Efficacy of Psychosocial Interventions in Inducing and Maintaining Alcohol Abstinence in Patients With Chronic Liver Disease: A Systematic Review.

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Efficacy of Psychosocial Interventions in Inducing and Maintaining Alcohol Abstinence in Patients with Chronic Liver Disease – A Systematic Review

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Abstract

Background & Aims—We conducted a systematic review of efficacy of psychosocial interventions in inducing or maintaining alcohol abstinence in patients with chronic liver disease (CLD) and alcohol use disorder (AUD).

Methods—We performed structured keyword searches in PubMed, PsychINFO, and MEDLINE for original research articles, published from January 1983 through November 2014, that evaluated the use of psychosocial interventions to induce or maintain alcohol abstinence in patients with CLD and AUD.
Results—We identified 13 eligible studies, comprising 1945 patients; 5 were randomized controlled trials (RCTs). Delivered therapies included motivational enhancement therapy (MET), cognitive behavioral therapy (CBT), motivational interviewing (MI), supportive therapy and psychoeducation either alone or in combination in the intervention group and general health education or treatment as usual in the control group. All studies of induction of abstinence (4 RCTs and 6 observational studies) reported an increase in abstinence among participants in the intervention and control groups. Only an integrated therapy that combined CBT and MET with comprehensive medical care, delivered over 2 years, produced a significant increase in abstinence (74% increase in intervention group versus 48% increase in control group; \( P = .02 \)), reported in 1 RCT. All studies of maintenance of abstinence (1 RCT and 2 observational studies) observed recidivism in the intervention and control groups. Only an integrated therapy that combined medical care with CBT produced a significantly smaller rate of recidivism (32.7% in integrated CBT group versus 75% decrease in control group, \( P = .03 \)), reported from 1 observational study. However, data were not collected for more than 2 y on outcomes of patients with CLD and AUD.

Conclusion—In a systematic analysis of studies of interventions to induce or maintain alcohol abstinence in patients with CLD and AUD, integrated combination psychotherapy with CBT, motivational enhancement therapy, and comprehensive medical care increased alcohol abstinence. No psychosocial intervention was successful in maintaining abstinence, but an integrated therapy with CBT and medical care appears to reduce recidivism.

Keywords
MET; alcoholism; alcohol abuse; cirrhosis; Alcohol; alcohol use disorder; abstinence; relapse prevention; psychosocial interventions; behavioral therapy; chronic liver disease

Introduction
Alcohol use disorder (AUD) is a major contributor to the global burden of chronic liver disease (CLD)\(^1\). According to the Center for Disease Control, nearly 50% of annual mortality from CLD in the United States is attributable to excessive alcohol use. In Europe, alcohol related liver disease (ALD) is the most common cause of CLD and accounts for over 75% of cases with cirrhosis\(^2, 3\). ALD alone\(^4\), or in combination with other risk factors for CLD, such as chronic viral hepatitis\(^5\) or nonalcoholic fatty liver disease (NAFLD)\(^6\), predisposes to advanced liver injury, and an increased risk of overall as well as liver-related mortality. Indeed, even moderate alcohol consumption portends an increased risk of mortality in patients with CLD\(^7, 8\). Consequently, an important treatment goal in patients with CLD is to achieve and maintain long-term abstinence from alcohol. Abstinence improves clinical outcomes in all stages of CLD; the survival benefits of alcohol abstinence extend to patients even after the development of cirrhosis\(^9, 10\).

However, treatment of AUD in patients with CLD remains problematic. Pharmacologic options for managing drinking in patients with CLD are limited\(^12\). Although disulfiram, naltrexone and acamprosate have been found to be effective in managing AUD,\(^12\) there is paucity of data regarding their safety in treatment of AUD in HCV-infected individuals or patients with CLD. Only baclofen has been shown to be safe and effective in patients with CLD and AUD\(^13, 14\) and is approved for use in the patients in the United States. Substantial
evidence exists demonstrating the value of psychosocial interventions in treating AUD in patients without liver disease\textsuperscript{15, 16}. However, patients with CLD may be a special population due to heavier drinking histories, relatively little insight into the relationship between their drinking and CLD development, refusal to accept referral to conventional alcohol treatment programs, and difficulty achieving or maintaining abstinence despite being at substantial risk of developing life threatening hepatic decompensation\textsuperscript{17}. Given this, it is plausible that patients with CLD may respond differently to psychosocial interventions than those without CLD.

Therefore, we conducted the first systematic review of relevant literature to synthesize the evidence of the efficacy of psychosocial interventions to induce and maintain alcohol abstinence in patients with CLD and AUD, and to identify intervention features that might explain their varying effects.

**Methods**

We conducted our systematic review in accordance with the PRISMA guidelines\textsuperscript{18} including use of an \textit{a priori} designed study protocol that guided our literature search, study selection and data synthesis.

**Study Selection**

We searched for all original research studies published between January 1983 and November 2014, regardless of language or design. We included both randomized (randomized controlled and quasi-experimental designs) and non-randomized or observational (cohort, case control, controlled before-after, historically controlled and cross sectional) studies. We did not include case reports, case series or studies where the sample size was smaller than 20 participants.

We included adult patients (\textgeq;18 years) with CLD and AUD. Eligible CLD patients included those with ALD (including alcoholic steatosis, alcoholic hepatitis, alcoholic fibrosis and alcoholic cirrhosis), chronic viral hepatitis, NAFLD, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson’s disease, alpha-1 antitrypsin disease, or hemochromatosis. We classified patients as subjects with advanced liver disease if they had a Child Turcotte Pugh score \textgeq;7, a MELD score \textgeq;10, decompensated cirrhosis (e.g., ascites, hepatic encephalopathy or variceal bleeding) or were defined by study authors as such. \textit{A priori}, we decided to include studies if more than 50% of study sample consisted of patients with CLD, even if the results were not reported separately for CLD patients. The considered interventions were any psychosocial interventions described by the study’s authors as such including Motivational Enhancement Therapy (MET), Cognitive Behavioral Therapy (CBT), Motivational Interviewing (MI), Psychoeducation and Contingency Management. The interventions could be individual or group-based, in-patient or outpatient based and integrated or non-integrated with medical care. Integrated interventions entailed mental health services being co-located in the same clinic with medical services or increased communication between the mental health and medical care providers or a single provider delivering both medical and mental health services. Studies that included control arms were
required to compare a psychosocial intervention to a different psychotherapy or pharmacotherapy or standard of care.

**Outcome of Interest**

The outcome of interest was post-intervention alcohol abstinence data as measured by either biological marker, self-report or collateral informant.

**Search Strategy and Study Identification**

Two independent reviewers (AK and AT) performed structured keyword searches in PubMed (1966 to November 2014), MEDLINE (1946 to November 2014), and PsycINFO (1987 to November 2014). Search terms included alcohol (as well as alcohol use disorders), various psychosocial interventions (i.e., psychotherapy, behavior therapy, motivational interviewing) and numerous descriptors for liver disease (i.e., cirrhosis, fatty liver). We did not apply any restrictions on language and translated non-English language papers, when needed (see Appendix for the full search strategy). We scanned the bibliographies of all relevant studies and recent review articles to identify additional citations not identified by our keyword searches. We retrieved the full articles for all titles and abstracts that appeared to fulfill the inclusion criteria of the study. Study eligibility was determined by consensus and as necessary with adjudication with a third reviewer (FK).

**Data extraction and management**

Both reviewers independently extracted data using a standardized approach. Data extracted included individual study characteristics (study design, sample size, study setting and length of follow-up), baseline patient characteristics (age, gender, ethnicity, years of alcohol abuse and presence of advanced liver disease) and intervention characteristics (type of psychosocial intervention, timing and duration of intervention, delivering provider, integrated or non-integrated, group, individual or family based and additional use of pharmacotherapy). We contacted authors of all included studies for missing or unclear information.

**Assessment of risk of bias in included studies**

Both reviewers also independently assessed the methodological quality of studies using the risk of bias tool from the Cochrane Collaboration for RCTs, and a checklist designed by Downs and Black for non-randomized studies. For RCTs, we classified each of the following items at being “low,” “unclear,” or “high” risk of bias: adequate sequence generation, allocation concealment, blinding for objective outcomes, incomplete outcome data and free of selective outcome reporting. For non-randomized studies we classified studies as having a “low”, “medium” or “high” risk of bias based on scoring for quality of reporting, internal validity (bias and confounding), power and external validity. We resolved disagreements by discussion and consensus.

**Statistical Analyses**

We planned to conduct 2 meta-analyses to obtain pooled estimators for efficacy of psychological interventions for RCTs and observational studies with control groups,
respectively if we found 2 or more comparably conducted studies (with similar intervention and control group) that reported data on the 2 outcomes.

Results

Study selection

We screened 3055 potentially eligible studies and then examined in detail 32 full text articles. Of these, we excluded 19 studies. The most common reasons for ineligibility of reviewed studies were inability to report alcohol abstinence as an outcome (N = 8) or lack of inclusion of patients with CLD (N = 6) (See Study Flow Chart presented in Figure 1).

Study characteristics

We included 5 randomized controlled trials (RCTs) and 8 non-randomized or observational studies (N = 2 non-randomized cohort studies with historical control groups and N = 6 uncontrolled studies using pre-post design conducted in patients with CLD and HCV or ALD. We did not find any studies that included patients with CLD from other etiologies.

Randomized controlled trials

The study characteristics are summarized in Table 1. All 5 RCTs were conducted in United States and included a total of 367 participants in the intervention arms and 349 participants in the control arms. Mean age of participants was 48 years and more than 90% were males. Two RCTs included patients with chronic HCV, two RCTs included patients with alcoholic cirrhosis and one RCT included patients with ALD and advanced liver disease.

We found four RCTs that reported data on induction of alcohol abstinence and one RCT that reported data on maintenance of alcohol abstinence. The results were not pooled in a meta-analysis owing to a substantial clinical heterogeneity.

Two RCTs were at a low risk of bias and 3 RCTs were at a high risk of bias (Table 3) given selection bias due to significant differences in patient age, alcohol consumption and inappropriate randomization. The risk of bias for individual studies is summarized in (Table 3). Compliance to intervention ranged from 50–88% in the intervention arm and 35–74% in the control arm.

Induction of Alcohol Abstinence—Four RCTs aimed to induce alcohol abstinence. The studies considered four different psychosocial interventions grouped into four comparisons: (1) CBT versus general health education (one study; N=355 participants), (2) Brief MI versus usual care (one study; N=71 participants), (3) MET versus general health education or usual care (two studies; N=229 participants) and (4) Integrated combination therapy with MET, CBT and comprehensive medical care versus usual care (one study; N= 61 participants). Overall, the proportion of patients reporting abstinence was higher in the intervention (average 45.4%, range 25.4–74%) than the control groups (average 36.7%, range 19.7–50%). However, only one study by Willenbring et al.

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found a statistically significant increase in alcohol abstinence in the intervention compared to the control group. In this study, the investigators randomized 61 patients with alcoholic cirrhosis or symptomatic alcoholic hepatitis and severe alcohol abuse with a history of several previous failed alcoholism treatments to integrated therapy with a combination of CBT and MET in combination with comprehensive medical care delivered by a primary physician or nurse-practitioner once or twice monthly over two years versus treatment as usual. At the end of 2-year follow up, 74% of patients in the intervention group compared with 45% in the control group reported abstinence (P=0.02) likely related to the greater treatment engagement in the intervention group (42 mean number of visits over 2 years in intervention group versus 17 mean number of visits over 2 years in control group, P<0.001). Although the intervention and control groups were generally well matched, the intervention group was younger than the control group (mean age of intervention group = 53 years versus 57 years in control group, P=0.04), which gave the study an overall high risk of bias.

Psychosocial interventions did not have a significant effect on the likelihood of achieving alcohol abstinence in the other RCTs. Dieperink et al\(^\text{22}\) randomized 139 patients with chronic HCV to MET delivered by one physician and five psychologists over 3 months versus general health education. While participants attended approximately the same number of sessions in each group, a small non-significant increase in abstinence favoring MET (25.4% versus 19.7% respectively) was reported at 6-month follow-up (P=0.14). Drumright et al\(^\text{23}\) randomized 355 participants with chronic HCV to CBT and contingency management therapy delivered by public health professionals versus general health education and contingency management therapy with 50% of participants in intervention and control groups reporting abstinence at 6 months. Kuchipudi et al\(^\text{25}\) randomized 71 patients with alcoholic cirrhosis admitted to an acute medical unit to a brief 2-hour motivational interview delivered by a medicine resident, gastroenterology fellow, social worker with training in alcoholism treatment and psychiatric nurse therapist versus regular medical care with a small non-significant increase in abstinence favoring brief motivational intervention (32% versus 29% respectively) at 10–14 week follow-up (P>0.05).

**Maintenance of alcohol abstinence**—Only one RCT studied maintenance of alcohol abstinence\(^\text{24}\) and randomized 91 patients with alcoholic cirrhosis awaiting orthotopic liver transplantation to MET delivered by an addiction therapist over 6 months versus standard intensive outpatient therapy. Although at baseline, nearly 90% participants were abstinent, in an intention to treat (ITT) analysis, almost majority of patients relapsed with a non-significant decrease in recidivism favoring MET (84.8% versus 93.4%, respectively) reported at 6 month follow-up (P=0.95).

**Observational Studies**

We included eight observational studies, with all but three\(^\text{28, 29, 32}\) conducted outside the United States (Table 2). Two were non-randomized cohort studies with historical controls\(^\text{26, 27}\) comparing supportive therapy and alcohol education to standard medical care (1 study\(^\text{26}\), N = 33 participants) and integrated CBT to supportive therapy (1 study\(^\text{27}\), N = 92 participants). The other 6 employed a pre-post design and examined CBT (2 studies\(^\text{30, 32}\), N=809), psychoeducation (2 studies\(^\text{31, 33}\), N=195 participants), combination therapy with
MET, CBT and psychoeducation (1 study\textsuperscript{28}, N=53 participants) and combination therapy with MET, CBT and MI (1 study\textsuperscript{29}, N=47 participants). All eight non-randomized studies were judged to be at medium risk of bias based on Downs and Black bias scale ratings\textsuperscript{20} (Table 4). Compliance to intervention was variable and ranged from 14 – 95%.

**Inducing alcohol abstinence**—Five studies (1 non-randomized study with historical control group\textsuperscript{26} and 4 pre-post studies\textsuperscript{28, 29, 32, 33}) reported data on achieving alcohol abstinence. Andersen et al in their non-randomized historically controlled study reported a higher likelihood of achieving alcohol abstinence in patients with ALD and advanced liver disease receiving supportive therapy by a nurse, weekly for one year versus usual therapy at one-year follow up (26% versus 7.1% respectively). In uncontrolled studies, a small increase in abstinence was reported (average 28.6%, range 17.3 – 44%).

**Maintaining alcohol abstinence**—Three studies (1 non-randomized study with historical control\textsuperscript{27} and 2 pre-post studies\textsuperscript{30, 31}) reported data on maintaining alcohol abstinence. Addolorato et al.\textsuperscript{27} compared 55 patients who received an integrated CBT intervention to 37 historical patients who received only supportive therapy pre-transplant. Less than one-third of patients in the intervention group relapsed post-transplant compared to 75% of controls (P<0.01). Two uncontrolled pre-post studies\textsuperscript{30, 31} delivered CBT and psychoeducation respectively pre-transplant with 31–45% patients relapsing at longest follow-up.

**Characteristics of Interventions**

We found one RCT and 3 observational studies that used integrated therapy with the same provider delivering mental health and liver disease care\textsuperscript{21} or an integrated multidisciplinary team approach by both liver disease and mental health providers in the same location with close communication\textsuperscript{27, 29}. Integrated therapy resulted in a significantly higher rate of alcohol abstinence compared to control group in one RCT\textsuperscript{21}. Data from the observational studies supported the positive effect of integrated therapies on achieving alcohol abstinence. Integrated interventions had a beneficial effect in all studies regardless of whether the studies included patients with mild or advanced disease.

A total of 4 RCTs\textsuperscript{22–25} and 5 observational studies\textsuperscript{26, 30–33} used non-integrated therapies. In the studies designed to induce abstinence, the RCTs showed a trend towards higher abstinence in the therapy group, however this effect was not as large as that found in the studies that delivered integrated therapy\textsuperscript{21}. Similar findings were seen in observational studies.

For studies designed to maintain alcohol abstinence, one RCT which delivered non-integrated MET therapy showed a high rate of recidivism than the control group. The rates of recidivism were somewhat lower in observational studies that used non-integrated interventions (range 31.2–47.9%).
Discussion

Substantial evidence exists to support the use of non-integrated, stand alone psychosocial interventions in treating alcohol use disorder in non-CLD population\textsuperscript{37–39}. Our systematic review suggests that integrated combination psychotherapy with CBT, MET and comprehensive medical care may increase alcohol abstinence in patients with CLD and AUD. Most other interventions did not impact induction of abstinence in patients with CLD. We also found that therapies that used integrated care resulted in better outcomes than those that did not use an integrated approach. Specifically, we found four studies (1 RCT and 3 observational studies) that evaluated an integrated approach and reported a similar magnitude of effects (36\%–75\%). These studies examined a range of psychotherapies (combination therapies which included combinations of CBT and MET\textsuperscript{21}, CBT, MET and psychoeducation\textsuperscript{28} and CBT, MET and MI\textsuperscript{29}) and enrolled patients with varying degree of liver disease severity. Besides the integrated care delivery, it is difficult to isolate intervention characteristics that resulted in better alcohol use outcomes given the wide range of therapeutic approaches employed. For example, results of a single study using a combination of CBT, MET and comprehensive medical care delivered monthly for two years by a physician or nurse practitioner with no specialized training demonstrated a significantly improved rate of abstinence suggesting that interventions that use a combination of psychosocial therapies may be more efficacious than single modality therapy in promoting alcohol abstinence in patients with CLD. Another study by Weisner et al\textsuperscript{40}, which used an integrated services model where a combination of primary health care was provided along with CBT, supportive therapy and psychoeducation within the same unit in patients with alcohol-abuse related medical conditions demonstrated a significantly improved rate of abstinence compared to an independent treatment-as-usual model, where medical care was received in primary care clinics independently from alcohol abuse treatment (80\% vs 65\%, $P = .002$). The study was not included in this review, as the number of patients with CLD was not specified. However, we also observed a significantly smaller rate of recidivism in a study that used only CBT but integrated psychological treatment with medical care delivered by clinicians with expertise in alcoholism, hepatology & neuroscience. These data suggest that patients with AUD and CLD represent a special subgroup that may need intensive behavioral therapies that are integrated within the context of ongoing medical care. This implies shifting away from the practice of relying solely on referral of patients to community rehabilitation facilities which are not integrated with medical care.

We also assessed for factors that may explain varying effects of behavioral therapy in the included studies. For example, the level of adherence to interventions was variable and ranged from 14\%–95\%. Non-adherence to behavioral therapy was often associated with social impediments and poor functional status that are common in patients with CLD. Outreach efforts that extend beyond the traditional clinic setting, such as tele health and home visits, may be a way to enhance patient engagement and improve outcomes. Our review found one study that delivered a psychoeducation intervention by a dedicated nurse who sometimes visited the patients with decompensated liver disease in their home\textsuperscript{26}. It remains to be seen...
whether similar models that improve access to care through utilizing delivery methods outside the infrastructure of traditional clinic environment, are feasible and sustainable.

We did not find any studies that compared pharmacotherapy to psychosocial interventions in achieving and maintaining alcohol abstinence. While few studies reported concomitant use of pharmacotherapy among study participants, there were too few of them to allow for assessment of potential subgroup effects. This is not unexpected given that pharmacotherapies are often contraindicated in patients with CLD.

Our review has several strengths. We used a rigorous and systematic approach, measured alcohol abstinence and not reduction in drinking as our key outcome, examined the full range of psychosocial interventions available for treatment of AUD and did not limit our studies to English language only. However, our review also has several limitations. First, there were a limited number of studies that were too disparate in study subjects, study design, and employed interventions to allow a meta-analysis many studies had small sample size and several were at a high risk of bias. This highlights the importance of additional research to examine the role of behavioral therapy in patient with AUD and CLD. Further, there were few data on women with CLD (for example, 2 RCTs included 100% males)\textsuperscript{22, 26}. Although males are disproportionately more impacted with advanced liver disease, substantial and growing number of women with AUD and CLD suggest importance of research on more diverse populations allowing for evaluation of potential differences in effects across genders. With the exception of one study, no study reported outcomes beyond 2 years. It is therefore not possible to determine if any of the interventions had a long-term beneficial effect on alcohol abstinence. It is possible that some of the differences between the intervention and control groups underestimated the true intervention effects because control groups received some type of psychosocial support in most studies.

In conclusion, our systematic review of psychosocial interventions suggests that integrated combination psychotherapy may increase alcohol abstinence in patients with CLD and AUD. Although no psychosocial intervention was successful in maintaining alcohol abstinence long-term, an integrated CBT intervention holds promise as a strategy to reduce recidivism.

Acknowledgments

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Abbreviations

\begin{itemize}
  \item \textbf{AUD} alcohol use disorder
  \item \textbf{CLD} chronic liver disease
\end{itemize}
References


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Appendix: Search Strategy

MEDLINE SEARCH

1. alcohol drinking/ or binge drinking/ or alcoholic intoxication/ or alcoholism/
2. (alcohol* or drunkenness or sober or sobriety).ti,kw,ab.
3. 1 or 2
4. (“clinical trial” or “clinical trial, phase i” or “clinical trial, phase ii” or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or “multicenter study” or “randomized controlled trial”).pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask))).ti,ab.
5. educational program evaluation/ or mental health program evaluation/ or program evaluation/ or Treatment Effectiveness Evaluation/
6. program development/ and (evaluation/ or Evaluation Criteria/ or needs assessment/ or risk assessment/)
7. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
8. Intervention Studies/ or evaluation studies/ or evaluation studies as topic/ or program evaluation/ or validation studies as topic/ or ((pre-adj5 post-) or (pretest adj5 posttest) or (program* adj6 evaluat*)).ti,ab. or (effectiveness or intervention).ti,ab.
9. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or retrospective studies/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
10. ((program or treatment) adj5 (efficacy or effectiveness or evaluat* or significant or reduction or reduce or reducing)).ti,ab,kw.
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 3 and 11
13. psychotherapy/ or behavior therapy/ or aversive therapy/ or biofeedback, psychology/ or cognitive therapy/ or “acceptance and commitment therapy”/ or mindfulness/ or relaxation therapy/ or meditation/ or feedback, psychological/ or

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hypnosis/ or nondirective therapy/ or psychoanalytic therapy/ or psychotherapeutic processes/ or psychotherapy, brief/ or psychotherapy, multiple/ or psychotherapy, psychodynamic/ or psychotherapy, rational-emotive/ or reality therapy/ or milieu therapy/ or psychotherapy, group/ or couples therapy/ or family therapy/ or marital therapy/ or psychodrama/ or role playing/ or sensitivity training groups/ or residential treatment/ or Combined Modality Therapy/ or substance abuse treatment centers/

14. counseling/ or directive counseling/ or motivational interviewing/ or pastoral care/

15. ((alcohol and rehabilitation) or alcoholics anonymous or aversion therapy or behavior modification or behavior therapy or psychotherapy or client centered therapy or cognitive behavior therapy or cognitive restructuring or cognitive techniques or cognitive therapy or covert sensitization or Family Therapy or gestalt therapy or group therapy or hypnosis or hypnotherapy or insight therapy or motivational enhancement therapy or motivational intervention or motivational interviewing or Network Therapy or psychoeducation or client education or psychotherapeutic counseling or psychotherapy or behavior therapy or reality therapy or rehabilitation counseling or self management or therapeutic community or combined modality or (integrated and (therapy or treatment))).ti,ab,kw.

16. px.fs.

17. 13 or 14 or 15 or 16

18. 12 and 17

19. (18 not adolescen*.ti.) or (18 and adult*.ti.)

20. liver diseases/ or liver cirrhosis/ or fibrosis/ or fatty liver/ or liver diseases, alcoholic/ or Liver Cirrhosis, Alcoholic/ or hepatitis/ or liver/ or liver function tests/ or jaundice/ or liver neoplasms/

21. (liver disease* or cirrho* or (liver and fibrosis) or steatosis or “hepatitis c” or hcv or hepatocellular cancer* or liver cancer*).ti,ab,kw.

22. (substance abuse-related medical conditions or “Medically ill alcoholics”).ti,ab,kw.

23. 20 or 21 or 22

24. 19 and 23

PsycInfo

1. alcohol abuse/ or alcohol drinking attitudes/ or alcohol drinking patterns/ or alcohol intoxication/ or alcohol withdrawal/ or alcoholism/ or binge drinking/ or sobriety/ or social drinking/

2. (alcohol* or drunkenness or sober or sobriety).ti,id.

3. 1 or 2
4. clinical trials/ or “treatment outcome clinical trial”.md. or ((randomi?ed adj7 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*)) or (controlled adj3 trial*) or (clinical adj2 trial*)).ti,ab,id.

5. educational program evaluation/ or mental health program evaluation/ or program evaluation/ or Treatment Effectiveness Evaluation/

6. program development/ and (evaluation/ or Evaluation Criteria/ or needs assessment/ or risk assessment/)

7. (“longitudinal study” or “retrospective study”).md. or time series/ or “followup studies”/ or followup study.md.

8. ((pre-adj5 post-) or (pretest adj5 posttest)).ti,ab,id.

9. ((program or treatment) adj5 (efficacy or effectiveness or evaluat* or significant or reduction or reduce or reducing)).ti,ab,id.

10. intervention.ti,ab,id. and “empirical study”.md. and “quantitative study”.md.

11. 4 or 5 or 6 or 7 or 8 or 9 or 10

12. 3 and 11

13. alcohol rehabilitation/ or alcoholics anonymous/ or aversion therapy/ or behavior change/ or behavior modification/ or behavior therapy/ or brief psychotherapy/ or client centered therapy/ or cognitive behavior therapy/ or cognitive restructuring/ or cognitive techniques/ or cognitive therapy/ or covert sensitization/ or Family Therapy/ or gestalt therapy/ or group psychotherapy/ or humanistic psychotherapy/ or hypnotherapy/ or individual psychotherapy/ or insight therapy/ or integrative psychotherapy/ or interpersonal psychotherapy/ or motivational interviewing/ or Network Therapy/ or psychoeducation/ or client education/ or psychotherapeutic counseling/ or psychotherapy/ or rational emotive behavior therapy/ or reality therapy/ or rehabilitation counseling/ or self management/ or Supportive Psychotherapy/ or therapeutic community/

14. (alcohol rehabilitation or alcoholics anonymous or aversion therapy or behavior modification or behavior therapy or psychotherapy or client centered therapy or cognitive behavior therapy or cognitive restructuring or cognitive techniques or cognitive therapy or covert sensitization or Family Therapy or gestalt therapy or group therapy or hypnosis or hypnotherapy or insight therapy or motivational enhancement therapy or motivational intervention or motivational interviewing or Network Therapy or psychoeducation or client education or psychotherapeutic counseling or psychotherapy or behavior therapy or reality therapy or rehabilitation counseling or self management or therapeutic community).ti,ab,id.

15. 13 or 14

16. 12 and 15

17. (16 not adolescen*.ti.) or (16 and adult*.ti.)

18. 17 and journal.pt.
19. liver disorders/ or “cirrhosis (liver)”/ or jaundice/
20. hepatitis/
21. (liver disease* or cirrho* or (liver and fibrosis) or steatosis or “hepatitis c” or hcv).ti,ab,id.
22. 19 or 20 or 21
23. 18 and 22

Pubmed

2. (alcohol*[tiab] OR drunkenness[tiab] OR sober[tiab] OR sobriety[tiab])
3. #1 OR #2
5. educational program evaluation[mesh:noexp] OR mental health program evaluation[mesh:noexp] OR program evaluation[mesh:noexp] OR Treatment Effectiveness Evaluation[mesh:noexp]
(pretest[tiab] AND posttest[tiab]) OR (program*[tiab] AND (evaluat*[tiab] OR effectiveness[tiab])) OR intervention*[tiab]


11. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

12. #3 AND #11


16. “psychology” [Subheading]

17. #13 OR #14 OR #15 OR #16

18. #12 AND #17

19. (#18 not adolescen*[ti]) OR (#18 AND adult*[ti])


22. (substance abuse-related medical condition*[tiab] OR Medically ill alcoholic*[tiab])

23. #20 OR #21 OR #22

24. #19 AND #23
Figure 1.
Search flow diagram, assessment and reporting of included and excluded studies
## Table 1

Participants in alcohol cessation counseling in RCTs: Mean baseline characteristics and rate of alcohol abstinence at follow-up

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Sample Characteristics (N=187)</th>
<th>Participants (N)</th>
<th>Pre-intervention Abstinence (%)</th>
<th>Liver Disease / On OLT List</th>
<th>Intervention Setting</th>
<th>Data Collection</th>
<th>Intervention Elements</th>
<th>Intervention Delivery By</th>
<th>Intervention Format</th>
<th>Treatment Sessions (N)</th>
<th>Session Time Extension (months)</th>
<th>Treatment Duration (months)</th>
<th>Concurrent Pharmacotherapy Use</th>
<th>Alcoholic Abstinence (%) at longest follow-up</th>
<th>P-value</th>
<th>Longest Follow-up (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorevitch 2014 (22)</td>
<td>Age 59.8 years, Race 66.5% white, 26.8% black, 5.7% other; Male 97.4%</td>
<td>70</td>
<td>0</td>
<td>IVF, Oligo of Stress NR / No</td>
<td>Outpatient &amp; Multicenter</td>
<td>Nov 2008 - July 2012</td>
<td>MET</td>
<td>1 physician &amp; 5 psychologists</td>
<td>Individual</td>
<td>4</td>
<td>30 – 45</td>
<td>3</td>
<td>None</td>
<td>26.8; B1, B2, B3, B6</td>
<td>0.05</td>
<td>6</td>
</tr>
<tr>
<td>C. Age 56.2 years, Race 46.2% white, 30.9% black, 23% native American; Male 94.1%</td>
<td>68</td>
<td>0</td>
<td>IVF, Oligo of Stress NR / No</td>
<td>General health education</td>
<td>Individual</td>
<td>4</td>
<td>30 – 45</td>
<td>3</td>
<td>1 comprehensive month supply of Naltrexone</td>
<td>19.7; B1, B2, B3, B6</td>
<td>0.05</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinrich 2011 (26)</td>
<td>Age 56.5 years, Race 39.8% white &amp; 17% other; Male 84.9%; 20.5 years of alcohol abuse</td>
<td>46</td>
<td>0</td>
<td>Alcoholics anonymous (MELD 14, CTP 6.5)</td>
<td>Outpatient &amp; Multicenter</td>
<td>June 2000 - Jan 2004</td>
<td>MET</td>
<td>Addiction therapy</td>
<td>Individual</td>
<td>7</td>
<td>50</td>
<td>6</td>
<td>None</td>
<td>15.7; B.1, D</td>
<td>0.05</td>
<td>6</td>
</tr>
<tr>
<td>C. Age 49 years, Race 76% white &amp; 22% other; Male 62.5% 15 years of alcohol abuse</td>
<td>45</td>
<td>0</td>
<td>Alcoholics anonymous (MELD 14, CTP 6.5)</td>
<td>Referral to community Alcoholics Anonymous &amp; standard intensive outpatient therapy</td>
<td>NA</td>
<td>Individual</td>
<td>NA</td>
<td>50</td>
<td>6</td>
<td>None</td>
<td>6.7; B, D</td>
<td>0.05</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donaire 2011 (27)</td>
<td>Age 26.7 years, Male 729</td>
<td>187</td>
<td>27.3</td>
<td>IVF, Oligo of Stress NR / No</td>
<td>Outpatient &amp; Multicenter</td>
<td>Apr 2012 - May 2014</td>
<td>CBT</td>
<td>Public health professionals</td>
<td>Group-based</td>
<td>6</td>
<td>120</td>
<td>3 weeks</td>
<td>NR</td>
<td>50A</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>C. Age 26.7 years, Male 729</td>
<td>168</td>
<td>27.3</td>
<td>IVF, Oligo of Stress NR / No</td>
<td>General health education</td>
<td>Public health professionals</td>
<td>Group-based</td>
<td>6</td>
<td>120</td>
<td>3 weeks</td>
<td>NR</td>
<td>50A</td>
<td>6</td>
<td></td>
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</tr>
<tr>
<td>C. Age 52.8 years, Race: 94% white; Male 100%</td>
<td>29</td>
<td>0</td>
<td>Alcoholics anonymous or alcoholic hepatitis / No</td>
<td>1 or 2-day inpatient stay followed by outpatient visits to single center</td>
<td>Individual &amp; family therapy</td>
<td>24 - 48</td>
<td>NR</td>
<td>24</td>
<td>NR</td>
<td>72A</td>
<td>24</td>
<td>0.02</td>
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<tr>
<td>C. Age 57.2 years, Race: 60% white; Male 100%</td>
<td>32</td>
<td>0</td>
<td>Alcoholics anonymous or alcoholic hepatitis / No</td>
<td>Outpatient at single center</td>
<td>Physicians &amp; mental health providers</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>48</td>
<td>24</td>
<td></td>
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</tr>
<tr>
<td>Wilensky 1999 (21)</td>
<td>Age 51 years, Race: 39% white, 39% black, 9% other; Male 100%</td>
<td>35</td>
<td>0</td>
<td>Alcoholics anonymous / No</td>
<td>Intervention, Aduro medical unit at single center</td>
<td>Motivational interviewing</td>
<td>Director of medical unit, medicine resident, nurses (aide), social worker with training in alcoholism &amp; psychiatric services</td>
<td>Individual &amp; group based</td>
<td>5</td>
<td>All 5 sessions completed in 12 sessions</td>
<td>32; D</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Age 53 years, Race: 39% white, 17% black &amp; 36% other; Male</td>
<td>36</td>
<td>0</td>
<td>Alcoholics anonymous / No</td>
<td>Regular medical care</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>26; D</td>
<td>4</td>
<td>0.05</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Study (Reference)</td>
<td>Sample Characteristics</td>
<td>Participants (N)</td>
<td>Pre-intervention Abstinence (%)</td>
<td>Liver Disease / OLT List</td>
<td>Intervention Setting</td>
<td>Data Collection</td>
<td>Intervention Elements</td>
<td>Intervention Delivered By</td>
<td>Intervention Format</td>
<td>Treatment Sessions (N)</td>
<td>Session Time (minutes)</td>
<td>Treatment Duration (months)</td>
<td>Concurrent Pharmaco-therapy Use</td>
<td>Alcohol Abstinence (%) at longest follow-up</td>
<td>P-value</td>
<td>Longest Follow-up (Months)</td>
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</tr>
<tr>
<td>Khan et al. 2017</td>
<td>100%: 22 years of alcohol abuse</td>
<td>100%: 22 years of alcohol abuse</td>
<td>C = control group, I = intervention group, MET = motivational enhancement therapy, NR = not reported. Measurement of abstinence: A = self-reported, B = biomarker of alcohol use; b1 = breathalyzer; b2 = Carbohydrate-Deficient Transferrin; b3 = Ethyl Glucuronide; b4 = Ethyl Sulfate; b5 = Gamma Glutamyl Transferase / Mean Cellular Volume / AST: ALT ratio&gt;2; b6 = blood alcohol level; C = collateral informant (spouse / family member)</td>
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<tr>
<td>Study, Country (Reference)</td>
<td>Data Collection Setting</td>
<td>Intervention Duration (months)</td>
<td>Concurrent Medication Use</td>
<td>Alcohol Abstinence at Longest Follow-up (months)</td>
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<tr>
<td>Addolarato 2013, Italy (27)</td>
<td>NR</td>
<td>NA</td>
<td>None</td>
<td>25A, B1, B5, D</td>
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<tr>
<td>Proeschold-Bell 2012, United States (28)</td>
<td>NR</td>
<td>NA</td>
<td>16% received baclofen</td>
<td>67.3A, B1, B2, B5, D</td>
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<tr>
<td>Dieperink 2010, United Kingdom (29)</td>
<td>NR</td>
<td>NA</td>
<td>None</td>
<td>36A</td>
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<tr>
<td>King 2012, United States (30)</td>
<td>NR</td>
<td>NA</td>
<td>Acamprosate (n=3) and disulfiram (n=1)</td>
<td>44A</td>
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<tr>
<td>Georgiou 2003, United Kingdom (31)</td>
<td>NR</td>
<td>NA</td>
<td>None</td>
<td>55A, B6, D</td>
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<tr>
<td>Anderson 2013, Denmark (26A, D)</td>
<td>NR</td>
<td>NA</td>
<td>None</td>
<td>26A, D</td>
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</tr>
<tr>
<td>Khan et al. 2013, Italy (35)</td>
<td>NR</td>
<td>NA</td>
<td>None</td>
<td>68.8B1</td>
<td></td>
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</tr>
</tbody>
</table>

**Notes:**
- NR: Not reported.
- **I:** Age: 55 years (median); 63% males; 23.64 years of alcohol abuse; 23.9% with HCV; 7.6% with HBV; 64% white, 36% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **C:** Age: 54.5 years (median); 79% males; 18 years of alcohol abuse; 49.8% with HCV; 11% with HBV; 74% white, 26% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **C:** Age: 47.97 years; 89% males; 23.6 years of alcohol abuse; 30% with HCV; 20% with HBV; 71% white, 29% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 50.33 years; 89% males; 18 years of alcohol abuse; 30% with HCV; 20% with HBV; 71% white, 29% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 48.7 years; 60.4% males; 17 years of alcohol abuse; 30% with HCV; 20% with HBV; 71% white, 29% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **C:** Age: 48.9 years; 60.4% males; 17 years of alcohol abuse; 30% with HCV; 20% with HBV; 71% white, 29% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.3 years; 60.4% males; 19 years of alcohol abuse; 30% with HCV; 20% with HBV; 71% white, 29% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.1 years; 62% caucasian, 16% black, 17% Hispanic; 19% with HCV; 11% with HBV; 74% white, 26% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.3 years; 60.4% males; 19 years of alcohol abuse; 30% with HCV; 20% with HBV; 71% white, 29% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.1 years; 62% caucasian, 16% black, 17% Hispanic; 19% with HCV; 11% with HBV; 74% white, 26% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.3 years; 60.4% males; 19 years of alcohol abuse; 30% with HCV; 20% with HBV; 71% white, 29% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.1 years; 62% caucasian, 16% black, 17% Hispanic; 19% with HCV; 11% with HBV; 74% white, 26% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.3 years; 60.4% males; 19 years of alcohol abuse; 30% with HCV; 20% with HBV; 71% white, 29% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.1 years; 62% caucasian, 16% black, 17% Hispanic; 19% with HCV; 11% with HBV; 74% white, 26% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.3 years; 60.4% males; 19 years of alcohol abuse; 30% with HCV; 20% with HBV; 71% white, 29% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
- **I:** Age: 51.1 years; 62% caucasian, 16% black, 17% Hispanic; 19% with HCV; 11% with HBV; 74% white, 26% black, 4% Hispanic, 2% Asian & Native American, 1% other races.
<table>
<thead>
<tr>
<th>Study, Country (Reference)</th>
<th>Sample Characteristics (Mean)</th>
<th>Participants (N)</th>
<th>Pre-intervention abstinence</th>
<th>Liver disease / On OLT list</th>
<th>Data Collection</th>
<th>Intervention setting</th>
<th>Intervention elements</th>
<th>Intervention Delivered By</th>
<th>Intervention Format</th>
<th>Treatment Sessions (N)</th>
<th>Session Time (minutes)</th>
<th>Treatment Duration (months)</th>
<th>Concurrent Pharmacotherapy use</th>
<th>Alcohol Abstinence at longest follow-up</th>
<th>P-value</th>
<th>Longest Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieber 2003, United States (32)</td>
<td>Age: 48.8 years; 97% male; 19 years of alcohol abuse</td>
<td>789</td>
<td>0</td>
<td>Alcoholic fibrosis / No</td>
<td>NR</td>
<td>Outpatient; Multicenter</td>
<td>CBT</td>
<td>Nurse; Physician</td>
<td>Individual</td>
<td>Monthly for 4 years</td>
<td>NR</td>
<td>None</td>
<td>17.3 A, B, 2</td>
<td>NR</td>
<td>A, B, 24</td>
<td>NR</td>
</tr>
<tr>
<td>Ink 1991, France (33)</td>
<td>Age: 42 years; 70.7% males</td>
<td>147</td>
<td>0</td>
<td>Alcoholic cirrhosis &amp; decompensated alcoholic cirrhosis / No</td>
<td>Jan 1983 – Jan 1987</td>
<td>Inpatient; Hepatogastroenterology unit at single center</td>
<td>Psychoeducation</td>
<td></td>
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</tr>
</tbody>
</table>

C=control group, HCC=hepatocellular carcinoma, I=intervention group, MET=motivational enhancement therapy, NR=not reported, Measurement of abstinence: A=self-reported, B=biomarker of alcohol use; b1=breathalyzer; b2=Carbohydrate-Deficient Transferrin; b3= Ethyl Glucuronide; b4= Ethyl Sulfate; b5= Gamma Glutamyl Transferase / Mean Cellular Volume / AST: ALT ratio>2; b6= blood alcohol level; C= collateral informant (spouse / family member)
<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Treatment allocation</th>
<th>Similarity of groups</th>
<th>Implementation of blinding</th>
<th>Transparent patient flow</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Summarized validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dieperink 2014</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
</tr>
<tr>
<td>Weinrieb 2011</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
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<tr>
<td>Drumright 2011</td>
<td>Low risk of bias</td>
<td>Unclear risk of bias</td>
<td>High risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
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</tr>
<tr>
<td>Willenbring 1999</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>High risk of bias</td>
<td>Unclear risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
<td>High risk of bias</td>
</tr>
<tr>
<td>Kuchipudi 1990</td>
<td>High risk of bias</td>
<td>Unclear risk of bias</td>
<td>Low risk of bias</td>
<td>Unclear risk of bias</td>
<td>Low risk of bias</td>
<td>Low risk of bias</td>
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</tr>
</tbody>
</table>
## Table 4

### Risk of bias of non-randomized trials

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Reporting</th>
<th>External validity</th>
<th>Internal validity - bias</th>
<th>Internal validity - confounding (selection bias)</th>
<th>Power</th>
<th>Cumulative Score</th>
<th>Cumulative risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2013</td>
<td>0 0 1 1 0 1 1 0 0 0</td>
<td>1 Were the subjects asked to participate in the study representative of the entire population from which they were recruited?</td>
<td>1 Was an attempt made to blind study subjects to the intervention they have received?</td>
<td>1 Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?</td>
<td>1 Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?</td>
<td>0</td>
<td>Medium</td>
</tr>
</tbody>
</table>

- **Is the hypothesis/aim/objective of the study clearly described?**
- **Are the main outcomes to be measured clearly described in the Introduction or Methods section?**
- **Are the characteristics of the patients included in the study clearly described?**
- **Are the interventions of interest clearly described?**
- **Are the distribution of principal confounders in each group of subjects to be compared clearly described?**
- **Are the main findings of the study clearly described?**
- **Does the study provide estimates of the random variability in the data for the main outcome?**
- **Have all important adverse events that may be a consequence of the intervention been reported?**
- **Have the characteristics of patients lost to follow-up been described?**
- **Have actual probability values been reported for the main outcomes, except where the probability value is less than 0.001?**

1. Anderson 2013
<table>
<thead>
<tr>
<th></th>
<th>Reporting</th>
<th>External validity</th>
<th>Internal validity - bias</th>
<th>Internal validity - confounding (selection bias)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
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<td>Addolorato 2013</td>
<td>1 1 1 1 0 1 0 0 0 1 1 1 0 0 1 1 1 1 0 0 0 0 0 1</td>
<td>0 0</td>
<td>1 1 1 1 1 0 0 0 0 1</td>
<td>0 0</td>
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<tr>
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<td>1 1 1 1 0 1 0 0 1 1 1 1 1 1 0 1 1 NA 1 1 1 NA NA NA NA 0 1</td>
<td>0 0</td>
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<td>0 0</td>
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<td>Georgiou 2003</td>
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