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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.

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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[9–11]

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[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[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[18] including use of an *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 (≥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 ≥7, a MELD score ≥10, decompensated cirrhosis (e.g., ascites, hepatic encephalopathy or variceal bleeding) or were defined by study authors as such. 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[19] for RCTs, and a checklist designed by Downs and Black[20] 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)[21–25] and 8 non-randomized or observational studies (N = 2 non-randomized cohort studies with historical control groups[26, 27] and N = 6 uncontrolled studies using pre-post design[28–33]) 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[21–25]. Mean age of participants was 48 years and more than 90% were males. Two RCTs[22, 23] included patients with chronic HCV, two RCTs[21, 25] included patients with alcoholic cirrhosis and one RCT[24] included patients with ALD and advanced liver disease.

We found four RCTs[21–23, 25] that reported data on induction of alcohol abstinence and one RCT[24] 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[22, 24] were at a low risk of bias and 3 RCTs[21, 23, 25] were at a high risk of bias (Table 3) given selection bias due to significant differences in patient age[21], alcohol consumption[23] and inappropriate randomization[25]. 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[21–23, 25]. The studies considered four different psychosocial interventions grouped into four comparisons: (1) CBT *versus* general health education (one study; N=355 participants)[23], (2) Brief MI *versus* usual care (one study; N=71 participants)[25], (3) MET *versus* general health education or usual care (two studies; N=229 participants)[22, 24] and (4) Integrated combination therapy with MET, CBT and comprehensive medical care *versus* usual care (one study; N= 61 participants)[21]. 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[21]

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-practioner 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[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[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[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[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[28, 29, 32] conducted outside the United States (Table 2). Two were non-randomized cohort studies with historical controls[26, 27] comparing supportive therapy and alcohol education to standard medical care (1 study[26], N = 33 participants) and integrated CBT to supportive therapy (1 study[27], N = 92 participants). The other 6 employed a pre-post design and examined CBT (2 studies[30, 32], N=809), psychoeducation (2 studies[31, 33], N=195 participants), combination therapy with

MET, CBT and psychoeducation (1 study[28], N=53 participants) and combination therapy with MET, CBT and MI (1 study[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[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[26] and 4 pre-post studies[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[27] and 2 pre-post studies[30, 31]) reported data on maintaining alcohol abstinence. Addolorato et al.[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[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[21] or an integrated multidisciplinary team approach by both liver disease and mental health providers in the same location with close communication[27, 29]. Integrated therapy resulted in a significantly higher rate of alcohol abstinence compared to control group in one RCT[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[22–25] and 5 observational studies[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[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[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[21], CBT, MET and psychoeducation[28] and CBT, MET and MI[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 practioner 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[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[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)[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.

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Abbreviations

AUD	alcohol use disorder
CLD	chronic liver disease

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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

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

1. alcohol drinking[mesh:noexp] OR binge drinking[mesh:noexp] OR alcoholic intoxication[mesh:noexp] OR alcoholism[mesh:noexp]
2. (alcohol*[tiab] OR drunkenness[tiab] OR sober[tiab] OR sobriety[tiab])
3. #1 OR #2
4. “Clinical Trial” [Publication Type:NoExp] OR “clinical trial, phase i”[publication type] OR “clinical trial, phase ii”[publication type] OR “clinical trial, phase iii” [publication type] OR “clinical trial, phase iv”[publication type] OR “controlled clinical trial”[publication type] OR “multicenter study”[publication type] OR “randomized controlled trial”[publication type] OR “Clinical Trials as Topic” [mesh:noexp] OR “clinical trials, phase i as topic”[MeSH Terms:noexp] OR “clinical trials, phase ii as topic”[MeSH Terms:noexp] OR “clinical trials, phase iii as topic”[MeSH Terms:noexp] OR “clinical trials, phase iv as topic”[MeSH Terms:noexp] OR “controlled clinical trials as topic”[MeSH Terms:noexp] OR “randomized controlled trials as topic”[MeSH Terms:noexp] OR “early termination of clinical trials”[MeSH Terms:noexp] OR “multicenter studies as topic”[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB]))
5. educational program evaluation[mesh:noexp] OR mental health program evaluation[mesh:noexp] OR program evaluation[mesh:noexp] OR Treatment Effectiveness Evaluation[mesh:noexp]
6. program development[mesh:noexp] AND (evaluation[mesh:noexp] OR Evaluation Criteria[mesh:noexp] OR needs assessment[mesh:noexp] OR risk assessment[mesh:noexp])
7. cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]
8. “Intervention Studies”[mesh:noexp] OR “evaluation studies”[pt] OR “evaluation studies as topic”[mesh:noexp] OR “program evaluation”[mesh:noexp] OR “validation studies as topic”[mesh:noexp] OR (pre-[tiab] AND post-[tiab]) OR

(pretest[tiab] AND posttest[tiab]) OR (program*[tiab] AND (evaluat*[tiab] OR effectiveness[tiab])) OR intervention*[tiab]

9. "Case-Control Studies"[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR "Control Groups"[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR "control group"[TIAB] OR "control groups"[TIAB]
10. ((program[tiab] OR treatment[tiab]) AND (efficacy[tiab] OR effectiveness[tiab] OR evaluat*[tiab] OR significant[tiab] OR reduction[tiab] OR reduce[tiab] OR reducing[tiab]))
11. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. #3 AND #11
13. psychotherapy[mesh:noexp] OR behavior therapy[mesh:noexp] OR aversive therapy[mesh:noexp] OR biofeedback, psychology[mesh:noexp] OR cognitive therapy[mesh:noexp] OR "acceptance AND commitment therapy"[mesh:noexp] OR mindfulness[mesh:noexp] OR relaxation therapy[mesh:noexp] OR meditation[mesh:noexp] OR feedback, psychological[mesh:noexp] OR hypnosis[mesh:noexp] OR nondirective therapy[mesh:noexp] OR psychoanalytic therapy[mesh:noexp] OR psychotherapeutic processes[mesh:noexp] OR psychotherapy, brief[mesh:noexp] OR psychotherapy, multiple[mesh:noexp] OR psychotherapy, psychodynamic[mesh:noexp] OR psychotherapy, rational-emotive[mesh:noexp] OR reality therapy[mesh:noexp] OR milieu therapy[mesh:noexp] OR psychotherapy, group[mesh:noexp] OR couples therapy[mesh:noexp] OR family therapy[mesh:noexp] OR marital therapy[mesh:noexp] OR psychodrama[mesh:noexp] OR role playing[mesh:noexp] OR sensitivity training groups[mesh:noexp] OR residential treatment[mesh:noexp] OR Combined Modality Therapy[mesh:noexp] OR substance abuse treatment centers[mesh:noexp]
14. counseling[mesh:noexp] OR directive counseling[mesh:noexp] OR motivational interviewing[mesh:noexp] OR pastoral care[mesh:noexp]
15. ((alcohol[tiab] AND rehabilitation[tiab]) OR "alcoholics anonymous" [tiab] OR "aversion therapy" [tiab] OR "behavior modification" [tiab] OR "behavior therapy" [tiab] OR psychotherapy[tiab] OR "client centered therapy" [tiab] OR "cognitive behavior therapy" [tiab] OR "cognitive restructuring" [tiab] OR cognitive technique*[tiab] OR cognitive therap*[tiab] OR "covert sensitization" [tiab] OR "Family Therapy" [tiab] OR "gestalt therapy" [tiab] OR "group therapy" [tiab] OR hypnosis[tiab] OR hypnotherapy[tiab] OR "insight therapy" [tiab] OR "motivational enhancement therapy" [tiab] OR "motivational intervention" [tiab] OR "motivational interviewing" [tiab] OR "Network Therapy" [tiab] OR "psychoeducation" [tiab] OR "client education" [tiab] OR "psychotherapeutic counseling" [tiab] OR psychotherapy[tiab] OR "behavior therapy" [tiab] OR "reality therapy" [tiab] OR "rehabilitation counseling" [tiab] OR "self

management" [tiab] OR "therapeutic community" [tiab] OR "combined modality" [tiab] OR ("integrated"[tiab] AND (therapy[tiab] OR treatment[tiab])))

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])
20. liver diseases[mesh:noexp] OR liver cirrhosis[mesh:noexp] OR fibrosis[mesh:noexp] OR fatty liver[mesh:noexp] OR liver diseases, alcoholic[mesh:noexp] OR Liver Cirrhosis, Alcoholic[mesh:noexp] OR hepatitis[mesh:noexp] OR liver[mesh:noexp] OR liver function tests[mesh:noexp] OR jaundice[mesh:noexp] OR liver neoplasms[mesh:noexp]
21. (liver disease*[tiab] OR cirrho*[tiab] OR (liver[tiab] AND fibrosis[tiab]) OR steatosis[tiab] OR "hepatitis c"[tiab] OR hcv[tiab] OR hepatocellular cancer*[tiab] OR liver cancer*[tiab])
22. (substance abuse-related medical condition*[tiab] OR Medically ill alcoholic*[tiab])
23. #20 OR #21 OR #22
24. #19 AND #23

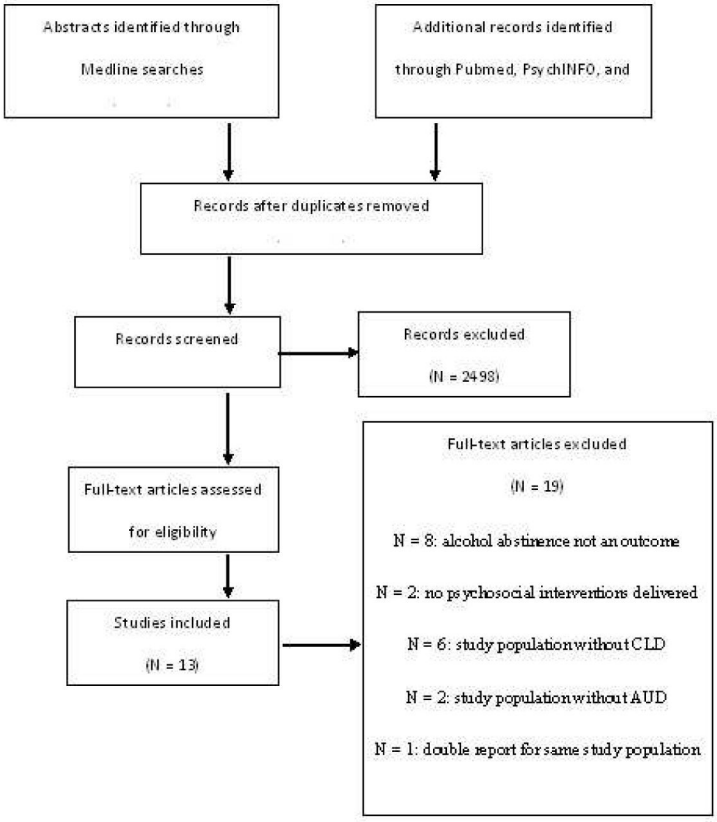

Figure 1.
Search flow diagram, assessment and reporting of included and excluded studies

Table 1

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

Study (Reference)	Sample Characteristics (mean)	Participants (N)	Pre-intervention Abstinence (%)	Liver Disease / On OLT List	Intervention Setting	Data Collection	Intervention Elements	Intervention Delivered By	Intervention Format	Treatment Sessions (N)	Session Time (minutes)	Treatment Duration (months)	Concurrent Pharmaco-therapy Use	Alcohol Abstinence (%) at longest follow-up	P-value	Longest Follow-up (Months)
Dieperink 2014 (22)	I: Age 55.8 years; Race 68.6% white, 28.6% black & 2.9% other; Male 97.1%	70	0	HCV (Stage of fibrosis NR) / No	Outpatient; Multicenter	Nov 2008 – July 2012	MET	1 physician & 5 psychologists	Individual	4	30 – 45	3	None	25.4[A, B1, B2, B3, B4]	0.45	6
	C: Age 55.2 years; Race 66.2% white, 30.9% black, 2.9% native American; Male 94.1%	68	0	HCV (Stage of fibrosis NR) / No			General health education	1 physician & 5 psychologists	Individual	4	30 – 45	3	1 control had 2 month supply of Naltrexone	19.7[A, B1, B2, B3, B4]		6
Weinrieb 2011 (24)	I: Age 50.5 years; Race 85% white & 15% other; Male 84.8%; 20.5 years of alcohol abuse	46	89.1	Alcoholic cirrhosis (MELD 14.5, CTP 8.5) / Yes	Outpatient; Multicenter	June 2000 – Jan 2004	MET	Addiction therapist	Individual	7	50	6	None	15.2[A, B1, D]	0.95	6
	C: Age 48 years; Race 78% white & 22% other; Male 82%; 15 years of alcohol abuse	45	91.1	Alcoholic cirrhosis (MELD 14, CTP 8) / Yes			Referral to community Alcoholics Anonymous & standard intensive outpatient therapy	NA	Individual	NA	50	6	None	6.7[A, B1, D]		6
Drumright 2011 (23)	I: Age 26.7 years; Male 75%	187	27.3	HCV (Stage of fibrosis NR) / No	Outpatient; Multicenter	Apr 2002 – May 2004	CBT	Public health professionals	Group based	6	120	3 weeks	NR	50[A]	>0.05	6
	C: Age 26.7 years; Male 75%	168	27.3	HCV (Stage of fibrosis NR) / No			General health education	Public health professionals	Group based	6	120	3 weeks	NR	50[A]		6
Willenbring 1999 (21)	I: Age: 52.8 years; Race: 94% white; Male 100%	29	0	Alcoholic cirrhosis or alcoholic hepatitis / No	1 or 2 day inpatient stay followed by outpatient visits at single center	NR	Integrated combination therapy with CBT, MET & comprehensive medical care	Primary care physician or nurse-practioner or both	Individual & family therapy	24 – 48	NR	24	NR	74[A]	0.02	24
	C: Age: 57.2 years; Race: 46% white; Male 100%	32	0	Alcoholic cirrhosis or alcoholic hepatitis / No	Outpatient at single center		Referral to general and specialty medicine clinics & mental health services of the hospital	Physicians & mental health providers	NA	NA	NA	NA	NR	48[A]		24
Kuchipudi 1990 (25)	I: Age: 51 years; Race: 38% white, 20% black % 1% oriental; Male 100%; 22 years of alcohol abuse	35	0	Alcoholic cirrhosis / No	Inpatient; Acute medical unit at single center	NR	Motivational Interviewing	Director of medical unit, medicine resident, nurse or gastroenterology fellow, social worker with training in alcoholism & psychiatric nurse therapist	Individual & group based	5	All 5 sessions completed in 120 minutes	NA	NR	32[A, D]	>0.05	4
	C: Age: 53 years; Race: 36% white, 17% black & 36% oriental; Male	36	0	Alcoholic cirrhosis / No			Regular medical care	NR	NA	NA	NA	NA	NR	29[A, D]		4

Study (Reference)	Sample Characteristics (mean)	Participants (N)	Pre-intervention Abstinence (%)	Liver Disease / On OLT List	Intervention Setting	Data Collection	Intervention Elements	Intervention Delivered By	Intervention Format	Treatment Sessions (N)	Session Time (minutes)	Treatment Duration (months)	Concurrent Pharmaco-therapy Use	Alcohol Abstinence (%) at longest follow-up	P-value	Longest Follow-up (Months)
	100%; 22 years of alcohol abuse 100%; 22 years of alcohol abuse															

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>2; **b6**= blood alcohol level; **C**= collateral informant (spouse / family member)

ention Delivered By	Intervention Format	Treatment Sessions (N)	Session Time (minutes)	Treatment Duration (months)	Concurrent Pharmacotherapy use	Alcohol Abstinence at longest follow-up	P-value	Longest Follow-up (months)
, 2 social workers, sician & dietician	Individual & family based	52 (Weekly for 1 year)	60	12	None	26A, D	NR	9
NA	NA	NA	NA	NA	NA	7.10A, D		10.3
physicians in training, logists (expertise in lism, hepatology & neuroscience)	Individual	Weekly for first month, every other week for second & third month and then monthly	30	NA	16% received baclofen	67.3A, B1, B2, B5, D	0.03	NR
iatrist (expertise in iction medicine)	NR	Monthly	NR	NR	None	25A, B1, B5, D		NR
specialist; Psychiatrist	Individual & group based for 6 months.	Weekly group therapy and biweekly individual therapy	NR	6	Acamprosate (n=3) and disulfiram (n=1	44A	<0.01	6
iatrists, 1 Psychiatric rse-specialist (PCNS); cologist; 1 Infectious specialist; 2 Nurse-practitioners	Individual	1 brief session; 4.5 sessions with PCNS	Brief session: 5 – 10; PCNS: 30	6	Pharmacotherapy using either naltrexone or disulfiram offered to all patients but none elected to receive	36A	NR	22
c nurse, psychiatrist & social worker	Family based	3	60	3	None	55A, B6, D	NR	6
NR	Group based	6	NR	6	None	68.8B1	NR	6

Study, Country (Reference)	Sample Characteristics (Mean)	Participants (N)	Pre-intervention abstinence	Liver disease / On OLT list	Data Collection	Intervention setting	Intervention elements	In
Lieber 2003, United States (32)	Age: 48.8 years; 97% male; 19 years of alcohol abuse	789	0	Alcoholic fibrosis / No	NR	Outpatient; Multicenter	CBT	
Ink 1991, France (33)	Age: 42 years; 70.7% males	147	0	Alcoholic cirrhosis & decompensated alcoholic cirrhosis / No	Jan 1983 – Jan 1987	Inpatient; Hepatogastroenterology unit at single center	Psychoeducation	

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 3

Risk of bias for randomized controlled trials

Study	Randomization	Treatment allocation	Similarity of groups	Implementation of blinding	Transparent patient flow	Incomplete outcome data	Selective reporting	Summarized validity
Dieperink 2014	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Weinrieb 2011	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Drumright 2011	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Willenbring 1999	Low risk of bias	Low risk of bias	High risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Kuchipudi 1990	High risk of bias	Unclear risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias

Table 4

Risk of bias of non-randomized trials

	Reporting										External validity			Internal validity - bias							Internal validity - confounding (selection bias)						Power			
Study, year	**1** Is the hypothesis/aim/objective of the study clearly described? **2** Are the main outcomes to be measured clearly described in the Introduction or Methods section? **3** Are the characteristics of the patients included in the study clearly described? **4** Are the interventions of interest clearly described? **5** Are the distribution of principal confounders in each group of subjects to be compared clearly described? **6** Are the main findings of the study clearly described? **7** Does the study provide estimates of the random variability in the data for the main outcome? **8** Have all important adverse events that may be a consequence of the intervention been reported? **9** Have the characteristics of patients lost to follow-up been described? **10** Have actual probability values been reported for the main outcomes, except where the probability value is less than 0.001?										**1** Were the subjects asked to participate in the study representative of the entire population from which they were recruited? **2** Were those subjects who were prepared to participate representative of the entire population from which they were recruited? **3** Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?			**1** Was an attempt made to blind study subjects to the intervention they have received ? **2** Was an attempt made to blind those measuring the main outcomes of the intervention? **3** If any of the results of the study were based on "data dredging", was this made clear? **4** In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? **5** Were the statistical tests used to assess the main outcomes appropriate? **6** Was compliance with the intervention/s reliable? **7** Were the main outcome measures used accurate (valid and reliable)?							**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? **2** Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? **3** Were study subjects randomised to intervention groups? **4** Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? **5** Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? **6** Were losses of patients to follow-up taken into account?						**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%?		Cumulative Score	Cumulative risk of bias
Anderson 2013	0	0	1	1	0	1	1	0	0	0	1	1	0	0	0	1	0	0	1	1	1	0	0	0	0	0	0		10/27	Medium

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	Reporting										External validity			Internal validity - bias							Internal validity - confounding (selection bias)						Power	
Addolorato 2013	1	1	1	1	0	1	0	0	0	1	1	1	0	0	0	1	0	1	1	1	1	0	0	0	0	1	0	14/27
Proeschold-Bell 2012	1	1	1	1	0	1	0	0	1	1	1	1	1	0	1	1	NA	1	1	1	NA	NA	NA	NA	0	1	0	16/27
Dieperink 2010	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	NA	1	1	1	NA	NA	NA	NA	0	1	0	16/27
Georgiou 2003	1	0	1	1	0	1	1	0	0	0	1	1	1	0	0	1	NA	0	1	1	NA	NA	NA	NA	0	1	0	10/27
Erim 2003	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	NA	1	1	1	NA	NA	NA	NA	0	1	5	16/27
Lieber 2003	1	1	1	1	0	0	1	0	1	0	1	1	1	0	0	1	NA	0	1	0	NA	NA	NA	NA	0	1	0	10/27
Ink 1991	1	1	1	1	0	1	1	0	0	0	1	1	1	0	0	1	NA	1	1	1	NA	NA	NA	NA	0	1	0	14/27

NA=0