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Review

The Added Value of Pharmacotherapy to Cognitive Behavior Therapy And Vice Versa in the Treatment of Alcohol Use Disorders: A Systematic Review

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Abstract

Aim: To explore whether combined interventions i.e. psychotherapeutic plus psychosocial interventions are more effective than monotherapies in the treatment of alcohol use disorders.

Methods: Systematic review of the results of randomized controlled trials that compared combined therapies with monotherapies (either pharmacotherapy or psychotherapy).

Results: The search resulted in 28 eligible studies. Data from these RCTs showed that 10 out of 19 RCTs (53%) demonstrated an added value of combined therapy (psychotherapy + pharmacotherapy) compared to psychotherapy only, whereas only three out of nine RCTs (33%) comparing combined therapy with pharmacotherapy showed a possible added value for combined therapy.

Conclusions: Pharmacotherapy is effective to treat AUD with or without psychotherapy and that psychotherapy can best be offered in combination with pharmacotherapy.

INTRODUCTION

Worldwide, the estimated last year prevalence of alcohol use disorders (AUDs) is 8.5%, with an estimated lifetime prevalence of 20% (Slade et al., 2016). In the US, the estimated last year and life-time prevalence of AUDs was 13.9 and 29.1% (Grant et al., 2015), and is increasing (Grant et al., 2017). AUDs are associated with high societal and health care costs and considerable social and financial burden (Bouchery et al., 2011; Sacks et al., 2015). AUDs are a significant cause of morbidity and mortality (Kendler et al., 2017), but remain underdiagnosed and undertreated (Mark et al., 2009; Grant et al., 2015). For instance, in 2018 in the USA, only 4.6% of people aged 12 or older with an AUD received specialized AUD treatment (SAMHSA, 2019). In the Netherlands, 10.3% of people aged 18 years or older received specialized AUD treatment (Tuithof et al., 2016). In 2015, 45% of the patients in specialized addiction treatment services has a primary AUD diagnosis (LADIS, 2016).

Psychotherapeutic or psychosocial AUD treatments, including cognitive-behavioral therapy (CTB), motivational enhancement therapy, and twelve-step programs (e.g. Alcoholics Anonymous) (Anton et al., 2006; Martin and Rehm, 2012; 1998) are effective and constitute the mainstay of AUD treatment worldwide (MATCH, 1998; Anton et al., 2006; Martin and Rehm, 2012; SAMHSA, 2014). Like psychotherapy, pharmacotherapy of AUD (e.g. disulfiram, acamprosate, nalmefene, naltrexone and topiramate) is known to be effective in improving alcohol consumption outcomes (prevention of relapse to any or heavy drinking) (Magill et al., 2019) and recommended by most clinical guidelines (Jonas et al., 2014; Donoghue et al., 2015). The American Psychiatric Association (APA) recommended to offer these medications to patients with moderate to severe alcohol use disorder (Reus et al., 2019). In meta-analyses, as well as other studies (Anton et al., 2006; Rösner et al., 2010a; Mann et al., 2013; Jonas et al., 2014; Akbar et al., 2018; Kranzler and Soyka, 2018), both acamprosate and naltrexone showed effectiveness in terms of return to any or heavy drinking or reduction in drinking days. Other effective agents to treat AUD were briefly reviewed recently (Kim et al., 2018). A more recent meta-analysis on interventions in primary care showed that only acamprosate was effective in maintaining abstinence among primary care patients with AUD for up to 12 months (Cheng et al., 2020).

The aim of psychotherapeutic interventions is to create and strengthen the mindset to reduce or to stop drinking, whereas pharmacotherapeutic agents are designed to inhibit the pathways of drinking induced pleasure and stimuli induced cue-reactivity and craving. As such, the combination of these two therapeutic approaches is believed to retain higher efficacy

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in the treatment of AUD than each approach separately. Despite this expectation, the added value of one therapeutic approach to the other has not been systematically evaluated. The objective of this review was not to assess how these two clinical interventions compare with each other, but whether the addition of a psychosocial intervention to medically prescribed pharmaceuticals improves treatment outcome in AUD and vice versa, i.e. whether prescribed pharmaceuticals have an added value to psychosocial interventions.

METHODS

Using the PRISMA-protocol, a systematic review was performed on 2 April 2022, to retrieve eligible 'Clinical Trials' or 'Randomized Controlled Trials', including published studies and studies ahead of print using PubMed, PsychInfo and EMBASE about the combined treatment (pharmacotherapy plus psychotherapy) of alcohol use disorder (AUD). For detailed search string and PRISMA checklist see Supplement.

After removal of duplicates, two authors (PB and RS) independently processed 454 publications to determine eligibility in two steps: (a) by screening the title and abstract and (b) by applying the inclusion- and exclusion criteria. Inclusion criteria: (a) clinical trials or randomized clinical trials testing the efficacy of psychotherapy as an add-on to pharmacotherapy for the treatment of AUD, and (b) clinical trials or randomized clinical trials testing the efficacy of pharmacotherapy as an add-on to psychotherapy for the treatment of AUD. Exclusion criteria: studies performed (a) in patients with a psychiatric diagnosis beyond alcohol dependence (i.e. double diagnosis), like depression, PTSD, bipolar disorder or cocaine dependence, (b) with samples smaller than 40 patients, (c) non-double blinded, (d) use of historical matched controls, (e) use of brief interventions, coping therapy, supportive therapy and (f) use of recommended by not-obligatory counselling i.e. no overall standardization of the psychotherapeutic intervention.

RESULTS

Based on the inclusion- and exclusion criteria, 21 studies were eligible for analysis. However, four publications reported on the same sample (Anton et al., 2006 and Donovan et al., 2008, as well as, Anton et al., 1999 and Anton et al., 2001) leaving 19 studies for analysis. Using the reference lists of five published meta-analyses and systematic reviews (Srisurapanont and Jarusuraisin, 2005; Roozen et al., 2006; Agosti et al., 2012; Jarosz et al., 2013; Gao et al., 2018; Ray et al., 2020), seven additional eligible studies were identified and included resulting in 28 studies for analysis. Fig. 1 shows the PRISMA flow chart for the identification, screening and inclusion of the studies.

Table 1 presents the results of the eligible studies on the added value of psychotherapy to pharmacotherapy: 9 studies with 590 AUD patients receiving monotherapy (medication) and 595 AUD patients receiving combined therapy (medication + psychotherapy). Three out of these nine studies (Balldin et al., 2003; Schaumberg et al., 2013; Berner et al., 2014) showed that the combination of psychotherapy and pharmacotherapy was more effective to prevent lapse to drinking than pharmacotherapy (monotherapy), whereas the other six studies showed no significant difference between the two treatment options. It should be noted, however, that the drop-out rate in the positive study of Berner et al. (2014) was very high (63% in both groups) raising doubt about the internal validity of this study. The other two studies showing a difference between the two treatments were performed in a specific group of AUD patients i.e. men having sex with men, which may not be representative for the AUD patients in general.

Table 2 presents the results of the eligible studies on the added value of pharmacotherapy to psychotherapy: 19 studies with 1241 AUD patients receiving monotherapy (psychotherapy) and 1653 AUD patients receiving combined therapy (psychotherapy + medication). The added value of combined therapy (psychotherapy + pharmacotherapy) to prevent relapse to alcohol use was demonstrated in 10 studies, whereas the remaining 9 RCTs failed to detect a significant difference between the two treatments of AUD.

DISCUSSION

The main result of the present systematic review is that 10 out of 19 RCTs (52.6%) about treatment of patients with AUD demonstrated an added value of combined therapy (psychotherapy + pharmacotherapy) compared to psychotherapy alone, whereas only three out of nine (33.3%) studies showed added value of combined therapy compared to pharmacotherapy alone.

The use of combinations of behavioral and pharmacological approaches in the treatment of alcohol dependence may theoretically have significant advantages over monotherapies, because they can allow dose-reduction and provide additive (or even synergistic) effects on efficacy (Hosking et al., 2005). The aim of the present study was therefore to assess the added value of pharmacotherapy to cognitive behavior therapy and vice versa in the treatment of alcohol use disorders. Typically, meta-analytic reviews in the AUD-literature have been conducted on groups of different pharmacotherapies, on some specific pharmacotherapy or on (specific) behavioral interventions. However, much less is known about the empirical added value of combined therapies over single interventions. In a systematic review and meta-analysis with 30 RCTs in SUD patients, Ray et al. (2020) concluded that in SUD patients the efficacy of combined treatment i.e. pharmacotherapy plus CBT (or other specific psychotherapies), is superior compared to pharmacotherapy (plus TAU i.e. plus treatment as usual). However, for several reasons, the results obtained by Ray et al. (2020) are not comparable with the currently presented results: first, only 15 of the 30 RCTs were conducted in AUD patients and second, only eight studies in their meta-analysis, evaluating the added value of combined therapy (CBT + Pharmacotherapy) vs. Pharmacotherapy (+ TAU) referred to AUD patients (O'Malley et al., 1992; Carroll et al., 1994; Carroll et al., 1998; Schmitz et al., 2001; Balldin et al., 2003; O'Malley et al., 2003; Schmitz et al., 2004; Wetzel et al., 2004). Except for the quantity outcome in the study by Schmitz et al. (2004), none of these studies showed a significant added value of CBT to pharmacotherapy. However, this study was excluded from our systematic review because the subjects included in this study were dependent on both cocaine and alcohol. The meta-analysis, however showed a small, but significant added effect of CBT ($g = 0.18$ on frequency outcomes and $g = 0.28$ on quantity outcomes). Interestingly, a

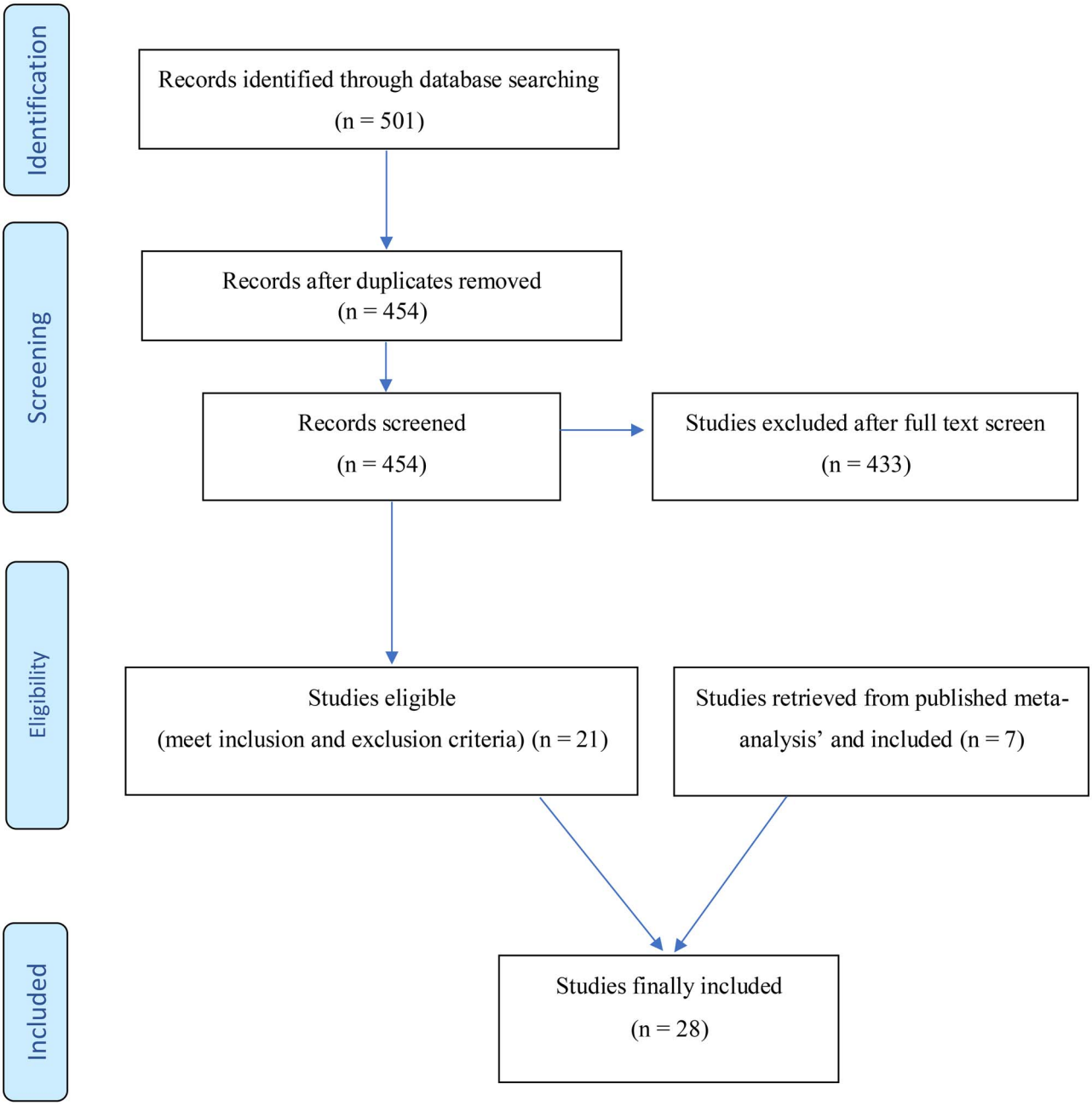

Fig. 1. PRISMA flow diagram.

meta-analysis comparing CBT + TAU + Pharmacotherapy vs. Pharmacotherapy + TAU (13 studies) showed no significant added value of combined therapy vs. pharmacotherapy. We, therefore, conclude that the conclusion drawn by Ray et al. (2020) that adding CBT to pharmacotherapy (combined therapy) has an added benefit compared with pharmacotherapy (alone or with TAU) is rather questionable for AUD patients. This complies with our finding that only three of the nine studies showed some indication for an added value of combined therapy compared to pharmacotherapy alone. Due to large differences in study design with respect to medications (doses), psychotherapies (types and number of sessions), motivation to stop drinking, and the number of patients per study, we concluded that it was not feasible to perform a valid meta-analysis. This renders our findings and conclusions somewhat less robust, but the overall conclusion that pharmacotherapy is effective to treat AUD with or without psychotherapy and that psychotherapy can best be offered in combination with pharmacotherapy is not jeopardized.

The current findings collectively suggest that best practices in addiction treatment should include pharmacotherapy with TAU and if not effective or requested by the patient pharmacotherapy plus CBT or another evidence-based psychotherapy, rather than TAU or nonspecific counselling services. These findings corroborate with previous data showing a lower relapse rate following psychosocial intervention in combination with pharmacotherapy as compared to psychosocial intervention alone (Irvin et al., 1999; Anton et al., 2006). The efficacy of the different evidence-based psychosocial interventions, such as social behavior, network therapy, CBT and MET

Table 1. Added value of psychotherapy to pharmacotherapy in the treatment of alcohol-dependent patients (dose of naltrexone (NTX) was 50 mg per day, unless otherwise stated)

No.	Monotherapy (pharmacotherapy)	Combined therapy (psychotherapy + pharmacotherapy)	Specifications of psychotherapy	Results	Ref.
1	Medical management (MM) + medication (NTX: $n = 24$; acamprosate 2 g/d, $n = 13$; placebo: $n = 11$). $N_{tot} = 48$	CBT + medical management + medication (NTX: $n = 22$; acamprosate: 2 g/d, $n = 18$; placebo: $n = 8$). $N_{tot} = 48$	CBT, 20 sessions over 4 month	NTX + CBT + MM more effective than NTX + MM: longer abstinence (hazard ratio: 0.54; 95% CI: 0.34–0.86, $P = 0.01$)	(Berner et al., 2014)
2	NTX ($n = 31$)	NTX + CBT ($n = 25$)	9 sessions supportive psychotherapy (40–60 min) over 12 weeks.	NTX + CBT more effective than NTX. First time to relapse ($F = 7.37$, df = 3, $P = 0.007$	(Balldin et al., 2003)
3[a]	NTX (100 mg/d) + medical management ($n = 51$)	NTX (100 mg/d) + CBT + MI ($n = 51$)	12 one-hour. sessions over 12 weeks. Self-identification as being sexually active with other men	NTX + CBT + MI more effective than NTX + MM to induce confidence in continuing changes without further medication (rating 6.9 vs. 6.2)	(Schaumberg et al., 2013)
4[a]	NTX (100 mg/d) ($n = 51$)	NTX (100 mg/d) + MI + CBT ($n = 51$)	12 one-hour MI + CBT sessions over 12 weeks. Self-identification as being sexually active with other men	NTX + CBT + MI not more effective than NTX on number of heavy drinking days	(Morgenstern et al., 2012)
5	NTX (100 mg/d) ($n = 39$)	NTX (100 mg/d) + CBT ($n = 40$)	CBT 18 sessions over 24 weeks.	NTX + CBT not more effective than NTX to improve drinking outcomes (% abstinence, days of heavy drinking)	(Oslin et al., 2008)
6	NTX + supportive therapy ($n = 26$)	NTX + CBT ($n = 30$)	Supportive therapy to remain abstinent without specific coping skills. CBT: 10 sessions of 50 min. Weekly over 10 weeks.	NTX + CBT not more effective than NTX + supportive therapy to prolong abstinence	(O'Malley et al., 2003)
7	NTX (100 mg/d; $n = 154$) or acamprosate (3 g/d; $n = 152$)	NTX (100 mg/d) + CBI ($n = 155$) or acamprosate (3 g/d) + CBI ($n = 151$)	20 CBI 50 min. Sessions over 16 weeks.	NTX + CBI not more effective than NTX to increase % days abstinent; acamprosate was not effective	(Anton et al., 2006; Donovan et al., 2008)
8	Acamprosate (20–30 mg/kg) ($n = 78$)	Acamprosate (20–30 mg/kg) + CBT ($n = 82$)	CBT (7 weekly sessions of 60 min) in week. 2–8.	Acamprosate + CBT not more effective than acamprosate on relapse or abstinence	(De Wildt et al., 2002)
9	Nefazodone + group counselling (GC, $n = 50$)	Nefazodone + CBT ($n = 53$)	24 GC (nonspecific support without psychotherapeutic issues). CBT: 18 90-min. Sessions over 12 weeks.	Nefazodone + CBT not more effective than nefazodone + GC to prolong abstinence or to reduce relapse rate or number of relapses	(Wetzel et al., 2004)

[a]Problem drinking in men who have sex with men; CBT: cognitive behavior therapy; MI: motivational interviewing; MET: motivational enhancement therapy; CBI: Combined Behavioral Intervention.

appears to be grossly similar (Srisurapanont and Jarusuraisin, 2005; Assanangkornchai and Srisurapanont, 2007).

Obviously, the sample characteristics and methodological features of AUD studies show a large variety, and all of these may moderate the treatment outcome and explain the differences found among the studies. Using the dataset of the COMBINE Study, one of the largest studies using combined treatment of AUD, various clinical and demographic factors i.e. moderators of treatment success could be identified. For instance, treatment-seeking predicted beneficial treatment outcomes (Ray et al., 2017). Behavioral markers of alcohol-induced stimulation, sedation and craving may also affect clinical trial outcomes (Ray et al., 2021) which may explain—at least for those highly susceptible to craving—the clinical benefit of naltrexone for AUD (Rösner et al., 2010b; Maisel et al., 2013) as it reliably blunts the reinforcing effects of alcohol (Hendershot et al., 2017; Ray et al., 2019).

The clinical treatment success may also depend on the length of the follow-up. For instance, a combination of naltrexone and psychotherapy results in high clinical efficacy in the treatment of alcohol dependent patients following short

Table 2. Added value of pharmacotherapy to psychotherapy in the treatment of alcohol-dependent patients (dose of naltrexone (NTX) was 50 mg/day, unless otherwise stated)

No.	Monotherapy (psychotherapy)	Combined therapy (psychotherapy + pharmacotherapy)	Specifications of psychotherapy	Results	Reference
1	Placebo + CBT ($n = 63$)	NTX + CBT ($n = 68$)	CBT: 12 weekly manual-guided sessions	NTX + CBT more effective than CBT to decrease rate to first relapse: Kaplan–Meier log-rank analysis, 3.90; $df = 1$; $P = 0.048$) (12% difference in final relapse rate)	(Anton et al., 1999) (Anton et al., 2001)
2	Placebo (25 μg/kg midazolam) + MET ($n = 23$)	Ketamine (0.71 mg/kg) + MET ($n = 17$)	MET: five weeks. Twice weekly spaced by 3–4 days; on 3 consecutive days in week. 2	NTX + MET across the 21 days follow-up more effective than MET + active control on alcohol abstinent days: $F = 8.21$, $df = 1, 797$, $P = 0.004$	(Dakwar et al., 2020)
3	CBT ($n = 43$)	NTX (50 mg/d) + CBT ($n = 43$)	8 one-hour sessions over the 12 weeks.	NTX + CBT more effective than CBT: longer abstinence ($P = 0.002$) and more abstinent ($P = 0.051$)	(Feeney et al., 2004)
4	CBT ($n = 59$)	All groups: $n = 59$. CBT + acamprosate (1332–1998 mg/d); CBT + NTX (50 mg/d); CBT + combined (NTX + acamprosate in dose as above)	CBT: one hour weekly for the first four weeks. Followed by fortnightly for the subsequent eight weeks.	NTX + acamprosate + CBT more effective than CBT alone with a mean difference of 19.7, $P = 0.034$. Cumulative abstinence duration (days): acamprosate + CBT: 45.1; NTX + CBT: 50.0; NTX + acamprosate + CBT: 53.6 and CBT: 33.9	(Feeney et al., 2006)
5	Placebo + CBT ($n = 35$)	Nalmefene (NAL; 20 or 80 mg/d for 12 weeks) + CTB ($n = 70$)	CBT: 45 min sessions, weekly for 12 weeks.	Nalmefene + CBT more effective than CBT to prevent relapse to heavy drinking: OR = 2.4; 95% CI: 10.5–5.59, $P < 0.02$	(Mason et al., 1999)
6	Placebo + support ($n = 99$)	NTX (50 mg/d) + support ($n = 93$)	Support: weekly group support for relapse prevention and individual counselling	NTX + CBT more effective than support to prevent relapse: 18.8 vs. 7.9% ($\chi^2 = 5.89$, $df = 2$, $P = 0.050$)	(Guardia et al., 2002)
7	Placebo + CBT ($n = 40$)	All groups ($n = 40$) received CBT. Acamprosate (1998 mg/d), NTX (50 mg/d) or both	CBT: 90-min group sessions, weekly for 12 weeks.	NTX + CBT or acamprosate + CBT or NTX + acamprosate + CBT more effective than CBT to reduce relapse rate than individual support ($P = 0.02$)	(Kiefer et al., 2003)
8	Placebo + group support ($n = 56$)	NTX (50 mg/d) + Group support ($n = 55$)	12 weekly 1.5 hour group sessions of psychological education and social support	NTX + CBT more effective to reduce relapse: 50 vs. 79% ($P = 0.001$), but no effect on the number of drinking days per week	(Morris et al., 2001)
9	Placebo + group counselling ($n = 54$)	NTX (50 mg/d) + group counselling ($n = 45$)	Group counselling related to alcohol dependence (2x weekly for 11 month)	NTX + CBT more effective than group counselling to prevent relapse: 23 vs. 54%, $P < 0.01$)	(Volpicelli et al., 1992)
10	Placebo + individual counselling ($n = 48$)	NTX (50 mg/d) + individual counselling for 12 weeks. ($n = 49$)	Individual relapse prevention counselling (first month: 2x weekly, then once weekly for 12 weeks.	NTX + individual counselling more effective than individual counselling to reduce drinking days (2.8 vs. 11.0, $P = 0.01$) and to prevent relapse (14 vs. 52%, $P = 0.002$)	(Volpicelli et al., 1997)
11	Placebo + intensive counselling (CBI) ($n = 156$)	NTX (100 mg/d) + CBI ($n = 155$) or acamprosate (3 g/d) + CBI ($n = 151$)	CBI: 20 50 min. Sessions over 16 weeks.	NTX + CBI not more effective than CBI to prolong abstinence (Cohen d: 0.07; 95% CI: −0.11-0.25 vs. Cohen d: 0.17; 95% CI: −0.02 to 0.35, respectively, $P = 0.009$)	(Anton et al., 2006)
12	Placebo (i.m.) + HaRT-A[2] ($n = 78$) + behavioral treatment	HaRT-A + NTX (380 mg i.m. extended-release) ($n = 74$)	Five sessions at baseline (week 0) and in weeks. 1, 4, 8 and 12	NTX + HaRT-A + behavioral treatment not more effective than HaRT-A + behavioral treatment on self-reported drinking during 24 weeks. Follow-up (quantity and frequency)	(Collins et al., 2021)
13	Placebo + CET + CST ($n = 128$)	NTX + CET + CST (50 mg/d; $n = 165$) for 12 weeks.	CET + CST: two weeks training in coping and communication skills	NTX + CET + CST at 12-month follow-up not more effective than CET + CST to reduce % heavy drinking days, nor to increase % relapse	(Monti et al., 2001)

(continue)

Table 2. Continued.

No.	Monotherapy (psychotherapy)	Combined therapy (psychotherapy + pharmacotherapy)	Specifications of psychotherapy	Results	Reference
14	Placebo + psychosocial treatment $n = 87$)	NTX (50 mg/d) + psychosocial treatment (Psy-Tr; $n = 84$)	Weekly one-hour sessions of psychosocial alcohol treatment program	NTX + Psy-Tr not more effective than Psy-Tr to increase abstinence rate at week 12: NTX + Psy-Tr (54%) vs. Psy-Tr (51%)	(Gastpar et al., 2002)
15	Placebo + individual support ($n = 20$)	NTX (50 mg/d) + individual support ($n = 20$)	Weekly 30-min sessions individual psychotherapy for abstinence and compliance enhancement for 12 weeks.	NTX + individual support not more effective than individual support to reduce relapse rates ($P = 0.67$)	(Huang et al., 2005)
16	Placebo + CBT ($n = 32$)	NTX + CBT ($n = 31$)	CBT: 21 days of dependency treatment	NTX + CBT not more effective than CBT to reduce craving nor recidivism after treatment	(Knox and Donovan, 1999)
17	Placebo + CBT ($n = 63$)	NTX + CBT (50 mg/d; $n = 61$) or nefazodone + CBT (400 mg/d; $n = 59$)	CBT: 12 weekly sessions	NTX + CBT not more effective than CBT to prevent relapse to heavy drinking or to reduce drinking days	(Kranzler et al., 2000)
18	Placebo + CBT-based counselling ($n = 32$)	Baclofen (50 mg/d) for 12 weeks. $n = 32$	Weekly support CBT-based counselling; motivational interviewing, education and therapy	Baclofen + CBT-based counselling not more effective than CBT-based counselling to prevent relapse to heavy drinking nor to increase abstinent days at 52 weeks. Follow-up	(Ponizovsky et al., 2015)
19	Placebo + IBT ($n = 125$)	Acamprosate (2 g/d) + IBT ($n = 124$)	24 IBT (integrative behavior therapy) 30-min sessions for 6 month	Acamprosate + IBT not more effective than IBT: rate of abstinence at 6-month follow-up (47.6 and 48.0%, respectively)	(Wölwer et al., 2011)

[a]Counselling sessions providing information about alcohol use and abuse, and the consequences of alcohol dependence; [2] HaRT-A: behavioral treatment, consisting of low-intensity not requiring abstinence; CBT: Cognitive Behavior Therapy; CBI: Combined Behavioral Intervention; IBT: integrative behavior therapy (relapse prevention, social skill trainings, and motivational and cognitive methods).

12–16 weeks of treatment, (Jarosz et al., 2013). Finally, a known confounder of clinical studies using pharmacotherapy, in general, is patient compliance with taking the medication and the context in which the medication is administered on which the effectiveness of pharmacotherapy depends (Starosta et al., 2006). Reduced medication compliance may also be related to the suggested decrease of the suppressant effect of naloxone on drinking behavior, which would be limited to the first 3 months of treatment (Volpicelli et al., 1997; Davidson et al., 2007). As such, enhancing compliance during treatment is crucial for treatment success with a two-fold higher treatment effect size in the most compliant individuals (Baros et al., 2008).

In conclusion, the current results suggest that pharmacotherapy is effective to treat patients with AUD either without or with psychotherapy and that psychotherapy can best be offered in combination with pharmacotherapy.

STATEMENT OF ETHICS

The paper is exempt from ethical committee approval.

AUTHOR CONTRIBUTIONS

Jv.A. and T.N. performed the systematic search and T.N., V.H., Jv.A. and Wvd.B. drafted the paper.

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CONFLICT OF INTEREST STATEMENT

Jv.A., P.B., R.S. and V.H. have no potential conflict of interest with respect to the research, authorship and/or publication of this article. Wvd.B. has a potential conflict of interest as a consultant for Lundbeck, D&A Pharma and Kinnov Therapeutics.

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