

Controlled drinking—non-abstinent versus abstinent treatment goals in alcohol use disorder: a systematic review, meta-analysis and meta-regression

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ABSTRACT

Background and Aims The proportion of untreated patients with alcohol use disorder (AUD) exceeds that of any other mental health disorder, and treatment alternatives are needed. A widely discussed strategy is to depart from the abstinence paradigm as part of controlled drinking approaches. This first systematic review with meta-analysis aims to assess the efficacy of non-abstinent treatment strategies compared with abstinence-based strategies. **Methods** CENTRAL, PubMed, PsycINFO and Embase databases were searched until February 2019 for controlled (randomized and non-randomized) clinical trials (RCTs and non-RCTs) among adult AUD populations, including an intervention group aiming at controlled drinking and a control group aiming for abstinence. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Collaboration guidelines, literature search, data collection and risk of bias assessment were carried out independently by two reviewers [International Prospective Register of Systematic Reviews (PROSPERO), registration no. CRD42019128716]. The primary outcome was the proportion of participants consuming alcohol at or below the recommended threshold. Secondary outcomes were social functioning, drinking reductions, abstinence rates and dropouts. Using random-effects models, RCTs and non-RCTs were analyzed separately. Sensitivity and subgroup analyses accounted for methodological rigor, inclusion of goal-specific treatment, length of follow-up and AUD severity. **Results** Twenty-two studies (including five RCTs) with 4204 patients were selected. There was no statistically significant difference between both treatment paradigms in RCTs [odds ratio (OR) = 1.32, 95% confidence interval (CI) = 0.51–3.39]. Non-randomized studies of free goal choice favored abstinence-orientation (OR = 0.60, 95% CI = 0.40–0.90), unless goal-specific treatment was provided (OR = 0.79, 95% CI = 0.40–1.56), or in studies of low risk of bias (OR = 0.73, 95% CI = 0.49–1.09) or with long follow-up (OR = 1.49, 95% CI = 0.78–2.85). Effect sizes were not clearly dependent upon AUD severity. Abstinence- and controlled drinking interventions did not clearly differ in their effect on social functioning and drinking reductions. **Conclusions** Available evidence does not support abstinence as the only approach in the treatment of alcohol use disorder. Controlled drinking, particularly if supported by specific psychotherapy, appears to be a viable option where an abstinence-oriented approach is not applicable.

Keywords Abstinence, alcohol use disorder, controlled drinking, drinking goal, meta-analysis, meta-regression.

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INTRODUCTION

Alcohol use disorders (AUD) and alcohol-related harm are among the most burdensome diseases, both at individual

and at societal levels [1]. With proportions of only approximately 20% of patients receiving treatment, the treatment gap for AUD exceeds that of any other mental health disorder [2–4]. This major unmet medical need, along with

the limited efficacy of treatments applied, is emphasized in several national treatment guidelines for alcohol-related disorders [5–7].

Reasons for a lack of successful treatment outcomes may include the severe nature of AUD, but also the strong focus on abstinence in current treatment strategies. Given a somewhat small proportion of patients capable of, and/or willing to, achieve abstinence [5,8,9], it is imaginable that, under an abstinence paradigm, some patients and clinicians lose confidence in the effectiveness of treatments and are discouraged by the perception that abstinence is the only viable goal. In what we sense as a gradual paradigm-shift in treatment recommendations in AUD, non-abstinence-oriented treatment options, namely dose-reduction strategies, have been included as intermediate treatment goals into the UK National Institute for Health and Care Excellence (NICE) guidelines [6] and recommendations by the European Medicine Agency (EMA) [10]. In addition to pharmaceuticals fostering abstinence (e.g. anti-craving drugs [11]), new pharmacological approaches, directed at reducing alcohol consumption (e.g. nalmefene), have been developed and absence of heavy drinking has now been accepted as an additional primary outcome for Phase 3 pharmacotherapy trials of AUD by the US Food and Drug Administration (FDA) [12].

Since the beginning of the debate on non-abstinent AUD treatments, ‘controlled drinking (CD)’ has been a controversial term [13]. We pragmatically choose ‘CD’ to generally specify a treatment goal where patients are aiming for a sustained pattern of drinking within rationally pre-defined limits of low-risk consumption. This is beyond merely striving for ‘moderation’ or ‘reduced drinking’, and rather than assuming that any AUD patient can return to such a sustained pattern of drinking we emphasize that these interventions merely accept CD as a potential outcome and a valid goal alongside abstinence.

Serious concerns about CD approaches have repeatedly been put forward, and acceptability among clinicians remains low [14,15]. This applies in particular to recommending CD as a final rather than intermediate goal, and to patients with alcohol dependence as opposed to harmful drinkers [16]. It is feared that CD may be against the best interests of individuals with AUD, harboring the risk of self-deception and the risk of undermining treatment attempts by offering and implementing an alternative to abstinence treatment, even though the latter is currently known to be associated with the least risk of harm for the patient [17,18]. At the same time, a number of clinical trials showed improvements and rates of remission to low-risk drinking with non-abstinent treatment strategies [19–21]. From a medical viewpoint it is also evident that drinking reductions decrease the risk of adverse consequences [9,17,22–26].

So far, it is unclear how useful a treatment goal of CD is relative to approaches aiming for abstinence: trials yielded contradictory results [19,27] and, in part, are circular, as defining abstinence as primary outcome favors abstinence-oriented treatments. The American Psychiatric Association (APA) has recently emphasized the lack of evidence regarding the comparison of CD and abstinence approaches and goal-choice paradigms in general [7]. To our knowledge, no systematic review including meta-analysis has been published. The present work is therefore the most comprehensive attempt aiming to estimate the comparative efficacy of CD approaches in relation to abstinence paradigms with regard to (1) alcohol consumption measures as well as (2) drinking-related and social outcomes, while (3) accounting for treatment and patient characteristics; namely, disorder severity, goal-specificity of treatment and definition of treatment goal.

METHODS

This is a systematic literature review and meta-analysis. We registered the study protocol on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42019128716). Methods followed guidelines by the Cochrane Collaboration for the conduction of systematic reviews [28] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [29].

Eligibility criteria: participants, intervention and control groups

We included prospective follow-up studies comparing the efficacy of non-abstinent versus abstinent treatment regimens, using samples of adult patients (≥ 18 years) with alcohol dependence or alcohol abuse/harmful use diagnosed according to standard operationalized criteria (i.e. Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5 or ICD-10). All treatment interventions aiming at controlling alcohol consumption (CD paradigms) on a non-abstinent basis were eligible.

We excluded studies that did not include a comparison group that aimed for abstinence. Concomitant pharmacological interventions were not an exclusion criterion, as long as these were given to both intervention and comparator groups.

Following recommendations by the Cochrane Collaboration [28], two reviewers independently carried out the screening of the references retrieved from the electronic databases (J.H., M.M.), applying the pre-defined inclusion/exclusion criteria (see above) first by considering all information provided in title and abstract, and then reading the full text of relevant studies.

Outcomes

By definition, intervention and comparison groups are aiming for different outcomes [abstinence (AB) versus CD], and outcomes for this study had to reflect both treatment goals. The primary outcome was defined as the difference in the probability of achieving CD between the subjects in the CD-oriented and AB-oriented study arms, with CD defined as low-risk drinking within recommended limits (following the study author's most rigorous definition), including abstinence. As recommended limits for low-risk drinking may differ, we decided on adopting the trial author's most rigorous, standardized definition that was most comparable to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) low-risk (non-binge) drinking levels [30] and World Health Organization (WHO) low- or medium-risk drinking levels [31]. This outcome can be equally reached by both interventions. However, health benefits may be higher with larger proportions of abstinent patients. In order to present the broader picture, we defined clinically relevant secondary outcomes, considering measures of social functioning, measures of alcohol consumption and drinking reductions, measures of abstinence and dropouts.

When a study provided data for more than one measure of treatment outcome, data for our primary outcome were considered using the following hierarchy: no drinking above recommended low-risk limits; no violations of a non-harmful, low-risk drinking goal (adopting the trial author's definition); and controlled, non-harmful drinking days.

Secondary outcomes were defined as: (i) treatment difference in efficacy on social functioning (considering, in hierarchical order: legal problems, accidents, occupational status/employment, relationships, inventories of drinking problems/consequences), (ii) treatment difference in efficacy on substantial improvement in drinking reduction (adopting the trial author's definition) and (iii) treatment differences in number of patients maintaining abstinence and abstinent days, in rates of subjects with relapse to heavy drinking and heavy drinking days (HDD), in drinks per drinking day (DDD) and in dropouts.

Literature search

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) until 18 February 2019. CENTRAL is focused upon randomized and non-randomized controlled studies. It comprises, among other sources, articles indexed in MEDLINE, PsycINFO and Embase databases as constantly screened by the Cochrane Drugs and Alcohol Group (CDAG), following the Cochrane highly sensitive searches. Additionally, we searched MEDLINE, PsycINFO and EMBASE from October 2018 onwards, as recommended by the CDAG (personal communication) to identify

studies that could have been missed due to a possible time lag in CDAG's screening schedule. In these searches, we used generic search terms for alcohol-use and drinking, combined with generic terms for abstinence and non-abstinent or controlled-drinking approaches (for explicit search entry, see Supporting information, Fig. S1). We supplemented the search by carrying out reference searches of all eligible articles, relevant review articles and the 'Mesa Grande Project' database, which was systematically updated on clinical trials for AUDs up to 2001 [32,33]. No further restrictions (e.g. for language or time period) were applied.

Data collection

Two researchers abstracted data from the original studies (J.H., H.C.). Unclear cases were solved by discussion with the senior author (C.B.). We retrieved data on the association between treatment goal and achieving successful treatment outcomes [e.g. odds ratio (OR)] or success rates and total number per group), with respective measures of statistical dispersion. If a trial provided data for more than one time-point per outcome, the longest follow-up was included for every outcome in our main analyses. For non-randomized studies, we primarily extracted outcome data based on a goal choice at study entry, if available. If data were presented in figures only, values were extracted using Engauge Digitizer version 11.2 MacOSX (M. Mitchell). Additionally, information on the following characteristics were retrieved from each of the included studies: randomization procedure, goal choice and goal-switching throughout follow-up, treatment intervention and goal-specificity of treatment, definition of the CD goal, proportion of patients with alcohol dependence in the study sample, additional psychopharmacological treatment and the proportions of female and male participants.

Risk of bias assessment

In accordance with the Cochrane Handbook [34], methodological rigor of studies was assessed using the Cochrane risk of bias tool for randomized controlled trials (RCTs) and the Newcastle–Ottawa Scale [35] for non-randomized studies. Judgments for each study were duplicated (J.H., H.C.). Additionally, a global rating for each study was conducted, considering those studies in the highest third of summary rating scores to be of 'lower' risk of bias.

Data analysis

Analyses are based on intention-to-treat (ITT) populations. If no ITT data were available, we included results on completer or per-protocol populations, in this order. Study arms characterized by an imposed goal of abstinence due

to baseline factors (such as particularly severe AUD) were excluded from our comparisons (applicable for Booth *et al.* [36]).

Summary effect estimates were calculated on the odds ratio scale [OR and 95% confidence interval (CI)] using random-effects models (DerSimonian & Laird method) as the studies differed in several methodological aspects, such as diagnostic criteria and specific interventions employed. Effect sizes from different, non-overlapping subgroups of populations within a study were pooled using a fixed-effect model, as recommended in the Cochrane Handbook [34] (three-level meta-analytical approach). Heterogeneity among studies was quantified with the I^2 statistic. An α of 0.05 was considered statistically significant for the primary outcome. For all other analysis, P -values are presented in an exploratory sense. The number needed to treat (NNT) was calculated for primary outcome analyses, using success rates of abstinence-oriented treatment arms as an approximation to the patient's expected event rate.

For the primary and the secondary outcomes, RCTs and non-randomized studies were analyzed separately. For the primary outcome, non-randomized studies were further analyzed in three consecutive steps, considering (1) all non-randomized studies, (2) those presenting data based on a goal choice of CD within actually defined low risk limits and (3) those providing goal-specific treatment intervention.

Sensitivity analyses

For the primary outcome we conducted an additional sensitivity analysis in which, if not otherwise stated or accounted for within the trial, cases lost to follow-up were considered as treatment failures (i.e. 'worst-case analysis').

Pre-specified subgroup and sensitivity analyses referred to: studies of higher methodological rigor; studies based on a CD goal within recommended (low risk) limits (as opposed to self-defined reduction or no specific goal at all); and studies offering goal-specific therapeutic intervention for patients in each group, respectively. To avoid undue reliance upon single trials, in primary outcome sensitivity analyses we removed all studies one by one from the analysis (leave-one-out analyses).

Meta-regression and moderator analysis

In random-effects meta-regression for our primary outcome, we investigated associations of the studies' effect estimates (log OR) with baseline severity of AUD (rating each study by the proportions of dependent patients and 'problem drinkers'/patients with harmful alcohol use), gender (percentage of female patients) and length of follow-up.

Publication bias

Possible publication bias for the primary outcome analysis was inspected assessing funnel plot asymmetry using Egger's test and by visually inspecting the funnel plot.

Analyses were conducted according to the Cochrane Collaboration Handbook [28] and using Comprehensive Meta-Analysis version 3 (Biostat, Engelwood, NJ, USA).

RESULTS

After screening of titles and abstracts of 6134 articles, 123 full texts were assessed for eligibility. Of these, 22 studies, published between 1973 and 2017, were eligible for systematic review (Fig. 1). Overall, the studies included 4204 patients, 2251 aiming for abstinence and 1953 aiming for CD. Five studies were RCTs [21,37–40] and one trial used a partially randomized design [41]. Sixteen studies allowed patients to choose their goal; eight of these also allowed for goal-switching during treatment. All five RCTs and nine of the non-randomized trials provided goal-specific treatment interventions, i.e. abstinence-fostering treatment for patients aiming for abstinence and CD-fostering treatment for patients aiming for CD. The remaining trials merely assessed patients' personal goal but provided no specific or abstinence-oriented treatment only. Four studies did not define a goal of CD as aiming for drinking within defined limits and included patients without a specific goal or those aiming for any drinking reduction into the CD-oriented groups [19,42–44]. Seven studies included patients with alcohol dependence only; the remaining included patients with harmful use in varying degrees. Four trials included psychopharmacological treatment [42,44–47]. One study included women only [48] and one man only [27] (Table 1). Individual definitions of the primary outcome for each study are presented in Supporting information, Table S2.

Primary outcome

Defining treatment success as abstinence as well as controlled, low-risk drinking within recommended limits, the following effect sizes resulted when comparing patients in abstinence-oriented treatment arms with patients aiming for CD:

In all following analyses, an $OR > 1$ favors CD-oriented study arms.

1. Two RCTs were summarized to an effect size of $OR = 1.32$ (95% CI = 0.51–3.39; I^2 : 0%) (Figure 2).

Quantitatively summarizing all of the five RCTs is impossible due to substantial methodological heterogeneity, and only two provided data suitable for our primary outcome. However, generally speaking, the remaining three RCTs showed no statistically significantly stronger effect

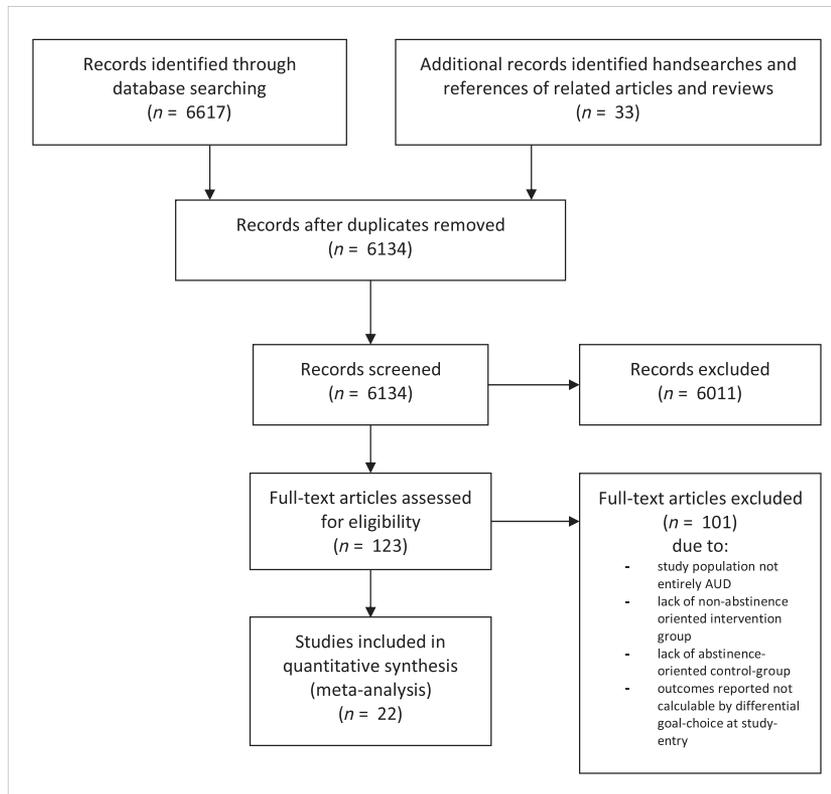


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart

for either treatment approach, but showed point estimates consistent with better outcomes in CD concerning alcohol consumption levels [39,40] and the percentage of patients who reduced their drinking [37]. Differential findings from all five RCTs are included in our secondary outcome analyses below.

2. (i) Of the non-randomized (observational) studies assessing goal choice, 12 provided data for our primary outcome and were summarized to an effect size of $OR = 0.60$ (95% $CI = 0.40-0.90$; $I^2 = 65.2\%$) (Figure 2).

(ii) Among these, 10 studies based analyses on a goal choice of CD within actually defined low risk limits (as opposed to no goal or any drinking reduction). These amounted to $OR = 0.68$ (95% $CI = 0.43-1.08$; $I^2 = 60.0\%$).

(iii) Of these, eight studies provided goal-specific treatment intervention (i.e. CD-fostering for CD groups and abstinence-fostering for AB groups), which were summarized to an effect size of $OR = 0.79$ (95% $CI = 0.40-1.56$; $I^2 = 68.0\%$).

Risk of bias

Summary ratings of methodological rigor of each study are presented in Table 1. The non-randomized studies with the highest ratings [seven of 18, with a score of 6

(range = 4–6)] were considered at a ‘lower’ risk of bias (Supporting information, Fig. S3).

Subgroup and sensitivity analyses

In all following analyses, an $OR > 1$ favors CD-oriented study arms.

Single trials did not greatly influence the calculations as indicated by leave-one-out analyses.

In all non-randomized studies of higher methodological rigor (i.e. lower risk of bias), the summary OR was 0.73 (95% $CI = 0.49-1.09$; $I^2 = 57.7\%$) (seven studies). Among non-randomized studies providing goal-specific treatment intervention, those at lower risk of bias were summarized to an OR of 0.98 (95% $CI = 0.44-2.20$, $I^2 = 69.7\%$) (five studies).

Broken down by group, and based on ‘worst-case’ analyses, 44.1% (95% $CI = 30.3-58.9\%$) of abstinence-oriented patients and 34.0% (95% $CI = 25.7-43.3\%$) of CD-oriented patients successfully exercised low-risk drinking (13 studies). Taking into account studies that defined a CD goal within limits and provided goal-specific interventions, success rates amounted to 39.9% (95% $CI = 24.7-57.2\%$) for abstinence-oriented patients and 36.1% (95% $CI = 28.5-44.4\%$) for CD-oriented patients. Among non-randomized studies of higher methodological rigor (low RoB only) providing goal-specific treatment

Table 1 Characteristics of trials (separate document).

Author, year of publication (study name)	Study participants	Allocation of the intervention	Switching	N CD	N AB	Follow-up (months)	Interventions	Comment	Risk of bias
Graber et al. 1988 [21]	Problem drinkers, DSM-III alcohol abuse, all but 4 patients diagnosed alcohol dependence at some point in their lives	Random		12	12	42	Goal-specific PT, BSCT		RCT, some concerns
Lee et al. 2009 [39]	Elderly at-risk drinkers	Random		14	20	6	PT, per site: integrated care, moderation-based, MI, individual versus enhanced referral, group, 1 2-Step AB-based	No data on primary outcome; study authors' definition of outcomes: <i>n</i> drinks, <i>n</i> binge episodes	RCT, some concerns
Pomerleau et al. 1978 [37]	Problem drinkers	Random		18	14	12	Specific, per group	No data on primary outcome; study authors' definition of outcomes: percentage abstinent/reduced/unimproved	RCT, some concerns
Sanchez-Craig et al. 1984 [38]	Problem drinkers, socially stable, but high intake consumption levels	Random	AB-CD only	35	35	6	Goal-specific PT, per group		RCT, low concerns
Stimmel et al. [40]	Methadone maintenance patients being 'active alcoholic' [National Council on Alcoholism criteria (<i>Am J Psychol</i> 1972)]	Random		42	42	(3-30)	Specific, per group	No data on primary outcome; study authors' definition of outcomes: 1-2-day alcohol consumption, blood alcohol level, clinic behavior	RCT, unknown/high concerns
Orford et al. 1986 [41]	17 of 30 men and 9 of 16 women 'definitively alcoholic' according to Rand criteria (approx. 'alcohol dependence'), further 6 men and 5 women 'borderline alcoholic'	Free goal choice, randomization for those without strong preference		27	16	12	Specific PT-intervention per group, brief versus intensive	Strict criterion for success (cat. I only) for primary outcome	Unknown/high
Adamson et al. 2001 [49]	Mild-moderate alcohol dependence, exclusion of severe dependence, history of withdrawal syndrome, sign. Raised liver enzymes	Free goal choice	No difference in retention during treatment, tendency towards CD afterwards up to 6 months	71	37	6	PT, MET (short-term) for 1/3 of patients, unspecific for CD or AB	Additional treatment group not aiming for controlled drinking within recommended non-abusive limits was excluded from analyses	Unknown/high
				339	403	12			Low

(Continues)

Table 1. (Continued)

Author, year of publication (study name)	Study participants	Allocation of the intervention	Switching	N CD	N AB	Follow-up (months)	Interventions	Comment	Risk of bias
Adamsen <i>et al.</i> 2010 [42] (UKATT) (alt. reports: Heather <i>et al.</i> 2010, UKATT 2001)	Diagnosis of alcohol dependence or abuse according to DSM-IV criteria (American Psychiatric Association, 1994). Alcohol had to be the client's main problem for which help is sought	Free goal choice; CD-goal without defined limits					PT, part MET (short-term), part SBNT, unspecific for CD or AB; disulfiram or acamprosate allowed, sign. Differences in intake between goal-choice groups	CD goal was not defined as within non-abusive limits	
Al-Otaiba <i>et al.</i> 2008 [48]	DSM-IV alcohol abuse or dependence, women only, 98% of samples alcohol dependence	CD goal: 1 drink per week only		22	35	18	PT, abstinence-oriented treatment only	Women only	Unknown/high
Berger <i>et al.</i> 2016 [44]	DSM-IV alcohol dependence, exclusion of withdrawal seizures and delirium tremens in history	Goal: self-defined reduction in consumption, CD-goal without defined limits	(May have taken place, but pretreatment goal for outcomes)	62	37	3	Brief behavioral counseling, unspecific/individual for CD or AB, acamprosate or PLC	CD goal: self-defined reduction in consumption, no defined limits	Unknown/high
Booth <i>et al.</i> 1984 [36]	Problem drinkers, on average 2 of 4 dependence score points	Free goal choice		12	15	12	PT, inpatient BSC individual	Additional treatment group with severe symptoms being assigned to a goal of abstinence excluded from analyses	Low
Booth <i>et al.</i> 1992 [50]	Problem drinkers, most experienced withdrawal some more severe symptoms of physical dependence	Free goal choice	AB goal 64% at baseline, 59% at discharge	41	59	12	PT, inpatient BSC individual		Low
Bujarski <i>et al.</i> 2013 [45] (COMBINE)	DSM-IV Alcohol dependence, patients drinking heavily for the 90-day period preceding study enrollment, no sign. Signs of alcohol withdrawal	Free goal choice		346	506	4	Pharmacotherapy (maltrexone, acamprosate, PLC), MM alone or MM + CBI, abstinence-oriented treatment only	COMBINE study sample, MM alone versus MM + CBI, pharmacotherapy	Unknown/high
Caddy <i>et al.</i> 1978 [27] (alt. reports: Sobell <i>et al.</i> , Maisto <i>et al.</i>)	Gamma alcoholics, alcohol addiction, male only	Free goal choice		40	30	36 months	Randomization to TAU, abstinence-oriented (control) or PT behavioral treatment (intervention)	Men only; outcome data primarily extracted from the Caddy <i>et al.</i> report of the study	Low

(Continues)

Table 1. (Continued)

Author, year of publication (study name)	Study participants	Allocation of the intervention	Switching	N CD	N AB	Follow-up (months)	Interventions	Comment	Risk of bias
Dunn <i>et al.</i> 2013 [46] (COMBINE)	DSM-IV Alcohol dependence, pat. Who had been drinking heavily for the 90-day period preceding study enrollment, no sign. Signs of alcohol withdrawal	Free goal choice	340	340	4, representing post-discharge, no further follow-up	pharmacotherapy (naltrexone, acamprosate, PLC), MM alone or MM + CBI, abstinence-oriented treatment only	(latest follow-up, independent author report) COMBINE study sample, matched pairs	Low	
Enggasser <i>et al.</i> 2015 [19]	Returning veterans, problem drinking, AUDIT-score between 8 and 25 for men and 5 and 25 for women (i.e. harmful or hazardous drinking but not likely to be heavily alcohol-dependent)	Free goal choice; self-defined reduction in consumption, CD-goal without defined limits	71% retained goal AB, 76% retained goal CD,	265	40	3	Web-based cognitive behavioral intervention	Subgroups initial goal choice unchanged versus initial choice switched; outcome is drinking within guideline-limits, but goal in moderation-arms: reduction irrespective of limits	Unknown/high
Haug <i>et al.</i> 2016/17 [51]	Outpatient alcohol treatment clients, alcohol consumption was main reason for treatment, at least 3 counseling sessions provided during treatment, mixed sample, partly aftercare following detoxication	Free goal choice	375	350	12	Specific individual PT, MI, CBT, BSCM; outpatient treatment	Separate outcome analyses for at-risk/non at-risk at baseline, partly non at-risk possibly more severely ill but detoxication prior to study entry	Low	
Hodgins <i>et al.</i> 1997 [52]	Adults seeking treatment for alcohol problems, alcohol is the major problem substance with at least 10 years of alcohol problems, appropriateness for outpatient therapy; 'clearly chronic alcoholics, long history + high MAST scores'	Free goal choice	34	69	12	Individual PT, SM, individual self-management training, outpatient treatment	Unknown/high		
Meyer <i>et al.</i> 2014 [53]	Alcohol use disorder, ADS-Score on average 19 of 36	Free goal choice	73% retained goal AB, 54% retained goal CD	53	99	12	PT, inpatient treatment, abstinence-oriented treatment only	Unknown/high	
	DSM-IV alcohol dependence			54	217	12			

(Continues)

Table 1. (Continued)

Author, year of publication (study name)	Study participants	Allocation of the intervention	Switching	N CD	N AB	Follow-up (months)	Interventions	Comment	Risk of bias
Mowbray <i>et al.</i> 2013 [43]		Free goal choice; CD-goal without defined limits; abstinence yes, no, maybe, do not know					Specific intervention per treatment site, but independent of patients' goal choice (87% received abstinence-oriented treatment)		Unknown/high
Mann <i>et al.</i> 2013 [47] (PREDICT) [alt. report: Gueorguieva <i>et al.</i> 2014, personal contact with study authors (Mann, Hoffmann)]	DSM-IV/ICD-10 alcohol dependence	Free goal choice		31	167	NA, survival analysis	Pharmacotherapy (naltrexone, acamprosate, PLC), MM, abstinence-oriented		Unknown/high
Öjehagen <i>et al.</i> 1989 [54]	DSM-III alcohol dependence	Free goal choice	Within 2 years, 20% of population From AB to CD, 24% back and forth, 56% always retained goal	18	32	24	Individualized goal-specific (CD or AB) outpatient treatment	Subpopulations: unchanged goal versus final goal after switching	Low
Vollmer <i>et al.</i> 1982 [55]	Alcoholics [according to KEA (Feuerlein <i>et al.</i> 1976)] (dependence or abuse), AUD on average persistent for 6 years, age 19–30 years, average daily consumption 210 g ethanol (range 80–430 g)	Free goal choice; goal choice after abstinence phase (halfway during treatment)		42	16	24	Individualized goal-specific (CD or AB) CBI, social competence training, outpatient treatment, average treatment duration 5 months		Unknown/high

COMBINE = Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence; PREDICT = Personalized Responses to Dietary Composition Trial; UKATT = United Kingdom Alcohol Treatment Trial; N CD = number of patients in controlled-drinking group; PLC = placebo; PT = psychotherapy; BSC = behavioral self-control; N AB = number of patients in abstinence oriented group; SBNT = social behavior and network therapy; CD = controlled drinking; AB = abstinence; TAU = treatment as usual; CBI = combined behavioural intervention; MM = medical management; MI = motivational interviewing; NA = not applicable.

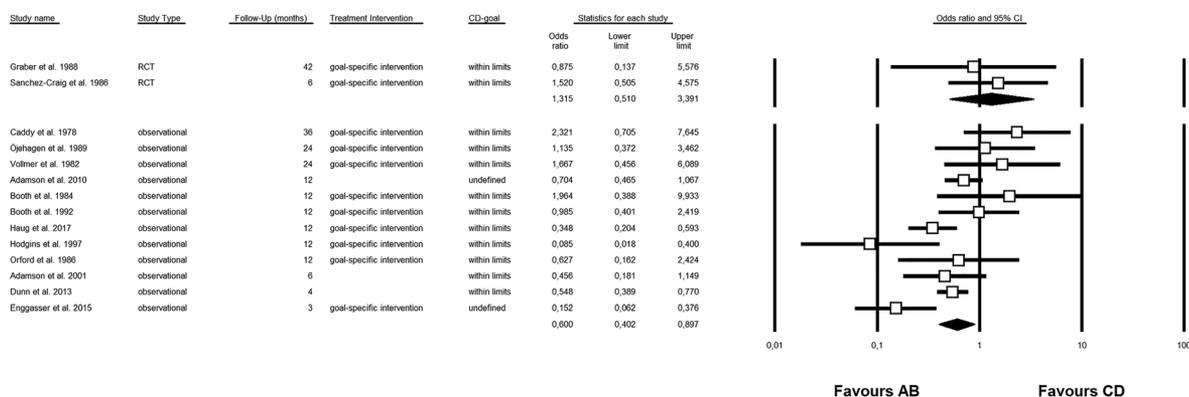


Figure 2 Forest plot, primary outcome (separate document)

intervention, success rates were: 37.6% (95% CI = 13.0–70.9%) of abstinence-oriented patients and 39.2% (95% CI = 33.8–44.9%) of CD-oriented patients.

Meta-regressions and moderator analyses

Length of follow-up

Meta-regression among studies ($n = 14$) providing outcome data for subsequent lengths of follow-up yielded a statistically significant decrease in differences between abstinence-orientation and CD-approaches over time (primary outcome), and effect sizes tended in favor of controlled drinking approaches with longer follow-up (statistically significant correlation [slope = 0.0428; degrees of freedom (d.f.) = 1; P -value (two-sided) = 0.0204; $R^2 = 0.25$] between effect size and length of follow-up (Supporting information, Fig. S4). Among investigations of follow-up periods of more than 12 months (i.e. 24–42 months), the summary OR was 1.49 (95% CI = 0.78–2.85; I^2 : 0%) (four studies). No interaction between length of follow-up and AUD severity at baseline was observed. Attrition rates were not substantially different between studies of shorter and longer follow-up.

AUD severity at baseline

In trials including patients with alcohol dependence only, goal choices did not differ statistically significantly in our primary outcome: OR = 0.61 (95% CI = 0.29–1.27; I^2 : 68.9%) (five studies). Similarly, meta-regression of our primary outcome analysis did not indicate interaction of effect size and AUD severity (Supporting information, Fig. S5).

Gender

Gender distribution in primary studies (as measured in percentage of female patients per study population) did not affect effect size (Supporting information, Fig. S6).

Numerical results from primary outcomes, subgroup and sensitivity analyses are summarized in Table 2.

Secondary outcomes

All secondary outcomes are presented in Fig. 3.

- In abstinence- and CD-oriented study arms, measures of social functioning improved equally.
- Equal proportions of patients achieved substantial improvement in drinking reduction. Broken down by group, 58.8% (95% CI = 51.2–65.9%) of abstinence-oriented patients and 58.3% (95% CI = 51.1–64.2%) of CD-oriented patients substantially improved regarding drinking severity.
- Briefly, there were no clear-cut differences between abstinence-oriented and controlled drinking approaches. Dropouts tended to occur more frequently in abstinence arms whereas abstinence was observed more often, but not exclusively, in abstinence arms. By group, 21.2% (95% CI = 15.5–28.3%) of abstinence-oriented patients and 9.7% (95% CI = 5.9–15.4%) of CD-oriented patients maintained abstinence at follow-up.

Publication bias

Regarding indication of small study effects, there was no obvious funnel plot asymmetry upon visual inspection and using Egger's test ($P = 0.462$; two-tailed) (Supporting information, Fig. S7).

DISCUSSION

Our analyses yielded the following main results. (a) With regard to controlled, low-risk use of alcohol, there was no statistically significant difference between abstinence- and CD-oriented approaches, based on data from the limited number of small RCTs. (2) In non-randomized studies analyzing free goal-choice behavior, no statistically significant difference was found when patients received goal-specific treatment interventions and the two approaches were observed to be of equal efficacy in the limited number of studies of higher methodological quality. With no specific or

Table 2 Numerical results—primary outcomes, subgroup and sensitivity analyses.

<i>Primary outcome</i>							
	OR	95% CI	P	I ² (%)	In favor of	NNT	n studies
RCT	1.32	0.51–3.39	0.57	0	CD	14	2
Non-RCT	0.60	0.40–0.90	0.013	65.2	AB	8	12
CD goal within defined low-risk limits	0.68	0.43–1.08	0.099	60.0	AB	11	10
Goal-specific treatment intervention, CD goal within low-risk limits	0.79	0.40–1.56	0.492	68.0	AB	19	8
<i>Subgroup and sensitivity analyses</i>							
Low risk of bias (non-RCT)	0.73	0.49–1.09	0.119	57.7	AB	15	7
goal-specific treatment intervention, low risk of bias (non-RCT)	0.98	0.44–2.20	0.967	69.7	AB	212	5
Alcohol-dependent patients only	0.61	0.29–1.27	0.183	68.9	AB	8	5
Follow-up 24–42 months	1.49	0.78–2.85	0.224	0	CD	12	4
<i>Per group analyses</i>							
	<i>AB oriented group</i>		<i>CD oriented group</i>		<i>In favor of</i>	<i>NNT</i>	<i>n studies</i>
	<i>Success rate</i>	<i>95%-CI</i>	<i>Success rate</i>	<i>95% CI</i>			
Worst case analysis	44.1%	30.3%–58.9%	34.0%	25.7%–43.3%	AB	9	13
CD goal within low-risk limits, goal-specific treatment intervention	39.9%	24.7%–57.2%	36.1%	28.5%–44.4%	AB	16	9
Goal-specific treatment intervention, low risk of bias (non-RCT)	37.6%	13.0%–70.9%	39.2%	33.8%–44.9%	CD	63	4

RCT = randomized controlled trial; OR = odds ratio; CI = confidence interval; NNT = number needed to treat; AB = abstinence; CD = controlled drinking.

abstinence-based treatment intervention only, however, patients were more likely to achieve low-risk drinking when aiming for abstinence. (3) Results on social parameters, improvements in drinking severity, relapse into heavy drinking and drinks per drinking day indicated equal efficacy of either treatment modality. Additional findings suggest that achieving controlled, low-risk drinking is more likely when patients aim for drinking within recommended, low-risk limits than when they follow a self-defined reduction. Effect sizes in observational trials were dependent upon length of follow-up and CD-oriented treatment were more effective in studies with a follow-up of 2 years and longer.

Implications

While one obvious inference of this investigation is the pressing need for high-quality RCTs in the future, clinicians and patients are currently facing clinical decision uncertainty regarding abstinence versus CD in the management of AUD. How can our results inform these decisions?

Our findings provide evidence to address some of the concerns that have been raised against the CD paradigm.

First, our results indicate that offering a goal of CD does not undermine patients' insight into necessary changes in behavior *per se*, as one-third of patients returning to low-risk drinking in CD-oriented arms maintained abstinence. More generally, a substantial proportion of individuals initially choosing CD switched to a goal of abstinence in trials allowing for realignment. Accordingly, with CD, patients seem to be open to proposals for change and previous work has found that patient participation in drinking goal choice increases goal commitment and self-efficacy [56], and goal acceptance seems to be correlated to a positive outcome [57]. Secondly, there is no indication from our meta-regression that severity of AUD predicts whether a patient will do better under an abstinence-oriented or a CD treatment regimen, as the results did not change between patients with alcohol dependence and hazardous/harmful drinkers. Therefore, our results do not confirm the conventional wisdom that CD is only acceptable in non-dependent patients.

In general, neither RCTs nor observational studies provide clear-cut support for a focus on abstinence- or CD-oriented treatment approaches. Wide CIs, contradictory signals from summary effects, substantive heterogeneity in several of our analyses, as well as only few and dated

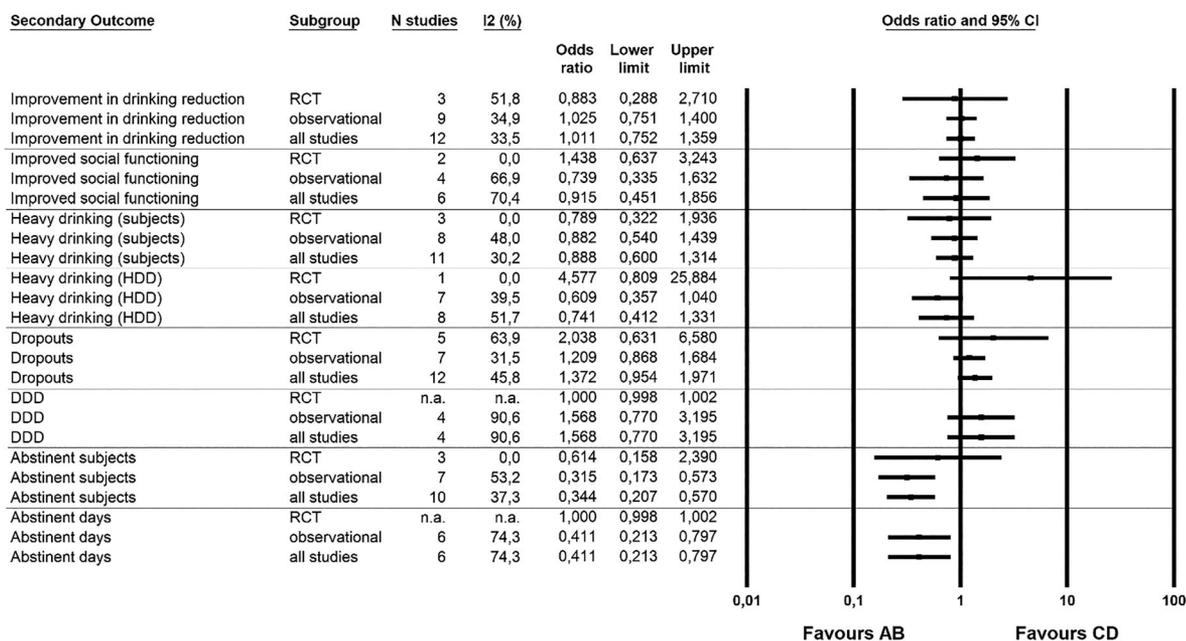


Figure 3 Secondary outcomes (separate document)

RCTs, mean that the case is still open as to whether CD or abstinence-orientation are similar in efficacy.

Certainly, more often than not, abstinence is desirable from a medical point of view [17] and, clearly, patients are more likely to maintain abstinence with AB-oriented interventions. Even beyond that, our 'worst-case scenario' analysis indicates that a larger proportion of patients will achieve controlled, low-risk drinking with a goal of abstinence (44% as opposed to 34% in CD-oriented arms). This analysis, however, entails patients in CD-oriented arms who were not aiming for low-risk drinking or who were offered no or abstinence-oriented treatments only, and 95% CIs were overlapping. The more patients are provided with a goal-specific treatment, the more CD orientation becomes a similarly effective approach. Nevertheless, 34% may be regarded a sizeable success rate in CD arms with respect to the current low treatment rates in AUD. Even beyond that, if low-risk drinking levels are not achieved, numerically equal proportions of patients in AB- and CD-goal treatment arms will benefit from treatments by improvements in drinking severity. Consistent with our findings, accumulating evidence confirms the achievability of non-abstinent recovery and—importantly—the associated improvements in physical and mental health [26], mortality [17], psychiatric comorbidity and quality of life [58,59] and social functioning [60,61]. Our findings seem particularly relevant to the field, given the low acceptability of non-abstinent treatment goals among clinicians in several countries [14,15,62,63].

The unsatisfactory success of current abstinence-oriented treatments points to the need for refinement of, or alternatives to, such approaches. Our results suggest that CD, when accompanied by CD-fostering

treatment intervention, is not inferior. In light of the remaining uncertainty and the experience in the field with the abstinence paradigm, CD may be seen as an option after abstinence has not been achieved or if patients are not at all willing to stop drinking altogether.

Strengths and limitations

This study has several strengths, but it is also not without limitations. First, selection bias is unlikely to have affected our review, as our search strategy followed the recommendations by the CDAG, and beyond database screening we searched reference lists of reviews and previous systematic search efforts (e.g. 'Mesa Grande Project'). We must acknowledge, however, the potential for studies to have been missed. Secondly, all steps of this review were duplicated, following best-practice methods. We also put substantial effort into contacting authors of relevant studies and received an unusual amount of feedback, including previously unpublished data. As a result, to our knowledge, this is the most comprehensive review on the topic to date. Thirdly, choice of the primary outcome was a challenge. Although reasonably pragmatic, it may still be slightly biased against abstinence strategies, because there may be more health benefit in groups with higher proportions of abstinent patients. Therefore, only with our secondary outcome analyses, we believe that our analyses present the full picture. Fourthly, our conclusions are limited by the limitations of primary studies. Many of them, especially the RCTs, date back more than 30 years. Several studies carried a high risk of bias, particularly non-randomized studies. Those trials, however, allow an approximation of the effect of goal-choice in a naturalistic setting and offer the

opportunity to study treatment details in a hypothesis-generating fashion. Fifthly, our analyses include patients with various degrees of severity of AUD. Meta-regression and moderator analyses, however, adjusted for illness severity, because high disorder severity has been discussed as a contraindication to controlled drinking. Interestingly, this was not confirmed by our findings. Sixthly, we found moderate to substantial between-study heterogeneity in our main analysis (except for RCTs). Therefore, we used random effects, carried out numerous sensitivity and subgroup analyses of more homogeneous samples and verified the robustness of results after leaving each study out. Even beyond that, our meta-regressions and moderator analyses pointed to the robustness of our findings. Seventhly, declining differences in efficacy with longer follow-up may be caused by higher dropout-rates in both treatment arms over time, resulting in decreased relative effect sizes between the two paradigms. Reassuringly, however, dropout rates were not substantially different between studies of longer and those of shorter follow-up.

Conclusions

The present evidence does not unequivocally favor abstinence-based approaches in the treatment of AUDs. In fact, the few, and methodologically limited, RCTs point to equal efficacy of either strategy. While summary effects of non-randomized controlled trials tended to favor abstinence-based approaches in the short term, CD-orientation proved to be non-inferior with specific treatment intervention, with ongoing follow-up and in studies of higher methodological rigor. The results, however, are marked by wide CIs and heterogeneity, indicating a need for sufficiently powered RCTs to guide clinical decision making. For now, CD, particularly if accompanied by specific psychotherapy support, seems to be a viable option where an abstinence-oriented approach is not applicable.

Declaration of interests

None.

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Author contributions

Jonathan Hensler: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; validation; visualization; writing-original draft; writing-review & editing. **Martin Müller:** Conceptualization; data curation; formal analysis; investigation; methodology; resources; validation; visualization; writing-original draft; writing-review & editing. **Helena Carreira:** Data curation; formal analysis; methodology; writing-original draft; writing-review & editing. **Tom Bschor:** Conceptualization; methodology; writing-original draft; writing-review & editing. **Andreas Heinz:** Conceptualization; methodology; writing-original draft; writing-review & editing. **Christopher Baethge:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization; writing-original draft; writing-review & editing.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 Database search entry – explicit entry terms.

Table S2 Study definitions of primary outcome.

Table S3 Risk of bias of individual studies.

Figure S4 Scatterplot – Meta-Regression of effects size (Log OR) on length of follow-up.

Figure S5 Scatterplot – Meta-Regression of effects size (Log OR) on AUD severity at baseline.

Figure S6 Scatterplot – Meta-Regression of effects size (Log OR) on percentage of female patients.

Figure S7 Funnel plot of primary outcome analysis.