AUD receive specialist treatment and less than 10% of people with risky drinking receive specific medical advice. The present paper highlights the recommendations of the Italian Society of Alcohology (SIA) for the treatment of AUD.

Multidisciplinary treatment in the outpatient setting is considered the best therapeutic option for AUD to improve recovery and reduce or eliminate alcohol consumption.

Several psychosocial treatments have proven efficacy, in particular brief intervention, motivational enhancement treatment, and various behavioral treatments; moreover, systemic family psychotherapy can play a key role when a patient's family is involved.

Different pharmacological treatments are approved for the treatment of AUD in developed countries, and some off-label treatments have good levels of evidence. Since these pharmacological agents have different characteristics and present evidence of efficacy for different therapeutic goals, personalized pharmacotherapy is necessary. For this purpose, a specific algorithm of choice is presented.

For patients resistant to outpatient treatment and with severe AUD, inpatient treatment in specific alcohol rehabilitation centers can be useful to improve recovery.

KEYWORDS

TREATMENT
PERSONALIZATION
ALCOHOL
PHARMACOTHERAPY
PSYCHOTHERAPY
SELF-HELP GROUP

INTRODUCTION

Worldwide, approximately 2.4 billion people consume alcohol, with 1.5 billion (1.4-1.6) current male drinkers and 0.9 billion (0.8-1.0) current female drinkers[1,2].

Alcohol use disorder (AUD), as defined by DSM V[3], is frequent globally: in 2016, its actual prevalence has been estimated to be equal to 5.1%: 4.9-5.4 of the general population, 8.6% (95% CI 8.1-9.1) of men and 1.7% (1.6-1.9) of women, respectively[4-6].

AUD is responsible for over 200 diseases and 14 different types of cancer involving every medical discipline[7,8].

In recent years, several scientific societies and health organizations have published national and international guidelines on AUD treatment, the most significant being: "National Institute for Health and Clinical Excellence (NICE) clinical guideline"[9], "American Psychiatry Association Practice guideline"[10], "French Alcohol Society Recommendations"[11], "World Federation of Society of Biological Psychiatry Treatment Guidelines"[12] and "Australian guidelines for the treatment of alcohol problems"[13]. The only attempt to develop national guidelines in Italy comprises "Italian Guidelines for the treatment of alcohol dependence"[14,15] drafted by the Interdisciplinary Study Group CRARL – SITAC – SIPaD – SITD – SIPDip not licensed by the Italian Ministry of Health.

The present paper is aimed at providing the recommendations of the Italian Society on Alcohology (SIA) for the treatment of AUD devoted to specialists in the alcohol addiction field and an algorithm for the choice of personalized AUD drugs.

MATERIALS AND METHODS

A panel of clinicians, psychologists, and social-health professionals consisting of specialists in gastroenterology, hepatology, clinical pharmacology, psychiatry, internal medicine, gerontology and toxicology, all experts in the AUD treatment, was identified by the SIA Board. In June 2019, the panel had a first meeting in Genova to draft the SIA criteria for the management of AUD patients.

This discussion lasted until March 28, 2023, and the position paper with its recommendations (Table 1) was produced with the intent of informing specialists in the alcohol addiction field. Management and treatment of intoxication and acute withdrawal syndrome were not discussed because they are included in a previous position paper16. In the present position paper, levels of evidence and grade of recommendation (Table 2) were evaluated using the same methodological approach of the previous paper[16].

The data used to prepare the position paper are based on a detailed analysis of the scientific literature published before June 30, 2023. Pharmacological treatments are more widely described than psychosocial treatment since a greater amount of scientific literature has been published, and thus, more specific recommendations were possible to formulate.

An algorithm for the choice of AUD personalized pharmacotherapy was also developed. The final paper was revised and approved by the SIA Board.

The following paragraphs describe data supporting the recommendations provided in Table 1.

Table 1. Recommendations.

Psychosocial treatment	Residential treatment
• Brief intervention is the gold standard for patients with hazardous drinking and mild AUD: 1A • Some psychosocial intervention (MET, CBT) are indicated for maintaining abstinence in the short-term, irrespective of the psychotherapy orientation or psychosocial approach: 1A • Other psychosocial interventions (CRA, SST, BSCT, BCT) are indicated for maintaining abstinence in the short-term, irrespective of the psychotherapy orientation or psychosocial approach: 1B • Family psychotherapy is useful when patient family involvement is indicated 3A	• Residential and semi-residential rehabilitation programs are effective for improvement of wellbeing and recovery in patients where the outpatient setting has failed: 3A • Offering AUDs a dedicated rehabilitation center is warranted to increase effectiveness: 6A
Self-help	**Pharmacological treatment**
• Patient should be invited and motivated to join a mutual self-help group in order to maintain abstinence in the medium-long term: 1A • Treatment services should facilitate participation in a mutual self-help group since it is more cost-effective than other non-pharmacological treatments: 3A	• Use of NMF or NTX for the goal of alcohol consumption reduction: 1A • Use of NTX for the goal of complete abstinence in case of binge drinking or prevalence of heavy drinking day in alcohol consumption pattern: 1A • Use of ACP for the goal of complete abstinence to prevent relapse after achieving abstinence: 1A • Use of SO for the goal of complete abstinence in high/very high alcohol consumption patients with of PWS after the resolution of AWS: 1A • Use of BCF for the goal of complete abstinence in cases of Liver Failure: 1B • Combine two drugs in cases of partial efficacy of monotherapy: 3A • Use off-label drugs when those on-label are ineffective or contraindicated: 3A

Table 2. Level of evidence and grade of recommendation.

Level of evidence	Grade of recommendation
Level 1 Data derived from meta-analyses or systematic reviews or from (multiple) randomized controlled trials with high quality *Level 2* Data derived from a single randomized controlled trial *Level 3* Data derived from multiple non-randomized studies *Level 4* Data derived from retrospective observational studies or case–control studies *Level 5* Data derived from case series studies without control groups *Level 6* Data derived from expert opinions or consensus conference	*A (strong)* Strong recommendation: factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes and cost *B (weak)* Weaker recommendation: variability in preferences and values, or more uncertainty *C* The existing evidence is conflicting, and does not allow a recommendation to be made for or against the use of the action; however, other factors may influence decision making *D* There is fair evidence to recommend against the action *E* There is good evidence to recommend against the action

Treatment

Treatment of AUD patients should certainly be managed by a multidisciplinary team of experts in dedicated alcohology services.

Many patients spontaneously reduce consumption due to the onset of internal diseases, social, work or family problems[17,18]. The follow-up of untreated or treated people in non-accredited facilities revealed an average abstention at one year of 21%[19].

After formal treatment, meta-analyses found abstinence among AUD patients ranging from 25 to 43%; these percentages vary in relation to the intensity of the treatment and the length of the follow-up[20-24]. At three months, drop-out rated ranged from 50 to 80%[25,26].

Since complete abstention is related to better outcomes, it is believed that this should be the final goal to pursue in a path for AUD[23].

The reduction in consumption, however, can have significance when it is envisaged as a bridge to abstention or in some selected clinical and environmental conditions. In the US, 42% of people who need treatment for AUD refuse it, because they do not feel ready to quit alcohol completely. It is appropriate to offer these subjects the opportunity to significantly reduce the amount of alcohol consumed[27]. The validity of the reduction in consumption is recognized in the European Medicines Agency (EMA) guidelines. These guidelines provide for the achievement of complete abstention or harm reduction[28]. Roereche and colleagues[29] found that the reduction of alcohol use is associated with a reduction of the risk of mortality among AUD people, with the smallest risk among people who achieve abstinence compared to those who reduce alcohol consumption without achieving abstinence and people who continue heavy use of alcohol.

In addition, it is important to underline that recovery from AUD is not only linked with alcohol consumption reduction but also with biopsychosocial functioning and quality-of-life[30].

Pharmacological and psychosocial activities are closely intertwined. The large Combining Medications and Behavioral Intervention (COMBINE) study showed how a combination of psychosocial support with anti-craving medication was significantly superior to pharmacological treatment alone in terms of percentage days abstinent and the risk of a heavy drinking day[31].

Furthermore, psychiatric and internist comorbidities are addressed in a multidisciplinary way.

It should be emphasized that a tardy or incorrect diagnosis of psychiatric comorbidity precludes therapeutic success and worsens the patient's quality of life[32].

In relation to the severity of alcohol consumption and AUD, different treatments are carried out.

Brief intervention

Specific educational intervention should be implemented, including by non-medical health and socio-health, in the case of low-risk alcohol consumption[9]: maximum 7 alcohol units/week for healthy women (no more than 3 unit for the occasion) and maximum 14 alcohol units for healthy men (no more than 4 unit for the occasion).

In the case of hazardous drinking (HZD), considered as more than low-risk consumption or as binge drinking, personalized brief intervention (BI) is strongly recommended and can also be performed in non-specialist and non-medical settings[33] such as schools and colleges[34]. However, careful monitoring is necessary to evaluate improvements or deterioration and enable a rapid change of treatment.

The number and duration of BI sessions may vary: a single session of 5-10 ' is a minimum intervention to be used, especially in a low-risk environment, while a three session of 20-30 minutes intervention is considered the most appropriate. This intervention become medium with 7 sessions and extended from 8 onwards[35-39].

BI is a tool with proven effectiveness when implemented systematically: it reduces consumption, including binge drinking and its effectiveness has been demonstrated in both sexes[38-40].

Psychosocial treatment

Miller et al.[41] identified more than 30 different psychosocial approaches, especially for the achievement and maintaining abstinence. The techniques with the strongest empirical support are Motivational Enhancement Treatment (MET) and various interventions of cognitive behavioral therapy (CBT) that base their resources on the principles of social learning theory and stress and coping theory[42-46]: Relapse Prevention (RP), Behavioral Self-Control Training (BSCT), couples therapy with cognitive-behavioral orientation (Cognitive-Behavioral Marital Therapy: CBMT), training in coping skills (Coping Skills Training: CST), aversion therapy (AT).

The psychosocial treatments with the best evidence of efficacy are MET, CBT, the community reinforcement approach (CRA), behavior contracting, social skills training (SST)[42,47-49]. Family therapy, proposed by the SIA consensus (described below), should also be noted.

Regarding psychoanalytic and psychodynamic therapy, the small number of studies published does not allow us to draw clear conclusions.

For most of these interventions, meta-analyses suggest effects of low to moderate range of efficacy[40,42,50-52].

When these interventions are compared with each other by well-designed clinical trials, no substantial differences emerge. There is no solid evidence for recommending one technique over another[53].

Overall, for psychosocial treatment, there is evidence for improved efficacy in the short rather than long term: one study[54] analyzed 381 experiences found "strong" evidence for the efficacy in the short term for MET and CBT; a meta-analysis of 53 trials found a small, but statistically significant, benefit for CBT[55]; in a meta-analysis of 72 trials, MET was found to be effective alone or when combined with other treatments. The short-term average of the typical effect was medium (0.77 Cohen d), falling to small (0.30 Cohen d) during the one-year follow-up[56]; a review of 11 CRA RCTs found strong evidence of the efficacy in reducing the drinking days in the short-term, but not in the long-term[55]; in a meta-analytic study including 53 RCTs, Magill and Ray found a small but statistically significant advantage of CBT over no treatment[57]. Again, efficacy tends to decline over time: the pooled effect was lower at 6-9 months and continued to diminish at 12-month follow-up[57].
A large multi-site RCT (Project MACH) found comparable results between Twelve Step Facilitation (TSF), CBT and MET after one and three years of follow-up[58,59].
Via a systematic review, Khan et al.[60] evaluated 13 studies involving 1945 patients with chronic liver disease (5 RCTs). The authors demonstrated that concomitant medical therapy with CBT in association with the strengthening of motivation increased the rate of participants who achieved abstinence (74% compared to 48% in the control group, p = .02). This approach of RP applied to alcohol or polysubstance use disorders resulted to be more effective when added to medications[61].
Group therapy efficacy has been shown in studies comparing individual CBT and MI versus the group format or both. Other authors have shown the efficacy of group CBT involving patients with dual diagnosis62-64.
Mindfulness-based intervention has been studied in the last decade in the field of addiction but the evidence is uncertain regarding the impact on AUD-related outcomes[65].
Contingency management (CM), consisting in reinforcing positive results in treatment (e.g., money, vouchers, prizes, or clinic privileges), is a strategy first experimented with AUD patients, highlighting its efficacy in reducing alcohol use and in maintaining abstinence in several studies[66,67]. Nonetheless, in the last decades, most of the studies on CM have been applied to patients with substance use disorders[68] and only a few on AUD[69,70]. CM is an important behavioural strategy, often associated with other psychosocial or pharmacological treatment[42,71], but in Italy, monetary-based and voucher-based reinforcements are not used in clinical practice.
A recent systematic review and network meta-analysis underline that, in adults with harmful use of alcohol, the highest effect size was observed when motivational interviewing plus cognitive behavioral therapy in multiple sessions via face-to-face[52].
Globally, it is difficult to demonstrate the superiority of a specific treatment compared to another[22,72,73]. Moreover, the literature underlines the influencing factors related to the therapist characteristics, such as clinical skills, empathy, and ability to ensure therapeutic alliance, over the specific psycho-therapeutic orientation, in determining the efficacy of treatment[74-77].
Albeit respecting the findings of data collected from the scientific literature review, the SIA panel strongly recommends the involvement of family members, both because they themselves are generally at risk of developing physical and psychological stress problems and may need support, and because their involvement is generally extremely useful for engaging and motivating the patient Therefore, according to the psychology experts of the SIA, the family psychotherapy pathway is strongly recommended[78-80].

Mutual Self Help Groups

Mutual self-help groups (SHGs) certainly represent an important support. In Italy, in alcohol field, SGHs are represented by Twelve Step program Groups (as Alcoholics Anonymous, AA, and AlAnon) and Club of Alcoholics in Treatment (CAT).
The clinical interest in AA is certainly relevant in inducing tension/sobriety and reducing relapses[81-83]. Scientific evidence demonstrates the efficacy of the method even where not associated with pharmacological and psychotherapeutic treatments[42,84-89]. The approach of the Twelve Step program Groups has often been compared with CBT and MET.
Some authors have shown that patients with severe AUD and no other comorbid mental disorders benefit most from group attendance[90-93]. The least compliant patients are those suffering from axis I mental disorders and associated with substance use disorder (SUD). In some studies, groups for patients with dual diagnosis were established in close association with the services. The results were satisfactory and, moreover, greater pharmacological compliance was found[94,95].
Evidence of the effects induced by attending AA mainly comes from prospective studies[96,97]; however, meta-analytical studies confirm the AA effectiveness for patients that accept this approach[82,98-102].
Some studies confirmed their efficacy even in cases of dual diagnosis, showing that patients who attend AA groups maintain abstinence for prolonged periods, adhere better to therapy, improve the quality of life[99] and report an improvement in depression assessed by the "Beck Depression Inventory - FDI" score[103].
CAT are based upon the Hudolin Method (social ecological approach) that is well described in literature, however to date there are a small number of validated studies supporting its efficacy[104,105].

In a 6-year experience, Rubio et al.[106] found that patients followed in Services who attended self-help groups achieved better results (better therapeutic adherence, higher abstention rates, minor impulsivity/anxiety, better quality of life) compared to patients who received usual care.
The efficacy of SHGs was recently confirmed by the Cochrane Systematic Review[87], which included 27 studies containing a total of 10,565 participants (21 RCTs/quasi-RCTs, 5 non-randomized, and 1 purely economic study). The study confirms that AA/TSF is more effective than other treatments (i.e., CBT) in both the short and long term, in maintaining abstinence and improving quality of life. In addition, a better economic yield is observed.
In the post-COVID era, some studies underline the relevance and efficacy of online SHGs[107,108].

Residential/semi-residential treatment – Rehabilitation Therapeutic Centre
The goal of this kind of program is principally rehabilitation, partly linked to their longer duration. For this reason, they are more oriented to educational and rehabilitative psychotherapy than to organic problem management. The SIA states that, within a framework of ongoing therapeutic assistance and in continuous coordination with territorial/hospital alcohol services, the availability of semi-residential/residential settings represents an important resource for complex cases that cannot be managed directly by a unique outpatient treatment program nor in a brief hospital program in which stable abstinence from alcoholic beverages cannot be achieved (art. 11 Law 125/2001 – Italy).
There is a need for a range of residential proposals to include a short-term rehabilitative accommodation program (from a period of about 30 days to 4 months) and therapeutic paths that are articulated in specific stages up to 18 months through a strong network of territorial support and operational harmony between the residential rehabilitation Centre, Day Centers and housing and work reintegration structures. There is initial evidence that residential treatments are effective for the improvement of wellbeing and recovery[109]. The prevailing position is that AUD-specific rehabilitation centers are needed110. This view is shared by the SIA expert panel.

Pharmacotherapy
Intoxication and hangover
Acute alcoholic intoxication is a transitory condition caused by drinking a considerable amount of alcohol in a short amount of time characterized by behavioral alterations, metabolic alterations, neurological complications, acute myopathy, cardiovascular effects, gastrointestinal effects and acute alcoholic hepatitis. Specific recommendations for these clinical conditions are available in the published SIA Position Paper[16].

Withdrawal Syndrome
About 50% of persons with an AUD may have symptoms of alcohol withdrawal syndrome (AWS) when they reduce or discontinue their alcohol consumption16. Principal symptoms are autonomic hyperactivity, increased hand tremor, insomnia, nausea or vomiting, transient visual/auditory/tactile hallucinations or illusions, psychomotor agitation, anxiety, and in 3-5% grand mal convulsions or severe confusion (delirium). Specific recommendations for this clinical condition are available in the published SIA Position Paper[16].

Maintenance treatment
Three drugs, Disulfiram (DF), Naltrexone (NTX) and Acamprosate (ACM) have been approved by international agencies like the Food and Drug Administration (FDA) and the EMA for the treatment of AUD[111]. Moreover, Nalmefene (NMF) is approved in the European Union, Sodium Oxybate (SO) is approved in Austria (and was approved in Italy until 2018), Baclofene (BCF) is approved in France and several other drugs are currently used with off-label indication[112,113].

Disulfiram
DF irreversibly inhibits the action of the aldehyde-dehydrogenase enzyme causing the accumulation of acetaldehyde during ethanol intake, which can lead to “acetaldehyde syndrome” characterized by heat in the face, purple rash in the neck and torso, tachycardia, hypertension, nausea, vomiting, diarrhea, and headaches with breathing alterations. Awareness of the risk of acetaldehyde syndrome acts as a deterrent for alcohol consumption[114].
The medical approach to DSF prescription has changed significantly since it was first marketed. Far from associating alcohol consumption and acetaldehyde intoxication symptoms, nowadays patients assume DSF to empower their ability to inhibit behavior, anticipating moments of potential craving, unleashed by an internal or external trigger[115,116].
Moreover, scientific literature in recent decades has shown that the efficacy of DSF cannot be evaluated on the basis of placebo-controlled studies because patients can easily discover if they are taking DSF or placebo by drinking a small amount of alcohol. In other words, DSF should be considered a non-pharmacological agent because, unlike all other drugs, it exerts a pharmacological effect only when the patient imbibes alcohol and thus when the treatment is not effective[117].

Considering DSF from this point of view, its efficacy is comparable to NTX or ACP[117].
Possible side effects are drowsiness (common) and hepatitis, neuropathy, optic neuritis, and epileptic crisis (rare)118. Due to the central nervous system effect of blocking dopamine beta-hydroxylase and increasing dopamine concentration, DSF has been tested for cocaine addiction treatment[119] and can induce psychosis in patients with a predisposition or a pre-existing psychotic disorder, so caution is advised with these patients[120].

Acamprosate
Due to its N-methyl- D-aspartate glutamate receptor antagonist activity, ACP can improve dysphoria, often found in chronic alcoholics, and indirectly reduce alcohol craving with the consequent reduction of consumption (relief craving)[121].
Studies have shown that ACP is particularly effective in preventing relapses in patients already abstinent from alcohol[121-123]. Therefore, the target population for this medication comprises patients who are able to achieve abstinence and are willing to maintain sobriety[121-125].
It is contraindicated only in cases of severe renal impairment (creatinine clearance less than 30 mL/min) and it appear to be safe also in pregnancy[126] and in patient with chirrosis[127]; common side effects are diarrhea, nausea, and the pharmacological interaction profile is the safest approved pharmacotherapy for AUD[128]. These considerations indicated ACP to be a really safe drug with moderate efficacy.

Naltrexone
Through its m, k, and d opioid receptor antagonist effects, NTX reduces dopamine release in the nucleus accumbens, enhancing its anti-reward craving effect[129].
Two broad reviews show the efficacy of NTX in reducing heavy drinking days, using the number needed to treat (NNT) to indicate the size of its efficacy (where NNT is the number of patients who need to be treated (in this case with naltrexone) vs. another treatment (in this case, placebo) for one additional patient to achieve the desired outcome). These reviews found a NNT equal to 12 both in reducing the heavy drinking days and a lower efficacy in achieving abstinence (NNT: 20)[125,129].
Therefore, the NTX target population comprises patients wishing to quit or reduce heavy drinking regardless of the goal of complete abstinence or reduced consumption[130]. From this point of view, importantly, some studies have demonstrated the efficacy of NTX in as-needed posology[131-132]. NTX is contraindicated chronic opioid treatment and in cases of decompensated liver disease[125]. The most common side effects are headaches, nausea, dyspepsia, anorexia, anxiety and sedation.

Nalmefene
Through its m-opioid receptor agonist effect, d-opioid receptor antagonist effect and k-opioid receptor partial agonist effect NMF enhances an anti-reward effect similar to NTX although differently modulated[133,134]. It is the first medication to have been approved with the specific indication of reducing alcohol consumption as opposed to alcohol abstinence[134]. Consistently with its indication and mechanism of action, NMF is taken on an as-needed basis, preferably 1-2 hours before drinking alcohol.
In a meta-analysis, NMF showed limited efficacy in reducing heavy-drinking days and decreased total alcohol consumption[135], although a post-hoc analysis[136] of the two principal RCTs ESENSE 1 and ESENSE 2[134,137], demonstrated efficacy in reducing the number of heavy drinking days and total alcohol consumption when a subpopulation of heavy drinkers was considered.
Thus, the target population for NMF comprises heavy drinking patients who want to reduce alcohol consumption, but who are not willing to achieve complete abstinence.
Moreover, NMF has a longer half-life than NTX and is not associated with liver dysfunction and is generally well tolerate[138]. NMF should be avoided in cases of chronic opioid therapy, and the principal side effects are nausea, dizziness, insomnia, headache, vomiting, and fatigue[134].

Sodium Oxybate
SO exerts an ethanol-mimicking effect on GABAB receptors in the central nervous system[139,140].
SO has proven efficacy in maintaining alcohol abstinence from the 90s, including a Cochrane review which concluded that SO is superior to NTX and DF in maintaining alcohol abstinence and superior to DSF in reducing alcohol craving[139-141]. More recent studies have confirmed the efficacy of SO in maintaining abstinence in particular in patients with very high drinking risk level[142,143]. Nevertheless, SO lacks sufficient evidence of efficacy to be approved by EMA, and therefore, in 2018, the authorization for maintenance treatment was revoked, including in Italy, although SO continues to be authorized by the Austrian Drug Authority (BASG).
Regarding its utilization as a “street drug” and the risks of overdose, craving, abuse and dependence on the drug, recent reviews have demonstrated that SO is safe in countries where it has been authorized[142-145]; the strategy to avoid possible abuse and misuse of the drug is to proscribe SO for patients at risk (psychiatric comor-

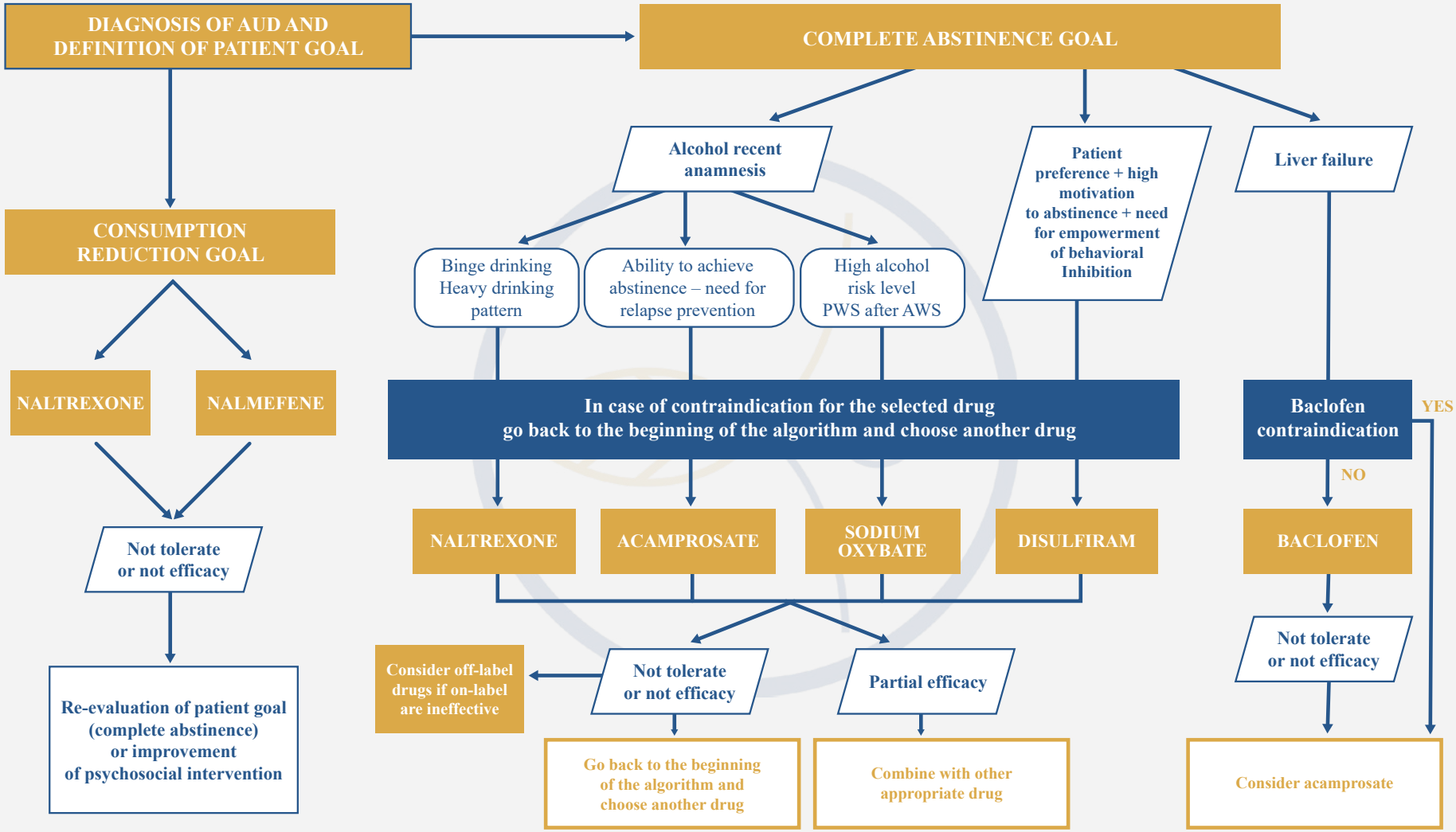
bidity, in particular borderline personality disorder, and active substance dependence) and prescribe the drug under medical supervision[112].
Recently, the use of this drug has been considered for the treatment of protracted withdrawal syndrome (PWS), characterized by the persistence of specific symptoms (i.e., anxiety, irritability, mood instability, insomnia, craving) after the resolution of AWS, due to the up-regulation of NMDA and the down-regulation of GABA induced by prolonged alcohol use[146].

Baclofen
Baclofen (BCF) is a GABAB receptor agonist with demonstrated efficacy in inducing and maintaining alcohol abstinence in alcoholics since 2002[147]. A series of studies have provided contrasting results[147], and BCF has not been approved by the EMA or FDA but only by the ANSM in France. In 2018, a group of international experts provided a Consensus on its use for AUD treatment[148]. According to this Consensus, BCF should be considered a second-line pharmacotherapy in AUD treatment; however, it may be considered first-line pharmacotherapy in patients with contraindications to approved medications like patients with advanced liver disease[148]. Its daily dose should be based on safety, tolerability, and patient's response, ranging over a ten-fold range[148]. Recent meta-analyses found that BCF, compared to placebo, reduces the risk of relapse to any drinking and increases the rate of abstinent days, mainly among detoxified[149] and anxious patients[150]. Given that BCF is the only drug with demonstrated efficacy and safety in patients with liver cirrhosis, it was included in the European Association for the Study of the Liver Guidelines[151] as the first-choice treatment of this specific population. Primary side effects include sedation, dizziness, and headache[149].

Other drugs
Several other drugs have been tested in the AUD treatment with the goal of maintaining abstinence or reducing alcohol intake but none has achieved enough evidence to be authorized by a national or federal drug administration. Nonetheless, since AUD is a treatment-resistant disorder, not uncommonly some of these drugs are used as a second or third line treatment, as stated in some reviews[152-154]. The most significant off-label drugs used for maintenance AUD treatment are two anticonvulsants: gabapentin (GBP) and topiramate (TPR).
GBP has shown efficacy in treating AWS, in increasing abstinence rates and decreasing heavy drinking days, alcohol craving and anxiety,[155] but these results were not confirmed in a recent multicenter trial[156].
TPR has shown efficacy in increasing abstinence from alcohol and lowering the rate of heavy drinking but its side effects are considerable, in particular cognitive and nerve impairment and dizziness[157].
Therefore, these drugs may be indicated for patients resistant to on-label treatment or when patients present comorbidity such as neuropathic pain, restless leg syndrome, insomnia (GBP) or migraine headaches or obesity/binge eating disorder (TPR)[152].

From evidence to guidelines
None of the National Guidelines for the treatment of AUD identified a "gold standard" for any of the above drugs. In particular, NICE guidelines, American Psychiatry guidelines and the French Guidelines consider NTX and ACP as first-line treatments and DSF as a second-line treatment, to be chosen in cases of patient preference, or side effects from the first-line treatments[9,10,11,158,159]. The French guidelines recommend BCF as a second-line treatment both in cases of seeking complete abstinence and where the aim is to reduce consumption; France is the only country in the world to have authorized BCF for the treatment of AUD[11].
The Dutch guidelines highlight clinical indications based on drug-specific characteristics: ACP is preferred for the prevention of relapse and NTX in cases of harm reduction and binge drinking. DSF is indicated in cases of patient preference and care-giver supervision[12,14].
This different approach, evident in numerous clinical reviews[114,123,128,158] leading to personalized treatment and precision medicine, is necessary to maximize clinical results[160-163] since none of the above drugs have demonstrated more than a modest efficacy when used in people with AUD.
Therefore, in consideration of all the published guidelines and evidence, we defined an algorithm for the personalization of pharmacological treatment to enable the physician to find the most appropriate drug for their AUD patients.

Pharmacological Treatment Algorithm (Figure 1)
A precondition for the algorithm is the diagnosis of moderate to severe AUD, since pharmacological maintenance treatment is not recommended in mild AUD or in patients without an AUD diagnosis[9,163]. Subsequently, the first step is to identify patient goal, in order to direct the physician to pharmacotherapy for consumption reduction or for complete abstinence.
In the case of consumption reduction goal NMF may be a choice, since is the only on-label drug with this aim. On the other hand, given that the pharmacodynamic effects of NTX are similar, and NMF is not available in many nations or can have higher cost for patients, it is possible to consider NTX as a valid alternative. Both


DIAGNOSIS OF AUD AND DEFINITION OF PATIENT GOAL
COMPLETE ABSTINENCE GOAL
CONSUMPTION REDUCTION GOAL
Alcohol recent anamnesis
Patient preference + high motivation to abstinence + need for empowerment of behavioral Inhibition
Liver failure
Binge drinking Heavy drinking pattern
Ability to achieve abstinence – need for relapse prevention
High alcohol risk level PWS after AWS
NALTREXONE
NALMEFENE
In case of contraindication for the selected drug go back to the beginning of the algorithm and choose another drug
Baclofen contraindication
YES
NO
Not tolerate or not efficacy
NALTREXONE
ACAMPROSATE
SODIUM OXYBATE
DISULFIRAM
BACLOFEN
Consider off-label drugs if on-label are ineffective
Not tolerate or not efficacy
Partial efficacy
Not tolerate or not efficacy
Re-evaluation of patient goal (complete abstinence) or improvement of psychosocial intervention
Go back to the beginning of the algorithm and choose another drug
Combine with other appropriate drug
Consider acamprosate

drugs have been successfully tested in the as-needed administration mode and NTX can be prescribed with a daily dose. Since there are no other pharmacological treatments for consumption reduction, where NTX or NMF prove ineffective, it is recommended to improve or modify the psychosocial part of the multidisciplinary program or to discuss with the patient the opportunity to change the aim to complete abstinence.

In the case of complete abstinence goal, since there is no clear evidence of the superiority of any drug to others and that the above drugs have significant differences in terms of the mechanism of action, we did not identify a first-line and second-line treatment, giving priority to the concept of personalized treatment: for each patient, it is possible to propose the most appropriate drug[164-169].

In this perspective, the physician must first identify patients suitable for aversion treatment rather than anti-craving treatment. These patients should be highly motivated and clearly express a preference for aversion treatment and physicians should identify the need to strengthen behavioral inhibition. In these cases, after excluding contraindications, DSF could be the most appropriate choice.

In all the other patients, anti-craving treatment is indicated and the choice of the most appropriate drug is based on the elementary alcoholic anamnesis to identify different patient profiles:

1) binge drinkers or people with a drinking pattern characterized by heavy drinking days alternated by abstinent days could benefit from NTX at the first attempt, once contraindications are excluded;

2) low-medium risk drinkers or high-risk drinkers who are able to abstain without AWS but need support to prevent relapse, and could benefit from ACP at the first attempt, once contraindications are excluded;

3) heavy continuous drinkers with symptoms of PWS after overcoming AWS who can benefit from SO at least until the resolution of PWS, once contraindications are excluded.

A particular condition highlighted by the algorithm is the presence of hepatic cirrhosis: since no treatment has demonstrated efficacy in this specific population except for BCF, it has to be considered the drug of choice in these cases.

After trying one of these drugs, the evaluation of alcohol outcomes is mandatory principally based on the ability to abstain (total days of abstinence) but also on the reduction of alcohol income expressed as drink per drinking day and heavy drinking days, and other significant variables such as intensity of craving and quality of life. If the treatment is not at all effective, the drug should be replaced with another listed in the algorithm, identifying the second most appropriate drug for the patient. On the other hand, if the chosen treatment is only partially effective (i.e., reduction of alcohol intake but no abstinence), another drug listed in the algorithm should be used in combination to increase the efficacy. The SIA experts consider that the pharmacological combinations to maintain abstinence are safe and effective in improving the efficacy of each medication alone, although the there is a lack of clear evidence coming from published studies[170-179].

The use of off-label drugs when on-label drugs are ineffective, or added to an on-label drug when only partially effective, is also to be taken into consideration, in particular if comorbidities do not contraindicate their use[113,152,180].

Statement of Ethics

Ethics approval was not required for this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Not applicable.

Author Contributions

The authors confirm their contribution to the paper as follows: study conception and design: T.V., F.C.; papers collection: T.V., F.C., G.T., R.A., V.Z.; analysis and interpretation of results: T.V., F.C., G.T., R.A., V.Z., M.F.A, C.M., M.R.R., T.F., P.A., S.A:, A.B., P.B., V.A.C., C.G., L.M., P.E.C.M.,D.M., A.N., M.P., A.Q., M.Q., D.R., P.C., F.M., V.P., E.S.; draft manuscript preparation: T.V., F.C., G.T., R.A., V.Z., M.F.A, C.M., M.R.R., T.F. All authors reviewed the results and approved the final version of the manuscript. All authors approved the final manuscript.

Data Availability Statement

Not applicable.

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