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Reduced Drinking in Alcohol Dependence Treatment, What Is the Evidence?

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Abstract
Abstinence from alcohol has been the prevailing treatment goal for individuals with alcohol dependence (AD) within the context of specialty alcohol treatment. Yet, alcohol use has been conceptualized as existing on a continuum. Importantly, most people who meet criteria for AD and could benefit from treatment never receive treatment. About half of these individuals do not seek treatment because they report a desire to continue drinking. To increase acceptability of treatment, reductions in alcohol consumption have been examined as alternative outcomes in treatment trials for AD. The current study reviews data which indicate that long-term reduction in alcohol consumption among patients with AD is possible. Controlled studies have tested reduced alcohol consumption and show sustained improvements in drinking reductions for many patients following behavioral treatments and pharmacotherapy. Evidence-based treatment guidelines and medicines development guidance authorities have taken note of these developments and accept "intermediate harm reduction" (European Medicines Agency) or "low-risk drinking limits" (US Federal Drug Administration) as optional trial endpoints. In conclusion, while abstinence remains the safest treatment goal for individuals with AD, evidence supports that reduced drinking approaches may be an important extension in the treatment of AD.

Introduction

In 2010, the European Medicines Agency (EMA) published a guidance paper for the development of medicinal products for treating patients with alcohol dependence (AD) [1]. While abstinence is the prevailing treatment goal, it also allows for an "intermediate harm reduction strategy." Establishing efficacy based on such an intermediate harm reduction strategy requires a clinically significant reduction in total alcohol consumption, as well as a clinically significant reduction in the number of heavy drinking days (with heavy drinking days defined as 60 g of pure alcohol in men and 40 g in women). In addition, the EMA considered evaluating the proportion of subjects with a "significant categorical shift" (p. 10) in World Health Organization (WHO) [2] risk levels of drinking (Table 1). The EMA argues that reducing drinking by at

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Table 1. World Health Organization drinking risk levels

	Males, g/day	Females, g/day
Risk levels of drinking		
Low risk	1–40	1–20
Medium risk	41–60	21–40
High risk	61–100	41–60
Very high risk	101+	61+
Criteria for risk of consumption on a single drinking day in relation to acute problems[1]*, g/day*		
Low risk	1–40	1–20
Medium risk	41–60	21–40
High risk	61+	41+

Criteria for risk of chronic harm [1].

Criteria proposed by the European Medicines Agency for risk levels of drinking [1], after [2].

According to the European Medicines Agency, the most acceptable level of consumption (apart from abstinence) concerning health outcome both at short- and long-term use is the low risk level (1–40 g of pure alcohol on a single drinking day for men and 1–20 g of women). Of note for really everyday consumption, WHO recommends currently a limit of 7 g pure alcohol and even this is considered too much for some special groups, such as pregnant women or patients with liver cirrhosis [1].

least 2 categories bears positive consequences for the individual and can thus be used as a viable secondary endpoint for clinical trials.

The EMA guidance paper and other recent reviews [3, 4] have kindled a renewed interest in an old question: can patients with AD who suffer from impaired control over alcohol intake regain less risky consumption for extended periods of time? In the current study, we shall briefly refer to the old debate on "controlled drinking" and provide an update on new evidence since the publication of recent reviews on the topic. This comprises studies comparing abstinence and reduced consumption goals and on the natural history of alcohol use disorders. Since, to date, only few controlled trials prospectively looked at the effect of reduced alcohol consumption, we shall also include other sources and allude to studies whose results indirectly support or refute the value of reduced consumption.

Alcohol-Derived Harm and Harm Reduction in AD

Alcohol use contributes considerably to mortality [5, 6]. Most risk curves relating disease and injury outcomes to average alcohol intake show a monotonic dose-response, where higher alcohol consumption is related to a higher risk of mortality. The most common shape of these risk curves is exponential [7]. There are, however, some exceptions, particularly for cardiovascular ischemic conditions [8] and diabetes [9], where the curve shows a J-shape and mortality risk is decreased with a low level of alcohol consumption, as compared to abstinence. Recent findings suggest that the J-shaped curve might not be applicable to ethnic and racial minorities [10] and meta-analyses show an exponential all-cause mortality increase after an average consumption of 10 g per day [11]. This debate is still ongoing with new analyses better adjusting for confounders [12–14] challenging the existence of a J-shaped relationship between alcohol consumption and all-cause mortality. Yet, it is important to note that even in the absence of a J-shaped curve the dose-response relationship has held across studies [15–17], thus higher alcohol consumption is related to higher risk of mortality and reductions in alcohol consumption are associated with a reduced risk of mortality [18] and improvements in physical and mental health [19].

Harm reduction has been defined as a "pragmatic approach to reduce the harmful consequences of drug use and other high-risk activities by incorporating several strategies that cut across the spectrum from safer use to managed use to abstinence" [20]. As a public health approach, harm reduction accepts alternatives to abstinence, including reductions in drinking as a useful and important treatment target [21]. The concept of harm reduction introduced for individuals with heroin addiction several decades ago was primarily concerned with directly targeting drug harms without necessarily reducing consumption itself [22]. In patients with AD, where abstinence is not achievable or not accepted by the individual, it has been postulated that harm reduction in terms of reduced alcohol consumption could improve the well-being and functioning [23].

Brief interventions which are widely used, especially in early stages of alcohol use disorders, are an example of an established harm reduction approach. Here a reduction of consumption from heavy drinking to moderate levels of drinking is the usual goal and abstinence is rare [24]. Typically, brief interventions are used for individuals with less severe AD [25] and only recently has it been proposed that harm reduction approaches may also be appropriate for more severely affected clinical populations of patients with AD who are seeking specialty AD treatment or alcohol medications [4]. Such a pragmatic definition of outcomes is common in other fields of psychiatry, such as depression or schizophrenia. They do not require or expect a complete absence of any depression or psy-

chotic symptoms. For example, a 50% reduction in depression ratings is accepted as an indicator of treatment success [26].

Treatment Gap in AD

One important stimulus to introduce a harm reduction approach to AD is that only a few people have been seeking treatment for AD. The so-called treatment gap pointed out in a review of epidemiology studies distinguishing 3 WHO world regions (Europe, US, Western Pacific; Table 2) [27], as well as in an analysis of the US National Epidemiological Study on Alcohol and Related Conditions (NESARC) survey [28] is a major problem: in Europe, AD treatment reaches only 10–15% [29] of the population in need (the treatment gap is approximately 85–90%), whereas the treatment gap is only 56% for affective disorders and 32% for schizophrenia [27]. When individuals who meet criteria for AD are asked why they do not want to receive treatment for an alcohol problem, surveys have found nearly half of all individuals with AD not seeking treatment because they do not want to give up drinking completely [30, 31]. Other research has suggested that the majority of people with DSM-5 AUD who do not seek treatment are less severe and, thus, these individuals do not consider taking treatment [32].

Given the large number of afflicted people, we therefore need to refine and extend treatment options for alcohol use disorders. While there is little hope for magic medication or perfect psychotherapies, 2 avenues hold promise: (i) personalized (precision) medicine [33, 34] and (ii) a harm reduction strategy, which accepts treatment goals below the high bar of abstinence [1]. In this study, we extend the prior review of van Amsterdam and van den Brink [4] by focusing on new data concerning the concept of harm reduction for AD whereby reductions in alcohol consumption are assumed to confer less harm, even if total abstinence is not achieved [20, 35, 36].

Table 2. The treatment gap in mental health [27]

WHO region	Percentage of patients not receiving treatment		
	Europe, %	USA, (%)	Western Pacific, (%)
Schizophrenia	18	57	36
Bipolar disorder	40	60	53
Major depression	45	57	48
Panic disorder	47	55	67
Generalized anxiety	62	50	56
Alcohol abuse/dependence	92	73	72

Examining Reduced Alcohol Consumption in Treatment Trials and Population-Based Studies

A number of small sample longitudinal studies have found that individuals often reduce their alcohol use over time in the absence of treatment [37, 38]. Even among those who receive treatment, many individuals with AD are able to achieve "low level," "social," and "normal" levels of drinking (with exact amounts of drinking defined differently across studies) [39–42]. The US Project MATCH (n = 1,726) compared 3 forms of psychotherapy, cognitive-behavioral treatment, motivation enhancement treatment, and 12-step facilitation treatment, in patients with AD. All 3 arms led to clear improvement in a number of domains. While the Project MATCH required an abstinence goal, secondary analyses of the Project MATCH data [43] identified many patients who were drinking moderately (defined as less than 5 standard drinks per occasion for men and less than 4 standard drinks per occasion for women) at the follow-up assessments, with between 10% (6 months) and 20% (12 months) of patients reporting moderate consumption in the 30 days prior to the assessment. Patients classified as moderate drinkers at the end of the first year had intermediate 3-year outcomes between results of abstainers and heavy drinkers [43]. However, other analyses found that the likelihood of maintaining moderate drinking was lower in severely dependent patients (more than 6 dependence criteria out of 9 [DSM-IIIR]) [44], which is consistent with several other studies showing that moderate drinking goals might be most appropriate for individuals with lower levels of AD severity [45–47]. Similarly, a recent secondary analysis of the COMBINE study data showed stability of no heavy drinking as an outcome within the first 4 months of treatment [48].

In the USA, the large general population NESARC study investigated transitions in and out of alcohol-dependence in individuals without offering treatment. Prior to wave 1 (2001/2002), 4,422 subjects had met lifetime criteria for AD of whom 2,109 were considered in remission (either abstinent, low-risk drinkers, or "asymptomatic risk drinkers"). Re-interviews in wave 2 (2004/2005) were done in 1,772 of the 2,109 remitted subjects. As expected, abstainers had the best 3-year full remission stability (93%), but the low-risk drinkers and the asymptomatic risk drinkers also showed stability of 73 and 49%, re-

spectively [49]. Most of the difference was carried by long-term abstainers (15+ years of abstinence) that were very unlikely to relapse during the 3-year follow-up. A recent analysis of the predictors of the DSM-5 alcohol use disorder in the smaller Dutch general population NEMESIS cohort showed complementary findings: the cumulative relapse rate 20 years after initial remission was low (12%); relapse risk was associated with past alcohol drinking level and lifetime number of alcohol use disorder symptoms [50].

Controlled Psychotherapy Trials with an Explicit Reduction Goal

The best known (and most controversial) study of psychotherapy with an explicit reduction goal was published by Sobell and Sobell [51], who randomized 70 "gamma alcoholics" to either a treatment as usual control group following an abstinence goal or to a behavioral self-control program aiming at "controlled drinking." Two years later, both groups did equally well, but of those who went back to drinking in the experimental group 23% of patients were able to drink in a "controlled" way compared to only 4% in the control group. These results were unexpected in the treatment field, and the authors were accused of bias and unprofessional conduct (for details, see [52]). At last, all accusations were proven wrong and Sobell [53] noted in retrospect that the discussion would have been less emotional had they chosen the term "return to low-risk-drinking" instead of "controlled drinking".

Similarly, Sanchez-Craig et al. [54] randomized 70 problem drinkers to cognitive behavioral treatment directed either to abstinence or controlled drinking. Follow-ups at 6 months and 2 years showed equally good improvement in both groups (no significant difference). More recently, a meta-analysis on 17 behavioral self-control training randomized controlled studies including patients with AD or problem drinking found a combined effect size across all studies was 0.33 [55]. The author found no difference between studies with alcohol-dependent patients versus problem drinkers who did not necessarily meet criteria for AD.

More generally, it may be important to consider the patient treatment goal in evaluating whether alcohol treatment is effective in producing reductions in alcohol consumption. For example, patient preferences for drinking goals were taken into account in the United Kingdom Alcoholism Treatment Trial. All 742 participants were specifically asked for their goal before treatment onset (abstinence or moderation) [45]. At the 12-month follow-up, 10% of the initially non-abstinent goal group was indeed abstinent versus 21.2% in the abstinent goal group [46]. Moderate drinking with "no problems" was reported by 12.8% in the non-abstinent goal group versus 8.5% in the group with an abstinence goal. Taken together, improvement to "no problems" (including abstinence) was noted in 22.8% of the non-abstinent goal group versus 29.7% in the abstinent goal group [46]. These findings are consistent with a re-analysis of the COMBINE study data, which also found that individuals who selected an abstinence goal were more likely to be abstinent at follow-up [56]. It is important to note that the COMBINE study inquired about abstinence versus moderate drinking goals, however, the treatment was abstinence-focused. Moreover, the results from Bujarski et al. [56] also indicated that those who selected a moderate drinking goal had significantly lower drinking intensity on occasions of drinking than those who selected (and violated) an abstinence goal.

Pharmacotherapy Trials Supporting the Reduction Concept

Traditionally, alcohol medicines have been approved by regulatory agencies, including the US Food and Drug Administration and the EMA, for their ability to promote abstinence. For most of the 20th century, only one medication, disulfiram, was approved for use in the treatment of AD in Europe and the US. Disulfiram inhibits the acetaldehyde dehydrogenase enzyme and interferes with alcohol metabolism. As such, any drinking while taking disulfiram is contraindicated and disulfiram is only used and effective in promoting abstinence while taking the drug [57].

In the late 20th century, more alcohol medications were tested and approved for use in the treatment of AD, and several other medications have been used off-label. For a broader description of commonly used alcohol medicines, we refer interested readers to recent reviews of available pharmacotherapies [4, 58–61] and their level of acceptance in different European countries [62]. The current review focuses explicitly on medicines that have shown benefit in promoting reductions in alcohol use. For example, acamprosate is effective in supporting abstinence following detoxification [63], however, it has not been shown to be superior to placebo in reducing alcohol consumption (as opposed to abstinence) [58]. It should also be noted that numerous randomized clinical trials of

alcohol medicines for AD have been problematic with respect to smaller sample sizes, analysis decisions, and reporting design characteristics [64, 65], thus more work in this area is needed.

Oral naltrexone: two pivotal trials using naltrexone showed a benefit over placebo and led the Food and Drug Administration to approve naltrexone for the treatment of AD in 1992 [66, 67]. As the trial endpoint for men was "relapse" to heavy drinking defined as 5 or more drinking days per week or 5 or more drinks on a single occasion, this endpoint allowed for subthreshold consumption and can be seen as an early step towards acceptance of moderation goals. "If return to any drinking had been the endpoint, no difference between naltrexone and placebo would have been found and the drug would not have been approved" [68]. The larger COMBINE study (n = 1,383) [69] and a Cochrane review [70] have provided evidence in support of oral naltrexone as a medication to reduce heavy drinking and number of drinking days, although there are some negative studies [71] and the effective sizes for naltrexone appear to be attenuating over time [72].

Injectable naltrexone: injectable naltrexone has received support for reducing drinking and supporting abstinence, and thus may be useful for treating a variety of patients with AD. Kranzler et al. [73] treated 315 patients with monthly injections of 300 mg naltrexone over 3 months. Patients were problem drinkers, but the majority fulfilled DSM-IV criteria for dependence. They were detoxified prior to study entry; follow-up was done after 3 months. The predefined endpoint (time to first heavy drinking day) showed no difference between injectable naltrexone and placebo. Secondary analyses reported a higher abstinence rate, reduced drinking, and a significantly longer period to the first drink (not heavy drinking) in favor of the medication. Garbutt et al. [74] investigated 624 patients over 6 months with a 6-month follow-up. Patients received either 190 or 380 mg of injectable naltrexone or placebo. No intention to abstain was required and patients could be included while drinking or while being abstinent. The event rate of heavy drinking declined in the 380 mg group by 25% ($p < 0.05$) and in the 190 mg group by 17% ($p = 0.07$). More recent reviews, including a Cochrane review [70], have been cautious about the efficacy of injectable naltrexone, given the limited longitudinal data and few large-scale studies.

Cholinergic agents: galantamine was the first cholinergic drug tested in patients with AD [75]. After detoxification, 149 abstinent patients were randomized to galantamine or placebo (one patch per day) over 24 weeks. The placebo group did significantly better in time to first heavy drinking day than patients on galantamine [75]. However, secondary analyses of patients who had relapsed in both groups revealed the same number of drinking days, but significantly lower alcohol consumption with galantamine [76]. Varenicline, an alpha4beta2 nicotinic receptor partial agonist, is labeled for smoking cessation in most countries [77]. Preclinical animal studies and human trials, and also observational studies have shown that varenicline can reduce alcohol use in heavy-drinking smokers [78, 79]. Randomized placebo-controlled trials exploring the efficacy of varenicline in alcohol use disorders have shown inconclusive results [78]. The largest trial of patients with AD (n = 200) showed a significant benefit of varenicline compared to placebo on percent heavy drinking days, drinks per day, drinks per drinking day, and alcohol craving [80]. The most recent trial of patients with AD (n = 160) [81] did not find significant effects of varenicline over placebo on self-reported drinking outcomes, but did find effects on biomarkers of drinking.

Review of Pharmacotherapy Trials Prospectively Testing an Explicit Reduction Goal

The potential mechanism of reduced drinking has been described in the 1970s by Sinclair [82]. They suggested that alcohol consumption as a learned behavior can be extinguished when the expected response repeatedly does not occur. Pharmacologically, this can be done by blocking the reinforcing effects of alcohol with opioid antagonists. This hypothesis derived from studies in rodents [83] was supported by studies in primates [84]. Hence, an opioid antagonist such as naltrexone or nalmefene (reviewed below) can only exert its therapeutic effect on drinking patients and no extinction is expected among abstinent individuals. Thus, drinking reduction, but not abstinence, may be critical for the effectiveness of certain pharmacotherapies for AD. Given the considerable number of controversies in this topic, we chose to provide a narrative review. We investigated whether reductions in alcohol use following pharmacological treatment can be observed among patients with AD. The goal of this review was to extend and update existing papers (such as by van Amsterdam and van den Brink [4]). We performed a search of PubMed, Google Scholar, Google Books, and references from relevant articles using the search terms "Alcohol dependence," "Alcohol use disorders," "Alcoholism," "Harm reduction," "Harm," "Abstinence," "Controlled drinking," "Moderation," "Heavy

Table 3. Examples of controlled pharmacotherapy studies assessing a reduction goal

Authors	Number	Medication	Follow-up	Result	Remark
Heinälä et al. [86], 2001	121	Naltrexone/placebo 50 mg	12 weeks fixed 20 weeks flexible	No relapse to heavy drinking: Naltrexone + coping significant	No detox targeted use
Johnson et al. [99], 2003	150	Topiramate/placebo 25–300 mg	12 weeks	Drinks per day significant	No detox daily use
Karhuvaara et al. [88], 2007	403	Nalmefene/placebo 10–40 mg	12weeks	Heavy drinking days significant	No detox targeted use
Johnson et al. [100], 2007	371	Topiramate/placebo	12 weeks	% heavy drinking days significant	No detox daily use
Mann et al. [89], 2013	604	Nalmefene/placebo 18 mg	26 weeks	Heavy drinking days and total alcohol consumption both significant	No detox targeted use
Gual et al. [90], 2013	718	Nalmefene/placebo 18 mg	26 weeks	Significant for heavy drinking days, but not for total alcohol consumption	No detox targeted use
Van den Brink et al. [91], 2014	675	Nalmefene/placebo	52 weeks	HDD and TAC not significant at predetermined time (6 months)	No detox targeted use, primary goal: safety

drinking." Using the same search strategy, we also selected relevant high-quality systematic reviews, meta-analyses, cohort studies, and population surveys. Selection criteria included articles published in English, German or French; with search years from 1990 to 2017.

Naltrexone: building upon a study with early problem drinkers who were given targeted naltrexone [85], Heinälä et al. [86] were the first to prospectively test this approach in alcohol-dependent non-abstinent patients. They treated 121 subjects with placebo or a fixed dose of naltrexone for 12 weeks and targeted medication (when craving occurred) for another 20 weeks. Patients were also randomized to either coping skills or supportive therapy. After 12 weeks of fixed dosage, the naltrexone plus coping skills group did best with 27% no heavy drinking days versus 3% in the placebo plus coping skills group. This difference remained throughout the 20 weeks targeted use of naltrexone (Table 3).

Nalmefene: this drug was tested in nine controlled trials, 4 of which looked prospectively at alcohol reduction with a targeted medication use (for details, see Table 3 and [87]). Patients did not undergo detoxification and were allowed to continue drinking alcohol. Nalmefene or placebo was supposed to be taken prior to an imminent consumption of alcohol ("targeted use"). Two studies showed a significant benefit in both primary endpoints [88, 89], one study in the reduction of heavy drinking days but not in total alcohol consumption [90], and the other 1-year safety study that was not significant at the predefined endpoint [91]. Several meta-analyses on the ITT analyses are available now, but many were not based on the specific population defined by the EMA approved indication ("targeted use in high-risk level drinking alcohol-dependent patients"), see [92, 93], and only the most recent takes the EMA-approved indication of nalmefene into account [87]. Here the average effect size for "the EMA indication" was 0.33, for the ITT population it was 0.20 [87].

Despite the efficacy in reducing heavy drinking among high-risk drinking level patients with AD, there is an ongoing debate in the field about the efficacy of nalmefene and on the process of approval [94]. Given the large number of heavy drinkers with AD who are not seeking treatment because they do not want to pursue an abstinence goal [30, 31], we feel the nalmefene debate needs to be considered within the larger context of a public health approach to the treatment of AD [95]. A recent micro-simulation study provides further support for nalmefene as a medication that could significantly reduce morbidity and mortality related to alcohol use [96].

Topiramate: this medication is approved as an antiepileptic drug. It is supposed to interact with alcohol's

reinforcing effects on the brain [97]. A recent meta-analysis found topiramate to be more effective than placebo in promoting abstinence and reducing heavy drinking, with effect sizes that exceeded those of acamprosate, nalmefene, and naltrexone [98]. Of greatest relevance to this review, 3 studies tested topiramate against placebo with the explicit goal of reducing alcohol. In all 3 studies, patients had no a priori detoxification and were allowed to continue drinking alcohol. Results of a single center pilot study as well as a large multicenter study showed reductions in both groups with a significant difference in favor of topiramate [99, 100]. Results were recently supported in a sample of heavy drinkers as well [101] with a significant advantage found for topiramate in the European-American subsample (n = 122) with a moderation effect of a single nucleotide polymorphism (rs2832407) in GRIK1, encoding the kainate GluK1 receptor subunit. Importantly, a recent secondary analysis found that the clinical efficacy of topiramate for reducing heavy drinking was supported even after adjusting for adverse events [102].

Consideration of New Clinical Guidance and Endpoints for AD Treatment

We believe the studies highlighted above illustrate how clinical trials designs progressively changed from abstinence maintenance or relapse prevention orientation to alcohol reduction without prior detoxification. Looking at a broader picture, a systematic review of naltrexone trials in AD published in 2006 showed that 70% of the trials that measured reductions in heavy drinking days found a superiority of naltrexone over placebo, whereas less than 40% of the trials that measured abstinence demonstrated a superiority of naltrexone [103]. The value of alcohol reduction endpoints was confirmed later by meta-analysis that showed that, compared to acamprosate, naltrexone is mainly effective in preventing heavy drinking, rather than maintaining abstinence [92, 104]. Consistent with these findings, an earlier systematic review searching PubMed, Embase, ClinicalTrials.gov, and the R&D Insight and Clinical Trials Insight databases identified a trend whereby more recent ongoing/unpublished trials were more likely to focus on alcohol reduction outcomes among patients who are actively drinking, as compared to older trials, which mostly focused on abstinence outcomes among patients who were detoxified and abstinent at the start of treatment [105]. Importantly, addiction treatment providers have also accepted the non-abstinence goals, particularly for patients with AD [106].

The oldest evidence-based guidelines referred to in this review come from Australia [107]. They are less specific than later guidelines mentioned below regarding harm reduction. Abstinence is considered the most realistic drinking goal for patients with severe AD, and/or with a significant level of comorbidity. The possibility that these patients may be reluctant to engage in abstinence should be dealt with by more intense "negotiations," which may involve a period of moderate drinking, to eventually lead the patient to engage in abstinence.

In the United Kingdom, the NICE guidelines investigated the scientific basis for treatment recommendations in problematic alcohol use [26]. Although their work was done before some of the recent empirical data relevant to the question of reduced drinking for alcohol-dependent individuals were published, their conclusions include recommendations for harm reduction under certain conditions (Table 4) [108] and are globally accepted as relevant recommendations in this matter. For example, the NICE recommendations have been accepted by the French guidelines [109–111] and in the German guidelines put together by a representative group of stakeholders from Germany, Switzerland, and Austria [112, 113].

Similar statements regarding treatment goals and harm reduction strategies can be found in older recommendations, such as the NIAAA clinician's guide (Table 5) [114]. All guidelines recommend to avoid drinking over "low-risk drinking" limits. However, the definitions of these limits differ across countries [115]. The World Health Organization, who has proposed 4 risk drinking levels for acute problems and 3 risk drinking levels for chronic harm (Table 1) [1, 2], may be more useful in defining a positive treatment response across countries, given the risk levels are defined by grams per day. Based on these WHO levels, the EMA has defined responder criteria for trials testing medications for AD. The definition of a positive treatment response is listed in Table 6. An example can be found in a responder analysis of the recent nalmefene trials [95].

Two recent studies have provided validation of the WHO endpoint. Analysis of the US population-based NESARC data [41, 116], already referred to above found reduced alcohol consumption, based on at least a one-level reduction in WHO risk level of drinking (Table 1) from wave 1 to wave 2 conveys significant benefits in the course of 3 years in terms of lower prevalence of AD. Similarly, a recent analysis based on the large US COMBINE study data (n = 1,383), which examined

Table 4. Treatment goals, as proposed in the UK NICE guidelines (2011) [108] also adopted by the German guidelines (2016) [112]

1. In the initial assessment in specialist alcohol services of all people who misuse alcohol, agree the goal of treatment with the service user. Abstinence is the appropriate goal for most people with alcohol dependence, and people who misuse alcohol, and have significant psychiatric or physical comorbidity (e.g., depression or alcohol-related liver disease). When a service user prefers a goal of moderation but there are considerable risks, advise strongly that abstinence is most appropriate, but do not refuse treatment to service users who do not agree to a goal of abstinence.
2. For harmful drinking or mild dependence, without significant comorbidity, and if there is adequate social support, consider a moderate level of drinking as the goal of treatment unless the service user prefers abstinence or there are other reasons for advising abstinence.
3. For people with severe alcohol dependence, or those who misuse alcohol and have significant psychiatric or physical comorbidity, but who are unwilling to consider a goal of abstinence or engage in structured treatment, consider a harm reduction program of care. However, ultimately the service user should be encouraged to aim for a goal of abstinence.
4. When developing treatment goals, consider that some people who misuse alcohol may be required to abstain from alcohol as part of a court order or sentence.

Table 5. Clinical guidelines issued by the US National Institute on Alcohol Abuse and Alcoholism (NIAAA 2005) [114]

"…Abstaining is the safest course for most patients with alcohol use disorders. […] Still, it is best to determine individualized goals with each patient. Some patients may not be willing to endorse abstinence as a goal, especially at first. If an alcohol-dependent patient agrees to reduce drinking substantially, it is best to engage them in that goal while continuing to note that abstinence remains in the optimal outcome."

Table 6. Guidance paper of the European Medicines Agency, 2010 [1]

"As the key secondary endpoint efficacy should also be evaluated in terms of responders, reflecting an expected significant improved health outcome on an individual patient level. This could be done by evaluating the proportion of subjects with a 50, 70, and 90% reduction in alcohol consumption as well as the proportion of patients achieving maintained abstinence. Another option would be evaluating the proportion of subjects with a significant categorical shift in WHO risk levels of drinking (i.e., proportion of patients with change of consumption to baseline from very high risk to at least medium risk level and change from high risk to at least low risk level, as well as the proportion of patients with full abstinence)."

combinations of pharmacotherapy and behavioral interventions for patients with AD, also found reductions in alcohol consumption, based on reductions in the WHO risk levels of drinking (Table 1) were associated with significant improvements in areas, such as mental health and consequences of drinking [117]. Specifically, even a one-level reduction in risk level of drinking from baseline to the end of the 16 weeks treatment period in COMBINE was associated with very large effect size reductions in alcohol-related problems and large effect size improvements in mental health functioning up to 1 year following treatment. Together, the analysis of the WHO risk level changes in the COMBINE study [64] and in the NESARC study [116] support earlier studies showing that alcohol reduction leads to a substantial reduction of mortality risk and a reduction of morbidity [118–120], as well as an increase in the quality of life [121–124].

Summary and Conclusions

Abstinence from any alcohol remains the safest treatment option for individuals with AD; patients who achieve abstinence are more likely to remain in long-term remission than subjects who return to asymptomatic drinking. However, observational studies have shown that non-abstinent remission from alcohol use disorders is frequent and more stable than expected earlier. In patients seeking treatment, psychotherapy trials have shown

that patients' drinking goal often relates to alcohol use disorder severity, and also to the type of outcome achieved, that is, moderation outcome is linked to moderation goal and abstinence outcome is related to abstinence goal.

Pharmacotherapy trials have traditionally aimed at complete abstinence, or – mainly in the USA – relapse prevention (no heavy drinking day) after a period of detoxification. A retrospective examination of studies performed before the turn of the century show that opioid antagonists have some efficacy in reducing alcohol intake, although the patients were instructed to avoid any drinking.

More recently, an increasing number of trials were designed to explicitly aim for a reduction goal. A number of placebo-controlled trials enrolling alcohol-dependent patients have confirmed that a 6–12 months stable reduction is achieved, even in placebo-treated subjects, and that the outcome can be significantly improved with opioid modulators (naltrexone, nalmefene), topiramate, or other drugs (with no replication publications yet).

Following the successful results of European studies, the EMA and other medicines regulation authorities are considering adopting less stringent endpoints when examining the labeling of medications for AD, leaving more possibilities for the development of a new avenue in the pharmacotherapy of AD.

Along with this trend, alcohol treatment guidelines are also including alcohol reduction as an alternative drinking goal in alcohol-dependent patients, along with abstinence. The NIAAA guidelines were probably first to advocate for individualized treatment goals, and accept reduction in alcohol-dependent patients unwilling to engage in abstinence. UK NICE elaborated more on this, also recommending that the therapist should agree to the patient's treatment goal in the initial assessment. Importantly, these guidelines emphasize that a harm reduction approach is far better than status quo.

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