The Efficacy of Disulfiram for the Treatment of Alcohol Use Disorder
Charlotte H. Jørgensen, Bolette Pedersen, and Hanne Tønnesen

**Background:** Alcohol use disorders (AUD) involving hazardous, harmful, and addictive misuse of alcohol are widespread in most parts of the world. The aim of this study was to review the effect of disulfiram in the treatment of patients with AUD. The effect of disulfiram was evaluated according to the primary outcome of an intake of alcohol below 30 and 20 g/d for men and women, respectively, as well as secondary outcomes such as days until relapse, alcohol intake, and numbers of drinking days.

**Methods:** A systematic review of the literature was conducted using MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL).

**Results:** Eleven randomized controlled trials were included with a total of 1,527 patients. They compared disulfiram treatment with placebo, none or other abstinence-supportive treatments. Overall, 6 studies reported a significant better effect on abstinence for patients treated with disulfiram. Six of 9 studies measuring secondary outcomes reported that patients treated with disulfiram had significantly more days until relapse and fewer drinking days, respectively. The quality of the included studies was moderate. Heterogeneity was significant in most of the meta-analyses, but valid results were found regarding the effect of disulfiram versus placebo over 12 months and unsupervised disulfiram versus other or no treatment. The vast majority of significant studies were of shorter duration, while only 3 studies of 12 months were significant regarding more days until relapse and/or reduction in drinking days.

**Conclusions:** Supervised treatment with disulfiram has some effect on short-term abstinence and days until relapse as well as number of drinking days when compared with placebo, none, or other treatments for patients with alcohol dependency or abuse. Long-term effect on abstinence has not been evaluated yet. However, there is a need for more homogeneous and high-quality studies in the future regarding the efficacy of disulfiram.

**Key Words:** Disulfiram, Alcohol Use Disorder, Alcohol Treatment, Alcohol Abstinence.

MORE THAN 75 million people worldwide are diagnosable with alcohol use disorders (AUD) involving the hazardous, harmful, and addictive misuse of alcohol (World Health Organization 1992, 2010).

A range of interventions has been developed to deal with alcohol-related problems, pharmaceutical as well as nonpharmaceutical (Ferri et al., 2006; Kaner et al., 2007; Mann, 2004; McQueen et al., 2005). The last group includes brief intervention, specialized treatment programs, and mutual help groups such as Alcoholics Anonymous. Brief intervention is most often used with patients who are not alcohol dependent, and its goal may be moderate drinking rather than abstinence. Specialized treatment programs often aim at the treatment for alcohol withdrawal symptoms and prevention of relapse as well as social and psychological rehabilitation (Room et al., 2005). In the forefront of the pharmacological options currently are acamprosate, naltrexone, and the eldest one disulfiram.

Disulfiram inhibits the liver enzyme aldehyde dehydrogenase. Alcohol intake during treatment leads to the accumulation of acetaldehyde, which probably causes the disulfiram–ethanol reaction in the form of increased pulse and respiration, tachycardia, facial flushing, nausea, vomiting, hypotension, and, at worst, cardiovascular collapse. Disulfiram is therefore indicated for patients who wish to remain abstinent (Center for Substance Abuse Treatment 1993). Today, disulfiram is used only in a supervised manner and, like acamprosate and naltrexone, combined with behavioral therapy in the treatment of persons with AUD. However, the effect of disulfiram treatment has not recently been systematically reviewed.

The aim of this review was therefore to evaluate the effect of disulfiram compared with placebo treatment as usual, none, or other interventions for patients with AUD.

**MATERIALS AND METHODS**

**Search Strategy**

The literature search was conducted in the following databases: MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL).
MEDLINE. The search was conducted on the word “disulfiram [Mesh],” restricted to randomized controlled trials (RCTs), and followed by this search strategy:

# 1: Alcohol cessation OR non-AUD OR non-AUD OR alcohol withdrawal OR alcohol relapse OR alcohol temperance OR alcohol reduction OR ethanol withdrawal OR ethanol relapse OR ethanol temperance OR ethanol reduction.

# 2: Disulfiram OR Disulfiram treatment OR Antabuse OR Antabuse treatment.

# 3: Ethanol use disorder OR AUD OR AUD OR alcohol misuse OR ethanol misuse OR alcohol* OR alcohol consumption OR ethanol consumption OR alcohol dependency OR alcohol dependence OR alcohol abuse OR alcohol relapse OR alcohol drinking OR ethanol drinking OR alcohol craving OR ethanol craving OR excessive drink* OR hazardous drink* OR binge drink* OR drinking problem OR alcoholic.

# 4: #1 AND #2 AND #3.

EMBASE AND CENTRAL. The search was conducted on the word “disulfiram” and restricted to RCTs.

Reference lists and related articles were reviewed manually to identify additional articles. After the systematic search and supplemental hand search, titles and abstracts were sorted and 2 persons independently evaluated potentially relevant studies. In 1 case, a correspondence with an author was established in order to clarify discrepancies in the study (Ulrichsen et al., 2010).

AUD were defined as an intake of alcohol above the criteria of risk drinking according to British Medical Association (BMA) (1995), described as >20 g/d for women and >30 g/d for men. AUD include hazardous and harmful use as well as the alcohol dependence syndrome (American Psychiatric Association 1994; World Health Organization 1992, 2010).

Outcomes

The primary outcome was continuous intake below 20 and 30 g/d for women and men, respectively, including abstinence at follow-up, and the secondary outcomes were number of days until relapse, reduced alcohol intake, and numbers of drinking days, all evaluated by the end of the study.

Criteria for Considering Studies for This Review

Types of Studies. Only RCTs were enrolled: trials studying disulfiram in various doses with or without a control group and/or trials investigating disulfiram against placebo, no treatment, or other medical or behavioral treatments.

Exclusion criteria were studies published several times, subanalyses of already published material, studies without relevant primary outcome (i.e., studies not reporting continuous alcohol intake below 30 and 20 g/d for men and women, respectively, including abstinence at the end of the study), studies that were not RCTs or not based on an intention-to-treat (ITT) analysis, and studies that combined disulfiram with other treatments.

Types of Participants. The enrolled patients were either inpatients or outpatients of 15 years of age or older diagnosed with AUD.

Types of Intervention. The intervention should consist of disulfiram treatment versus placebo, nothing, behavioral therapy, or other pharmacotherapies such as acamprosate and naltrexone.

Data Extraction and Analysis

The following data were extracted from the included studies: Authors, publication year, study design, the length of the study, inclusion and exclusion characteristics, number and characteristics of participants, baseline alcohol intake, alcohol intake before inclusion, type of intervention, degree of follow-up, outcomes, sequence generation, allocation concealment, blinding, inclusion, compliance and follow-up rate.

The RCTs included in this review were assessed for methodological quality using “The Cochrane Collaboration’s tool for assessing risk of bias” (Higgins, 2009) including adequate sequence generation, allocation concealment, blinding, incomplete data addressed, and the assessment of the presence of selective reporting or other bias. The blinding was considered sufficient even if only the investigator was blinded because the patient could easily break the blinding by ingesting alcohol.

Review Manager (RevMan) version 5.0 (2008) was used for data analysis. Heterogeneity among studies was calculated using the $I^2$ statistic, which describes the percentage of the variability in effect estimates that is attributable to heterogeneity rather than sampling error, that is, chance (Higgins, 2003).

Meta-analyses were not considered appropriate if the $I^2$ values exceeded 40%.

RESULTS

The search resulted in a total of 590 articles. Of these, 564 were excluded owing to the fact that they were duplicates or had no relevance to this study. The remaining 26 potentially appropriate studies were reviewed, and another 15 excluded in accordance with the inclusion criteria (Fig. 1).

Eleven remaining randomized clinical trials with a total of 1,527 patients fulfilled the inclusion criteria (Table 1).

Characteristics of Included Studies

The 11 randomized clinical trials were published from 1979 to 2010 and included between 26 and 605 patients—an average of 139 patients. The median inclusion rate was 58% (range 8 to 85), and the studies had duration of between 2 and 12 months with a mean of 8 months.

The studies originated from India (4), Denmark (2), United States (2), Austria (1), Finland (1), and Italy (1).

The patients consisted predominantly of men with alcohol dependence according to DSM system (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Nava et al., 2006; Niederhofer and Staffen, 2003) aged 15 to 76 years. In the 4 remaining trials, patients used alcohol in a hazardous way (Tonnesen et al., 1999), in a harmful/dependent way (Fuller and Roth, 1979; Fuller et al., 1986), or had alcohol dependence according to the International Classification of Diseases (ICD-10) (Laaksonen et al., 2008; Ulrichsen et al., 2010).

Patients were recruited through the media or contacted because they were under alcohol treatment or sought alcohol treatment themselves. Thus, patients in several studies were undergoing detoxification at the onset of the study (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Ulrichsen et al., 2010), and in 2 trials, patients were expected to have been abstinent for 14 and 5 days before enrollment, respectively (Nava et al., 2006; Niederhofer and Staffen, 2003).
In addition, it was required in 8 studies that the patient did not live alone or lacked a friend or spouse who could do the drug administration as well as provide information on patient compliance and alcohol ingestion (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Fuller and Roth, 1979; Fuller et al., 1986; Laaksonen et al., 2008; Nava et al., 2006). Baseline alcohol consumption ranged from 6 to 7 units (each of 12 g/d) (Tonnesen et al., 1999) (Danish study) to 9 to 11 units (each of 10 g/d) (Nava et al., 2006) (Italian study).

Three studies compared disulfiram with placebo (Fuller and Roth, 1979; Fuller et al., 1986; Niederhofer and Staffen, 2003), 2 compared disulfiram with a control group (Tonnesen et al., 1999; Ulrichsen et al., 2010), and 6 compared disulfiram with other abstinence-supportive drugs (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Laaksonen et al., 2008; Nava et al., 2006).

In 10 of 11 studies (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Fuller and Roth, 1979; Fuller et al., 1986; Laaksonen et al., 2008; Nava et al., 2006; Tonnesen et al., 1999; Ulrichsen et al., 2010), pharmacological treatment was supplemented with either cognitive therapy, psychotherapy, or alcohol counseling 1 to 2 times/wk, which in most cases was voluntary to the patient.

None of the studies used this review’s primary outcome as explicit outcome but instead used abstinence. The definition of abstinence and relapse varied between trials. Three studies (De Sousa and De Sousa, 2004, 2005; De Sousa et al., 2008) defined relapse as an intake of more than 5 units of alcohol (each of 8 g/d corresponding to a “heavy drinking day,” HDD) while abstinence in the other studies were similar to no alcohol intake. One study (Nava et al., 2006) defined an intake of more than 4 to 5 units/d as an HDD. Another study (Laaksonen et al., 2008) had included abstinent days per week, an average weekly alcohol intake as secondary outcome but used per-protocol analyses, and these results are therefore not included. However, we have included their results regarding time to first HDD and time to first drinking day after medication start, which were analyzed according to ITT.

Monitoring and control of abstinence and compliance were carried out with very different intervals and conducted using different methods. Overall, compliance and alcohol intake were assessed using self-report through interview techniques such as timeline follow-back in all of the studies (Carney, 1998). This was supplemented by the feedback of the relative in 6 of the 10 studies (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Fuller and Roth, 1979; Fuller et al., 1986) as well as pill/bottle counts, urine drug screenings, blood tests, and/or breathe analyzer in 6 trials (Fuller and Roth, 1979; Fuller et al., 1986; Laaksonen et al., 2008; Nava et al., 2006; Niederhofer and Staffen, 2003; Ulrichsen et al., 2010).

The patients that respectively took medication regularly and participated in a minimum of follow-up sessions were classified as compliant and completers. The median compliance rate was 85% (range 19 to 100), and the median follow-up rate was 93% (range 18 to 100) (Table 1).

**Assessment of Risk of Bias**

Overall, the studies were assessed to be at moderate risk of bias (Table 2). Only 3 studies were at low risk of bias (Fuller and Roth, 1979; Fuller et al., 1986; Tonnesen et al., 1999). Generation of sequence allocation and allocation concealment were adequate in all but 1 study (Niederhofer and Staffen, 2003). Blinding was considered adequate if only the investigator of outcomes was blinded, which was the case in only 4 of the 10 studies (Fuller and Roth, 1979; Fuller et al., 1986; Niederhofer and Staffen, 2003; Tonnesen et al., 1999). The remaining 7 were open studies not blinded to either participants or outcome assessors. All studies were assessed to be at low risk of bias regarding incomplete outcome data and selective reporting as well as other bias apart from 1 study (Ulrichsen et al., 2010).

**The Effect of Intervention**

**Disulfiram Versus Other Pharmacological Abstinence-Supportive Drugs.** The 6 studies that compared disulfiram with other abstinence-supportive pharmacotherapy had duration of, respectively, 6, 8, 9, 12, 12, and 12 months (Table 3). Four of these studies (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008) reported significantly more abstinent patients (respectively, 86 vs. 44%, 88 vs. 46%, 90 vs.
Table 1. Included Studies

<table>
<thead>
<tr>
<th>References</th>
<th>Inclusion rate (%)</th>
<th>Participants</th>
<th>Definition of AUD and other measures</th>
<th>Intervention</th>
<th>Compliance rate (%)</th>
<th>Follow-up rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Sousa and De Sousa (2004), India</td>
<td>55</td>
<td>100 patients with AUD 18 to 65 years</td>
<td>Alc. dependence (DSM-IV) Baseline: 12 to 13 units/d (1 unit = 8 g) Relapse defin.: &gt;5 units (40 g alc./24 h)</td>
<td>1: DIS 250 mg/d</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>De Sousa and De Sousa (2005), India</td>
<td>60</td>
<td>100 patients with AUD 18 to 65 years</td>
<td>Alc. dependence (DSM-IV) Baseline: 10 to 12 units/d (1 unit = 8 g) Relapse defin.: &gt;5 units (40 g alc./24 h)</td>
<td>1: DIS 250 mg/d</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td>De Sousa and De Sousa (2008), India</td>
<td>58</td>
<td>100 patients with AUD 18 to 65 years</td>
<td>Alc. dependence (DSM-IV) Baseline: 9 to 11 units/d (1 unit = 8 g) Relapse defin.: &gt;5 units (40 g alc./24 h)</td>
<td>1: DIS 250 mg/d</td>
<td>98</td>
<td>92</td>
</tr>
<tr>
<td>De Sousa and colleagues (2008), India</td>
<td>85</td>
<td>58 patients with AUD 15 to 18 years</td>
<td>Alc. dependence (DSM-IV) Baseline: 9 to 10 units/d (1 unit = 8 g) Relapse defin.: &gt;5 units (40 g alc./24 h)</td>
<td>1: DIS 250 mg/d 2: NTX 50 mg/d Supervised Duration: 6 months</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Fuller and Roth (1979), USA</td>
<td>25</td>
<td>128 patients with AUD &lt; 60 years</td>
<td>Baseline: Unknown</td>
<td>1: DIS 250 mg/d 2: NTX 50 mg/d Supervised Duration: 6 months</td>
<td>58</td>
<td>98</td>
</tr>
<tr>
<td>Fuller and colleagues (1986), USA</td>
<td>37</td>
<td>605 patients with AUD &lt; 60 years</td>
<td>Alc. dependence according to The National Council on Alcoholism (consistent with DSM and ICD) Baseline: 20 to 21 days with alc. intake the last month</td>
<td>1: DIS 250 mg/d (dbl.-blinded) 2: DIS 1 mg/d (dbl.-blinded) 3: Riboflavine (evaluator blinded) Duration: 12 months</td>
<td>19</td>
<td>95</td>
</tr>
<tr>
<td>Laaksonen and colleagues (2008), Finland</td>
<td>87</td>
<td>243 patients with AUD 25 to 65 years</td>
<td>Alc. dependence (ICD-10) Baseline: ~ 7 units/d (1 unit = 12 g) Relapse defin.: &gt;5 units (40 g alc./24 h)</td>
<td>1: NTX 50 mg/d 2: ACA 666 mg × 3/d 3: DIS 100 to 200 mg/d or 400 mg × 2/wk Duration: 12 months (follow-up: 18 months; overall: 52 months)</td>
<td>76</td>
<td>18</td>
</tr>
<tr>
<td>Nava and colleagues (2006), Italy</td>
<td>75</td>
<td>86 patients with AUD &gt; 18 years</td>
<td>Alc. dependence (DSM-IV) Baseline: 9 to 11 units/d (1 unit = 10 g) Relapse defin.: &gt;5 units (40 g alc./24 h)</td>
<td>1: GHB 50 mg/kg/d 2: NTX 50 mg/d 3: DIS 200 mg/d Supervised Duration: 12 months</td>
<td>Unknown</td>
<td>69</td>
</tr>
<tr>
<td>Niederhofer and Staffen (2003), Austria</td>
<td>Unknown</td>
<td>26 patients with AUD 16 to 19 years</td>
<td>Alc. dependence (DSM-IV) Baseline: Unknown</td>
<td>1: DIS 200 mg/d 2: Placebo Duration: 3 months 1: DIS 800 mg × 2/wk for 3 weeks 2: Control group (no treatment) Supervised Duration: 2 months (1 month prior to and 1 month after surgery)</td>
<td>35</td>
<td>53</td>
</tr>
<tr>
<td>Tonnesen and colleagues (1999), DK</td>
<td>Unknown</td>
<td>42 patients with AUD 37 to 76 years (elective surgery)</td>
<td>Baseline: 6 to 7 units/d (1 unit = 12 g) Relapse defin.: &gt;5 units (40 g alc./24 h)</td>
<td>1: DIS 800 mg × 2/wk for 3 weeks 2: Control group (no treatment) Supervised Duration: 6 months</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Ulrichsen and colleagues (2010), DK</td>
<td>8</td>
<td>39 patients with AUD 18 to 70 years</td>
<td>Alc. dependence (ICD-10) Baseline: Unknown</td>
<td>1: DIS 800 mg × 2/wk for 3 weeks 2: Control group (no treatment) Supervised Duration: 6 months</td>
<td>32</td>
<td>44</td>
</tr>
</tbody>
</table>

ACA, acamprosate; Alc, alcohol; AUD, alcohol use disorders; Defin, definition; DIS, disulfiram; DSM, Diagnostic and Statistical Manual of Mental Disorders; GHB, G-hydroxybutyrate; ICD, International Classification of Diseases; NTX, naltrexone; TPM, topiramate.

56%, and 79 vs. 52%). These studies as well as Laaksonen and colleagues (2008) showed significantly more days until relapse among patients treated with disulfiram. The sixth study showed nonsignificantly fewer abstinent patients and HDDs among the disulfiram-treated patients after 1 year (Nava et al., 2006).
**DISCUSSION**

In terms of the primary outcome, we found that disulfiram had a significantly better effect on abstinence when compared with placebo, none, or other treatment in 6 of the 10 studies (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Fuller and Roth, 1979; Fuller et al., 1986; Nava et al., 2006; Niederhofer and Staffen, 2003; Ulrichsen et al., 2010) could not confirm this effect, but no treatment showed to be significantly better than disulfiram either. Furthermore, 5 of 9 trials with secondary outcomes showed that patients treated with disulfiram had an increased number of days before relapse (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Laaksonen et al., 2008). Though, this positive result could be explained by homogeneity between the 4 studies as they were conducted by the same research group and had similar setup and patient groups.

Previous reviews dealing with the effect of disulfiram report ambiguous results (Garbutt et al., 1999; Hughes and Cook, 1997; Suh et al., 2006). They all point out the difficulties of most studies possessing shortcomings in research design and methodology including lack of blinding, no measurement of treatment adherence, and nonrandomization of subjects, overall leading to diverse outcomes in disulfiram research.

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**Table 2. Risk of Bias Assessment of Included Studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding (of investigator)</th>
<th>Incomplete outcome data addressed</th>
<th>Free from selective reporting</th>
<th>Free from other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Sousa and De Sousa (2004)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>De Sousa and De Sousa (2005)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>De Sousa and De Sousa (2008)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>De Sousa and colleagues (2008)</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Fuller and colleagues (1979)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<tr>
<td>Fuller and colleagues (1986)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Laaksonen and colleagues (2008)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Nava and colleagues (2006)</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Niederhofer and Staffen (2003)</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Tonnesen and colleagues (1999)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ulrichsen and colleagues (2010)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

+, low risk of bias; –, high risk of bias; ?, risk of bias unclear.
Table 3. Primary and Secondary Outcomes at Follow-Up

<table>
<thead>
<tr>
<th>References</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Sousa and De Sousa (2004)</td>
<td>Abstinence 43 (86) DIS, n (%) NTX 22 (44%)</td>
<td>Days until relapse 119 DIS 63 Riboflavin p-value 0.0002*</td>
</tr>
<tr>
<td></td>
<td>Abstinence 44 (88) DIS, n (%) ACA 23 (46%)</td>
<td>Days until relapse 123 DIS 71 Riboflavin p-value 0.0002*</td>
</tr>
<tr>
<td>De Sousa and De Sousa (2008)</td>
<td>Abstinence 45 (90) DIS, n (%) TPM 28 (56%)</td>
<td>Days until relapse 133 DIS 79 Riboflavin p-value 0.0002*</td>
</tr>
<tr>
<td>De Sousa and De Sousa (2008)</td>
<td>Abstinence 23 (79) DIS, n (%) NTX 15 (52%)</td>
<td>Days until relapse 84 DIS 51 Riboflavin p-value 0.0001*</td>
</tr>
<tr>
<td>Fuller and Roth (1979)</td>
<td>Abstinence DIS 250 mg (gr. 1) 9 (21%) DIS 1 mg (gr. 2) 11 (25%) 5 (12%) DIS &gt; riboflavin &gt;0.1</td>
<td>Drinking days DIS 250 mg (gr. 1) 31% DIS 1 mg (gr. 2) 32% Drinking days DIS 250 mg 65 41 NS</td>
</tr>
<tr>
<td>Fuller and colleagues (1986)</td>
<td>Abstinence DIS 250 mg 38 (19%) DIS 1 mg 46 (22%) 32 (16%) 0.25</td>
<td>Days until relapse DIS 250 mg 54 41 NS</td>
</tr>
<tr>
<td>Laaksonen and colleagues (2008)</td>
<td>(no ITT analysis)</td>
<td>Days to first HD day 47 NTX 22 ACA 18 Days until relapse 30 NTX 16 ACA 11 &lt;0.0001* (DIS &gt; NTX and ACA) 0.0002* (DIS &gt; NTX and ACA)</td>
</tr>
<tr>
<td>Nava and colleagues (2006)</td>
<td>Abstinence 12 (40) DIS, n (%) GHB 18 (65%) NTX 13 (49%) 0.08</td>
<td>Alcohol-free days 100 GHB 4 (14%) NTX 7 (26%) Alcohol-free days 100 GHB Control group 76 Control group 100 NS</td>
</tr>
<tr>
<td>Niederhofer and Stoffen (2003)</td>
<td>Abstinence 7 (54) DIS, n (%) Placebo 2 (15%) 0 (0%)</td>
<td>Days until relapse 96 Control group 76 Alcohol-free days 100 Control group 100 NS</td>
</tr>
<tr>
<td>Tonnesen and colleagues (1999)</td>
<td>Abstinence for 1 month DIS, n (%) Control group 20 (100) 0 (0%)</td>
<td>Alcohol-free days 100 Control group 100 NS</td>
</tr>
<tr>
<td>Ulrichsen and colleagues (2010)</td>
<td>Abstinence 5 (26) DIS, n (%) Control group 4 (20%)</td>
<td>Days until relapse 96 Control group 76 Alcohol-free days 100 Control group 100 NS</td>
</tr>
</tbody>
</table>

*Significant.

ACA, acamprosate; DIS, disulfiram; GHB, G-hydroxybutyrate; gr., group; HD, heavy drinking; ITT, intention-to-treat; NS, nonsignificant (p-value not reported); NTX, naltrexone; TPM, topiramate.
This is consistent with the findings of this review. The quality of studies in this review was moderate, and the methods of the studies were somewhat heterogeneous. The main purpose of the studies was not always to investigate the effect of disulfiram but the efficacy of other treatments or parameters as well as the definition of abstinence and relapse varied. Furthermore, the studies were rarely blinded and not all was performed in a supervised manner. These methodological limitations should be considered when interpreting the results of this review along with the possibility of reporting bias and the lack of search for unpublished studies.

Of the 6 studies comparing disulfiram with other pharmacological abstinence-supportive drugs (naltrexone, acamprosate, or topiramate), the majority showed that disulfiram
had a greater effect on abstinence and/or on number of days until relapse (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Laaksonen et al., 2008), while a sixth study showed no significant effect (Nava et al., 2006). All studies were open studies, and thus the expectations of the investigator or other medical staff could possibly have affected patients; however, this would have been possible for both intervention groups. Furthermore, in the studies of De Sousa and De Sousa (2004, 2005, 2008), the definition of relapse was an intake of 4 to 5 units a day, thereby presumably placing not entirely sober patients in the group of abstinent patients.

The 3 studies comparing disulfiram with placebo were all unsupervised. One study (Niederhofer and Staffen, 2003) reported on more abstinent patients among the disulfiram-treated in an unsupervised study of 3 months; however, the trial only included 26 patients. The 2 other studies (Fuller and Roth, 1979; Fuller et al., 1986) that sought to verify the psychological effect of disulfiram could not detect any difference between unsupervised disulfiram and placebo treatment. Compliance rates were, however, very low in all 3 studies—in particular 1 study (Fuller et al., 1986) where only approximately 20% of patients took the medicine. Given this, it is hardly reasonable to conclude anything about the effect of disulfiram, although Fuller and colleagues (1986) could demonstrate significantly fewer drinking days among patients treated with 250-mg disulfiram who had participated in all of the follow-ups. Despite the above-mentioned problems, we found an overall effect on abstinence in these 3 studies using unsupervised disulfiram.

Two small studies compared disulfiram with a control group. One study (Tonnesen et al., 1999) of 42 patients exposed to 1-month intervention showed that surgical patients with high alcohol consumption that were treated with supervised disulfiram and a supporting program twice a week had fewer postoperative complications than those who were not treated with disulfiram. The study lasted only a total of 2 months and tells us nothing about the efficacy of disulfiram in the longer term where surgery is not an influencing factor on the alcohol consumption of the patient.
Another study of 39 patients could not demonstrate any significant differences in abstinence, days until relapse, and alcohol-free days when disulfiram was compared with no treatment (Ulrichsen et al., 2010). However, among the 242 eligible patients in this trial, about 25% refused participation because they only wanted to be treated with disulfiram, which could have led to a subgroup of included patients less receptive to this treatment. This, as well as very low compliance and follow-up rates, could have affected the results of this open study.

Overall, studies of disulfiram have several challenges. Double blinding has been controversial in trials aiming to assess the efficacy of disulfiram, and although double blinding does increase the quality of the study, ethical considerations in treating patients with a not entirely risk-free aversive drug as well as the ease with which the patients can break the blinding by ingesting alcohol argue against this (Fuller, 2004; National Board of Health, 2006). Moreover, it is the fear and discomfort of the disulfiram–ethanol reaction as opposed to an actual pharmacodynamic effect that is presumed to be the action of disulfiram. Double-blinded treatment of patients randomized to a control and a disulfiram group, respectively, would therefore be meaningless in the study of the effects of disulfiram.

Another problem complicating the assessment of disulfiram is when patients do not take the medicine. Earlier on, this was unsuccessfully attempted counteracted by using disulfiram implants, but the bioavailability of these has not shown to be sufficient (Hughes and Cook, 1997). Instead, supervised disulfiram was applied, and it is now a general agreement that supervised disulfiram has better effect on outcome than unsupervised (Garbutt et al., 1999; National Board of Health, 2006; Suh et al., 2006).

That is also consistent with the results of this review, in which disulfiram was found significantly better in terms of abstinence and days until relapse in the supervised studies (De Sousa and De Sousa, 2004, 2005, 2008; De Sousa et al., 2008; Laaksonen et al., 2008; Tonnesen et al., 1999). It was, however, not possible to confirm this from a meta-analysis as the studies were too heterogeneous. This could be explained by 2 of the supervised studies (Tonnesen et al., 1999; Ulrichsen et al., 2010) differing considerably from the other supervised studies regarding objective, treatment duration, and sample size.

The effect of other pharmacological treatments like acamprosate and naltrexone for the maintenance of abstinence from alcohol is well investigated. Particularly, European studies have found that treatment with acamprosate leads to significantly more patients with sustained abstinence after 6 and 12 months compared with placebo (Bouza et al., 2004; Mann et al., 2004). Evidence from American studies on the other hand has been mixed.

The comprehensive COMBINE study showed that treatment with acamprosate was not superior to placebo. Also, no convincing evidence was found regarding the effect of naltrexone over placebo with regard to number of abstinence days (Anton et al., 2006). Other studies have predominately investigated the effect of naltrexone on short term (12 to 16 weeks) and found that naltrexone reduced recidivism significantly compared with placebo (Bouza et al., 2004; Srisurapanont and Jarusuraisin, 2005). A very recent study showed that disulfiram is superior to acamprosate in clinical routine and supports to doubt the effectiveness of acamprosate (Diehl et al., 2010).

Overall, the COMBINE study showed a reduction in alcohol consumption in all treatment groups. This is consistent with the study of Krampe and colleagues (2006) that conducted a 9-year prospective, nonrandomized, open study with supervised administration of respectively disulfiram and a “placebo” drug for the treatment of alcohol-dependent patients. The study showed that patients who took medication longer (>20 months) were also subsequently abstinent for a longer time and had fewer relapses regardless of medical treatment. This illustrates the psychological effect of compliant patients whatever treatment they receive, and the importance of continuous encouragement, guidance, and follow-up in the treatment of patients with alcohol dependence.

The results of this review are primarily representative of men between 15 and 76 years of age diagnosed with alcohol dependence according to the DSM system who sought treatment themselves or had been hospitalized in terms of detoxification prior to inclusion.

The treatment effect among patients with a hazardous use of alcohol is, by contrast, more uncertain, and the results give no information on the effect among patients suffering from other serious physical or mental illnesses. Distinguishing between different characteristics of patients may be of importance when predicting a good outcome as there is some evidence that different subgroups of patients benefit differently from disulfiram. Our results however cannot confirm whether there is a difference between patients with alcohol dependency and patients with a hazardous use of alcohol regarding the effect of disulfiram on abstinence.

By comparison, both randomized and clinical cohort studies have suggested that patient characteristics such as age, duration of AUD, and social stability are related to certain disulfiram treatment outcomes (Azrin, 1982; Fuller et al., 1986; Hughes and Cook, 1997; Suh et al., 2006), but the evidence remains questionable. Another clinical cohort study found that supervised disulfiram as part of comprehensive psychotherapy can be a successful treatment option for patients who do not benefit from other treatment alternatives, and who have high rates of social problems and comorbid psychiatric disorders; an association between age of the patients and treatment success was not found (Ehrenreich and Krampe, 2004). However, more research is needed to ascertain the traits generally associated with a successful outcome in order to select the people that will benefit the most from treatment with disulfiram.

The findings of this review was a tendency to some, albeit short-lived, effect on abstinence and days until relapse in primarily male patients with alcohol dependency treated with
supervised disulfiram. Furthermore, disulfiram tended to reduce the number of drinking days in compliant patients treated for up to 12 months; however, there is a need for more homogenous and high-quality studies in the future regarding the efficacy of disulfiram.

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REFERENCES


