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Supervised disulfiram as adjunct to psychotherapy in alcoholism treatment.

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Abstract

Supervised intake of the alcohol deterrent (AD) disulfiram has proven to be an effective adjunct to biopsychosocial alcoholism therapy for more than 60 years. This article summarizes disulfiram literature between 1937 and 2000 and reviews 13 clinical trials of disulfiram in alcoholism treatment from the years 2000 to 2008. After giving an update of general safety issues and recent case reports concerning safety problems with disulfiram, we focus on the introduction of psychotherapeutic application of supervised disulfiram. The results of our review show: (1) Disulfiram proved to be an effective therapeutic tool in all clinical studies published from 2000 to 2008. (2) Comparisons with other pharmacological agents - naltrexone, acamprosate, topiramate and gamma-hydroxybutyrate - indicate that disulfiram was equal in two trials but superior in the majority of trials. (3) Therapy programs that make use of the psychological effects of supervised disulfiram have - independently of the dose - better results than programs that neglect psychological effects. As a consequence, we suggest that supervised low-dose disulfiram (not more than 100mg/d), will show highest success when it is carefully integrated into psychotherapeutic alcoholism therapy. The major program of psychotherapy with disulfiram comprises the steps "Initial psychoeducation about the effect of disulfiram and its therapeutic implications", "Advanced psychoeducation", and "Disulfiram as coping skill and extension of repertoire of coping skills". As psychological mechanisms of supervised disulfiram we suggest: (1) deterrence; (2) (auto)suggestion; (3) therapeutic ritual around (4) a frequently renewed active decision process; (5) continuous reinforcement of a sober lifestyle and development of new coping skills.

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Disulfiram: an old therapeutic with new applications.

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Abstract

Disulfiram treatment, despite its limitations, remains a viable option as a treatment for alcohol dependence and has shown recent promise in treating (1) those with co-morbid alcohol dependence and post-traumatic stress disorder, (2) those with co-morbid cocaine- and alcohol-dependence, and (3) those with cocaine-dependence alone. Although disulfiram's mechanism of action in alcohol dependence was long thought to be its effects as a psychological deterrent, more recent studies have uncovered potential anti-craving effects as well as direct effects of disulfiram on cocaine abuse, highlighting a few of the many potential and unique benefits disulfiram may have through its inhibition of dopamine beta-hydroxylase. This article will review the major clinical trials of disulfiram spanning nearly 60 years. We will discuss the pharmacodynamics and pharmacokinetics of disulfiram, indications and limitations of its use, suggestions for appropriate patient populations, and monitoring for compliance and adverse effects. We will also review recent literature on newer potential applications for disulfiram use via its unique action on dopamine beta-hydroxylase.

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Alcohol Alcohol. 2010 May-Jun;45(3):271-7. Epub 2010 Mar 26.

Why is disulfiram superior to acamprosate in the routine clinical setting? A retrospective long-term study in 353 alcohol-dependent patients.

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Abstract

AIMS: To compare the long-term effectiveness of acamprosate (ACP) and disulfiram (DSF) in the treatment of alcohol dependence and their effectiveness in regard to patient characteristics, within a naturalistic outpatient treatment setting.

METHOD: Retrospective data from 2002 to 2007 were analysed on 353 alcohol-dependent subjects in outpatient treatment, who, according to the patient's and the clinician's mutual decision, received either supervised DSF (with thrice-weekly appointments) or ACP (once-weekly appointments) following an inpatient alcohol detoxification treatment. Abstinence was assessed by alcohol breathalyzer, patients' self-report, urine and serum analyses, and overall physicians' rating.

RESULTS: Baseline data in terms of current addictive behaviour and course of disease differed between groups to the disadvantage of the DSF group; compared to the ACP group, subjects treated with DSF showed a longer duration of alcohol dependence, higher amounts of daily alcohol consumption and more alcohol detoxification treatments in their history. In follow-up, Kaplan-Meier survival analysis revealed significant differences between groups in the primary and secondary measures of outcome (P always <0.01). Time elapsed before the first alcohol relapse as well as attendance to outpatient treatment and cumulative alcohol abstinence achieved within outpatient treatment was explicitly longer in the DSF group. A longer duration of alcohol dependence predicted a favourable treatment outcome in the DSF group, while for the ACP group the chances for a successful treatment increased with shorter duration of alcohol dependence.

CONCLUSIONS: This study supports the thesis that supervised DSF is an important component of alcoholism treatment, and it appears to be more effective than the treatment with ACP particularly in patients with a long duration of alcohol dependence.

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Alcohol Alcohol. 2005 Nov-Dec;40(6):545-8. Epub 2005 Jul 25.

An open randomized study comparing disulfiram and acamprosate in the treatment of alcohol dependence.

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Abstract

AIMS: To compare the efficacy of acamprosate (ACP) and disulfiram (DSF) for preventing alcoholic relapse in routine clinical practice.

METHODS: One hundred alcoholic men with family members who would encourage medication compliance and accompany them for follow-up were randomly allocated to 8 months of treatment with DSF or ACP. Weekly group psychotherapy was also available. The psychiatrist, patient, and family member were aware of the treatment prescribed. Alcohol consumption, craving, and adverse events were recorded weekly for 3 months and then fortnightly. Serum gamma glutamyl transferase was measured at the start and the end of the study.

RESULTS: At the end of the trial, 93 patients were still in contact. Relapse (the consumption of >5 drinks/40 g of alcohol) occurred at a mean of 123 days with DSF compared to 71 days with ACP (P = 0.0001). Eighty-eight per cent of patients on DSF remained abstinent compared to 46% with ACP (P = 0.0002). However, patients allocated to ACP had lower craving than those on DSF (P = 0.002).

CONCLUSION: DSF is superior to ACP for preventing relapse in alcohol-dependent men with good family support. Further comparisons between these two drugs in different treatment settings and populations are warranted.

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Disulfiram in severe alcoholism--an open controlled study.

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Abstract

BACKGROUND: Disulfiram is used to a great extent in Denmark to treat alcoholism but the evidence is limited.

AIM: To study the effect of supervised disulfiram treatment in alcohol dependence. Subjects were recruited from a psychiatric emergency ward following alcohol withdrawal treatment.

METHODS: A total of n=39 patients were openly randomized to either disulfiram 800 mg twice a week for 26 weeks (n=19) or no disulfiram (n=20). All patients were also treated with cognitive behavioural therapy (CBT) in groups.

RESULTS: The rate of abstinence was 20% and 26% in the control and disulfiram group, respectively. This difference was not statistically significant (NS). A trend towards increased mean time to first drink was found in the disulfiram group (96 vs. 76 days in the control group, NS), while fewer patients in this group completed CBT group therapy (41% vs. 67% in the control group, NS). Alcohol-free days were 100 days in both groups (NS).

CONCLUSION: Supervised disulfiram administration did not have any major impact on the treatment outcome.

Eur Arch Psychiatry Clin Neurosci. 2010 Nov;260 Suppl 2:S116-20. Epub 2010 Oct 16.

Individualised treatment in alcohol-dependent patients.

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Abstract

Long-term relapse prevention is the biggest challenge in treating alcohol-dependent patients. It is equally based on psychotherapy and pharmacotherapy. Psychotherapy includes motivational interviewing, community reinforcement, cognitive behavioural therapy, motivational enhancement, twelve-step facilitation, social network behaviour therapy, cue exposure, etc. For pharmacological treatment, we dispose of disulfiram, acamprosate and naltrexone. Reviews and meta-analyses reveal only modest effect sizes of these approaches probably because they are usually tested in large and heterogeneous samples where "one size does not fit all". However, attempts to form more homogeneous subgroups for which specific psychotherapies should be more effective ("matching") also failed. We suppose that this failure may have to do with the fact that these studies used only psychopathology and behavioural analyses as a basis for subtyping. Things look more promising once biologically defined endophenotypes are used as well in order to form more homogeneous subgroups. For example, naltrexone treatment seems more effective in carriers of a specific variant of the mu-opioid receptor gene. The same could be true for acamprosate if a newly found polymorphism was used to preselect potential responders. Very recently biological differences between patient groups are also being detected using functional imaging. Naltrexone is suggested to work better in a subgroup of patients with higher cue reactivity when shown appetitive alcohol pictures. MR spectroscopy of brain glutamate levels may detect potential acamprosate responders. On such a basis, an individualised approach in the treatment of alcoholism ("personalised medicine") seems to hold promise.

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Int J Immunopathol Pharmacol. 2010 Jul-Sep;23(3):847-55.

The effects of alcoholism pharmacotherapy on immune responses in alcohol-dependent patients.

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Abstract

Chronic alcohol use has profound modulatory effects on the immune system. Both the innate and the acquired immunity are compromised. The use of pharmacotherapy is increasingly applied to enhance the percentage of success in maintaining alcoholic patients in remission. Disulfiram, naltrexone and gamma hydroxybutiric acid are the drugs used for this purpose in Italian Addiction Services. In this study we analyze the effect of pharmacotherapy of alcohol dependence on immune responses in alcoholics. Six groups were studied. Group A included 10 patients who were still using alcohol. Group B consisted of 10 patients abstinent from alcohol in treatment only with group therapy. Groups C, D and E were composed of 10 patients each, treated for at least 6 months with oral doses of gamma hydroxybutiric acid, naltrexone or disulfiram respectively. Ten age- and sex-matched healthy volunteers who never misused alcohol were included as a control group. Lymphoproliferation and peripheral mononuclear cell production of the Th1 cytokines IL-2 and IFN-gamma, the Th2 cytokine IL-4, and of the pro-inflammatory cytokines IL-1 and TNF-alpha were evaluated in all the patients and controls. The level of activity of the hypothalamus pituitary adrenal axis was assessed. Both ACTH and cortisol levels in plasma were elevated in alcoholic patients with no treatment. In this group a significant alteration of cytokine production was observed. TNF and IFN-gamma were lower than controls, while the Th2 cytokine IL-4 was increased. These altered levels state for a Th1/Th2 unbalance characterized by decreased Th1 response in the presence of Th2 predominance. In patients undergoing pharmacological treatment, none of the immune parameters were different from those observed in healthy controls, independently of the type of drug administered. These data indicate that pharmacotherapy more than group therapy treatment is able to ameliorate the immune system functioning in alcoholic patients.

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Actas Esp Psiquiatr. 2010 Jan;38(1):8-12. Epub 2010 Jan 1.

Topiramate in the treatment of alcohol dependence: a meta-analysis.

[Article in English, Spanish]

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Abstract

Several controlled clinical trials have studied the efficacy of topiramate in the treatment of alcoholism. In this paper, we have performed a meta-analysis of those trials in which topiramate was compared with placebo and then we reviewed its efficacy in trials in which it was compared with other drugs. Method: A quantitative synthesis of data was per-formed using inverse variance weighting in a random effects model. Results: Based on three placebo-controlled trials, topiramate is more efficacious than placebo in reducing the percentage of heavy drinking days (23.2%, 95% confidence interval [CI]: 15.7 to 34.4), increasing the number of days of abstinence (mean difference: 2.9 days, 95% CI: 2.5 to 3.3),and lowering the logarithm of g-GT levels (mean difference:0.075 95% CI: 0.048 to 0.118). Two trials suggested that topiramate is also more efficacious than naltrexone, and one open-label study reported better results for disulfiram than for topiramate. Conclusion: Topiramate can be used in alcohol dependence. Adverse effects such as paresthesia or insomnia should be taken into account when prescribing topiramate.Its optimal dosage requires further research.

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Drug Alcohol Depend. 2011 Jan 15;113(2-3):184-91. Epub 2010 Sep 15.

Randomized, double blind, placebo-controlled trial of disulfiram for the treatment of cocaine dependence in methadone-stabilized patients.

Oliveto A, Poling J, Mancino MJ, Feldman Z, Cubells JF, Pruzinsky R, Gonsai K, Cargile C, Sofuoglu M, Chopra MP, Gonzalez-Haddad G, Carroll KM, Kosten TR.

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Abstract

This study examined the dose-related efficacy of disulfiram for treating cocaine dependence in methadone-stabilized cocaine dependent participants.

DESIGN: One hundred and sixty-one cocaine- and opioid-dependent volunteers were entered into a 14-week, double blind, randomized, placebo-controlled clinical trial at two sites.

METHODS: Participants were stabilized on methadone during weeks 1-2 and received disulfiram at 0, 62.5, 125 or 250 mg/day during weeks 3-14. All participants also received weekly cognitive behavioral therapy. Thrice-weekly urine samples and weekly self-reported drug use assessments were obtained.

RESULTS: Baseline subject characteristics, retention and drug use did not differ across groups. Outcome analyses were performed on those who participated beyond week 2. Opioid-positive urine samples and self-reported opioid use did not differ by treatment group. The prevalence of alcohol use was low prior to and during the trial and did not differ by treatment group. Cocaine-positive urines increased over time in the 62.5 and 125 mg disulfiram groups and decreased over time in the 250 mg disulfiram and placebo groups ($p < 0.0001$). Self-reported cocaine use increased in the 125 mg disulfiram group relative to the other three treatment groups ($p = 0.04$).

CONCLUSIONS: Disulfiram may be contraindicated for cocaine dependence at doses <250 mg/day. Whether disulfiram at higher doses is efficacious in reducing cocaine use in dually cocaine and opioid dependent individuals needs to be determined.

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Neuropsychopharmacology. 2010 Nov;35(12):2440-9. Epub 2010 Aug 25.

Disulfiram attenuates drug-primed reinstatement of cocaine seeking via inhibition of dopamine β-hydroxylase.

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Abstract

The antialcoholism medication disulfiram (Antabuse) inhibits aldehyde dehydrogenase (ALDH), which results in the accumulation of acetaldehyde upon ethanol ingestion and produces the aversive 'Antabuse reaction' that deters alcohol consumption. Disulfiram has also been shown to deter cocaine use, even in the absence of an interaction with alcohol, indicating the existence of an ALDH-independent therapeutic mechanism. We hypothesized that disulfiram's inhibition of dopamine β-hydroxylase (DBH), the catecholamine biosynthetic enzyme that converts dopamine (DA) to norepinephrine (NE) in noradrenergic neurons, underlies the drug's ability to treat cocaine dependence. We tested the effects of disulfiram on cocaine and food self-administration behavior and drug-primed reinstatement of cocaine seeking in rats. We then compared the effects of disulfiram with those of the selective DBH inhibitor, nepicastat. Disulfiram, at a dose (100 mg/kg, i.p.) that reduced brain NE by ~40%, did not alter the response for food or cocaine on a fixed ratio 1 schedule, whereas it completely blocked cocaine-primed (10 mg/kg, i.p.) reinstatement of drug seeking following extinction. A lower dose of disulfiram (10 mg/kg) that did not reduce NE had no effect on cocaine-primed reinstatement. Nepicastat recapitulated the behavioral effects of disulfiram (100 mg/kg) at a dose (50 mg/kg, i.p.) that produced a similar reduction in brain NE. Food-primed reinstatement of food seeking was not impaired by DBH inhibition. Our results suggest that disulfiram's efficacy in the treatment of cocaine addiction is associated with the inhibition of DBH and interference with the ability of environmental stimuli to trigger relapse.

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Pharmacotherapies for alcoholism: the old and the new.

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Abstract

Alcoholism and other alcohol use disorders are major public health problems, and the success rates of non-pharmacological treatment of these disorders such as psychotherapy, cognitive-behavioral therapy, group therapy, or residential treatment programs,remain only modest at best. High rates of recidivism (relapse) in alcoholics attempting to remain abstinent are prevalent worldwide. In recent years abundant evidence has accumulated demonstrating that alcoholism is a complex and multifaceted disease of the brain caused by numerous genetic, neurobiological, developmental, environmental, and socioeconomic factors that are still not yet fully understood.There is thus a great need to improve the success rates of all forms of treatment of alcoholism not only in preventing relapse, but curbing active alcohol consumption and craving. The development of improved pharmacotherapies that could be used as adjuncts to the aforementioned non-pharmacological treatment approaches is one avenue of great interest to the scientific community and the general public. Currently there are only three medications approved by the U.S. Food and Drug Administration (FDA) for use in the treatment of alcohol abuse and alcoholism--disulfiram, naltrexone, and acamprosate. Yet medication compliance issues and the modest efficacy of these compounds leave substantial room for improvement. This special issue is devoted to reviewing the current status of these FDA approved medications in the treatment of alcoholism. In addition, preclinical and clinical evidence suggesting that other classes of medications might also be of potential use are reviewed, including anticonvulsants, GABAB receptor agonists, cholinergic receptor partial agonists, corticotropin-releasing factor and cannabinoid CB1 receptor antagonists, nociceptin receptor ligands, and the novel antipsychotic aripiprazole.

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