

# Disulfiram therapy — adverse drug reactions and interactions

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**Abstract** — Adverse drug reactions (ADR) to disulfiram treatment have been reported as single cases, but few systematic investigations exist. In this study we analysed the spontaneous ADR reports to the Danish Committee on Adverse Drug Reactions during 1968—1991. In that period 154 ADRs to disulfiram were reported, mainly of hepatic, neurological, skin, and psychiatric reactions, in decreasing order of frequency. The safety of disulfiram, estimated on the amount produced and the number of reactions reported, corresponds to an intermediate rate of adverse reactions (1 per 200—2000 treatment year). Over the 23-year period, 14 deaths were reported in Denmark and this corresponds to a rate of 1 per 25,000 treatment year; the chief cause was liver toxicity. Reports to the WHO collaborating Centre for International Drug Monitoring in Uppsala, Sweden, showed the same ADR profile, although with a higher rate of neurological and psychiatric and a lower rate of hepatic reactions.

The latency time from the start of treatment to the manifestation of the ADR differed according to organ. Hepatitis occurred with a distinct peak after 2 months of treatment, skin reactions peaked after 2 weeks, and the rate of neurological ADR increased with duration of therapy. The relation of skin reactions and hepatitis to nickel allergy is discussed, as is the dose-dependency of neuropathy.

Concomitant disulfiram treatment affects the metabolism of several drugs and the dynamics of others, leading to a number of clinically important drug interactions. The disulfiram drug interactions are reviewed.

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## Introduction

Adverse effects of disulfiram have mainly been described in a large number of individual case reports. Few systematic investigations have been done. Disulfiram has been widely used as supportive therapy in the treatment of severe alcoholism, but also in a few cases for nickel allergy. We assessed existing case reports and analysed adverse effects reported to the Danish Committee on Adverse Drug Reactions and world-wide reports to the WHO Collaborating Centre for International Drug Monitoring in order to perform a safety analysis of disulfiram, and to determine the latency time of individual adverse effects.

## Material and methods

The Danish Committee on Adverse Drug Reactions (ADR) has received spontaneous reports from Danish physicians since 1968. During the period 1968—1991 this amounted to 124 reports of 154 ADRs. For comparison, data were obtained from the WHO Collaborating Centre for International Drug Monitoring,

Uppsala, Sweden. The Centre has compiled a total of 1131 reports, collected from a number of national centres around the World. It should be noted that the information is not homogenous with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction. The information provided does not represent an opinion of the World Health Organization.

In the Danish system ADR diagnosis is grouped solely in accordance with the affected organ system, whereas in the WHO data one diagnosis is allowed to appear under several such groups.

## Results

Table 1 shows the number of ADRs reported to the Committee on Adverse Drug Reaction in periods of 6 years. No definite trend has appeared over the years. Most of the drug reactions were related to four different categories: liver, neurological, skin, and psychiatric reactions (Fig 1.). Forty reports were related to symptoms with low frequency, i.e. less than 5 reports per 23 years.

## 155 DISULFIRAM ADR's ( DK )

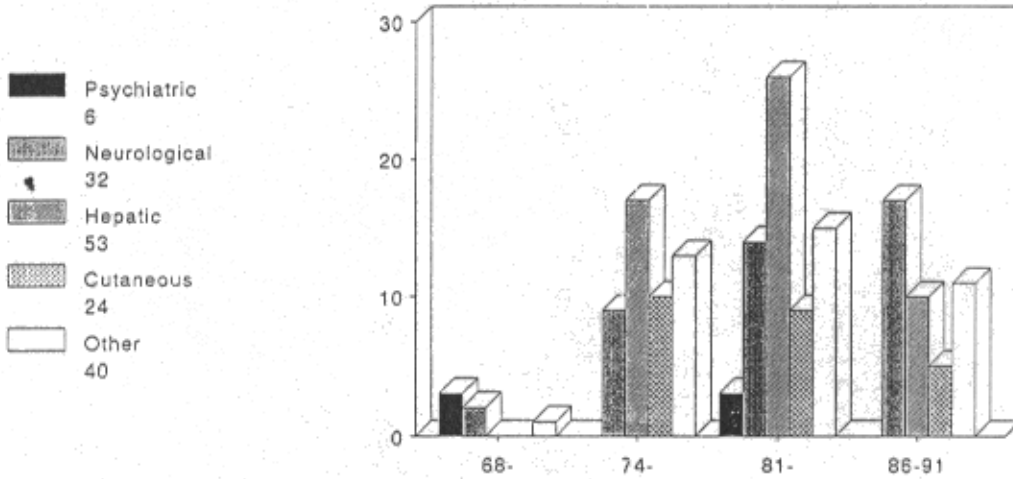


Figure 1. The Adverse Drug Reactions to disulfiram according to the four major organs reported. A remaining 40 reactions are not stratified, because of the small number of reactions with the same diagnosis.

### Disulfiram ADR's 1968-91 Latency time (DK)

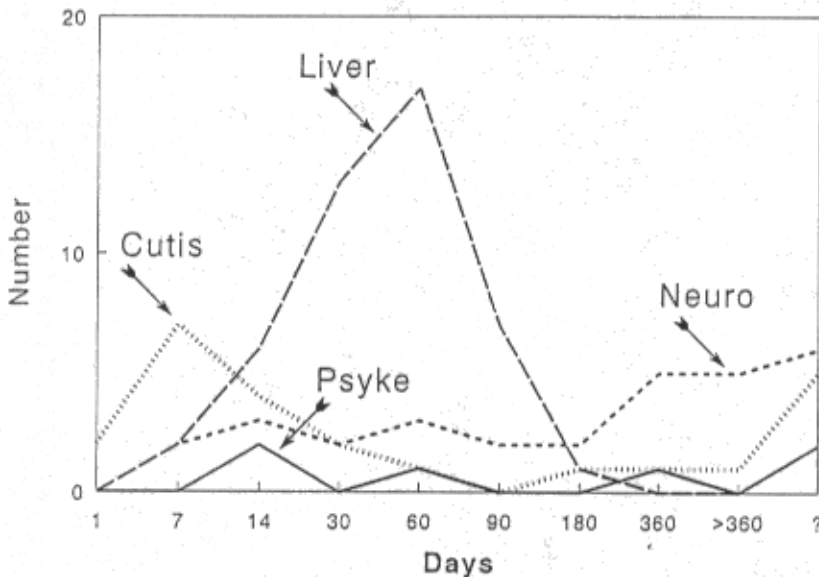


Figure 2. The latency time to the reactions in the four major organs during disulfiram treatment.

### Liver

Liver damage represented 53 reactions (34% of all), consisting of signs of acute hepatic necrosis. No cases of chronic liver damage were reported. The treatment time with disulfiram ranged from 16-120 days until the onset of toxic hepatitis, with a distinct maximum occurring after 60 days (Fig 2). Eleven fatal cases of liver failure were reported. The latency time between all liver reactions and fatal liver reactions did not differ significantly (Chi-square test,  $p = 0.34$ ).

Three other deaths related to disulfiram were reported, two of unspecified heart disease (after 2 and 70 days treatment) and one of congestive heart disease (after 2 years treatment). The 14 deaths represent 11% of the 124 reports.

In the WHO data base 19 cases were found under the diagnosis "death". Since the Danish reports are submitted to the WHO Centre, the number of fatal reactions found under this diagnosis in the WHO data base is clearly underestimated. The same problem exists in the Danish data base where the diagnosis "death" was used in only 4 of the 14 cases with fatal outcome.

### Nervous system

A total of 32 (21%) neurological reactions to disulfiram were included in the Danish material. The most frequent diagnosis was polyneuropathy (18 cases).

The latency time of occurrence of neurological ADRs shows a clear pattern, i.e. a slow increase with the duration of treatment. Continuous disulfiram treatment for periods longer than years is presumably seldom; a sequential pathophysiological examination of such patients is needed to verify this hypothesis (Fig 2).

Neurological ADRs represented 28% of the total number reported to the WHO, which makes the nervous system the most affected organ system. The neurological diagnoses arranged according to increasing number of reports were: optic neuritis, headache, dizziness, ataxia, paraesthesia, confusion, convulsions, and neuropathy.

### Skin

The Danish number of reported cutaneous reactions amounted to 24. The reports showed an early peak incidence after 7 days, but occurrence after all treatment intervals, i.e. from days to years of treatment. The pattern in the Danish reports was similar to that of the WHO reports, in which diagnoses arranged according to increasing frequency were: exfoliative dermatitis, dermatitis, urticaria, pruritus, and rash.

### Psychiatric reaction

Six reactions (4%) have been reported as psychiatric in Denmark. This is at variance with the WHO reports, in

which they constituted 13% of the total number of reactions. The most frequent diagnoses arranged according to increasing frequency were psychosis, confusion, sleep disorder, delusion, depression and anxiety.

### Safety evaluation

The production of disulfiram for the Nordic countries amounts to 2.4 million grams per year (data obtained from Dumex Ltd.). The defined daily dose is 200 mg. Thus, production corresponds to treatment of 33,000 patients per year. Assuming that sales in Denmark account for 50% of the production and that sales equals consumption, about 15,000 patients are treated per year in Denmark. The number of adverse reactions amounts to about 154 during a 22-year-period, i.e. 7 per year. Accordingly, the reported frequency is 1 ADR per 2000 treatment years. The true frequency of ADRs is unknown, but reporting probably varies between 10% and 100%. A rough estimate of ADRs from disulfiram is then between 1/200—1/2000 per treatment year. For comparison, a high rate of drug-induced illness has been arbitrarily defined as  $>1$  per 200 treatment year, and a low incidence as  $<1$  per 10,000 treatment year [1]. According to this definition, disulfiram has an intermediate rank with regard to ADRs.

As 14 deaths have been reported, approximately 1 death can be expected per 25,000 patients treated per year.

### Discussion

The major finding in this study was that the most reported ADRs during disulfiram treatment occur with intermediate frequency between 1 per 200 to 2000 reactions per treatment year. A distinct pattern in latency time emerged for the four major organs: Skin reactions showed a maximum after a few weeks of treatment, but occurred after all treatment periods. Hepatic reactions showed a clear maximum after 60 days of treatment and only very few cases were reported after treatment periods longer than six months. Neurological ADRs increased steadily throughout the treatment period.

Among the minor side effects well known from clinical experience, an excessive drowsiness is often reported during the first days of disulfiram treatment, probably because of the high initial dose traditionally recommended.

With regard to hepatic reactions, a surprisingly high number has been reported in patients treated for nickel allergy. The therapeutic mechanism in such patients is thought to be a reduction in the total body load of nickel brought about by the chelating effect of diethyldithiocarbamate (DDC) and increased excretion of nickel. In an uncontrolled, retrospective series [2] with

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61 non-alcoholic patients (33 with nickel allergy alone, 12 with both nickel and cobalt allergy, and 26 with positive patch tests for nickel as well as substances other than cobalt) hepatic reactions were observed in 11 (18%). Such reactions are probably underreported to a considerable extent both to the Danish and the WHO data bases. Four of the 11 patients had to be admitted to hospital because of severe symptoms. Liver biopsy revealed acute hepatitis in all 4; of the remaining 7 patients, 6 presented with slightly elevated serum transaminase activity, and one patient had biochemical evidence of hepatitis. Blood biochemistry normalized after cessation of disulfiram therapy in all patients. The doses varied from 50 mg to 400 mg daily.

The characteristic blood biochemical findings in disulfiram-induced hepatitis indicate hepatocellular damage with high transaminase values and jaundice, indistinguishable from that of alcoholic hepatitis. Of 453 male alcoholics randomly assigned to disulfiram or placebo and followed for up to 12 months, 201 patients, equally distributed between the two treatments, had elevated liver function tests at least once during the observational period [3]. Interviews twice monthly of the patients and their families disclosed that 179 of the patients were consuming alcohol during therapy, only 22 were abstinent. All the patients continued therapy and the tests became normal.

In 93 alcoholics tested before and after 1 year of supervised disulfiram ingestion (1400 mg/week), an initially elevated ASAT was found to be normal in 14 patients at 1 year; 4, whose values were normal before starting disulfiram therapy had slightly elevated values after 1 year; and 2 patients had values above the reference interval at both examinations [4]. Thus, no evidence of disulfiram-induced hepatitis was found.

A study of 50 male inpatients randomized to receive placebo, disulfiram 250 mg/day or 500 mg/day showed no differences in liver biochemistry [5]. Likewise, no long-term ill effects were seen in over 1500 consecutive patients treated with disulfiram [6]. However, many case reports have described hepatitis, often lethal, as a result of disulfiram [7]. The period between the start of disulfiram therapy and the appearance of symptoms varies widely from a few weeks to many months. This makes diagnosis difficult. The high peak incidence of hepatic reactions after 2 months of treatment should be noted, and analysis of serum transaminase levels is indicated in patients with general malaise after 1 to 6 months on successful therapy. Some authors recommend determination of liver biochemistry at intervals of a few weeks during the initial weeks of therapy and at 3–6-month intervals thereafter [8], whereas others do not consider guidelines and routine control to be necessary [9]. Severe hepatic reactions are an indication for liver biopsy.

Very high doses to rats for 3 months did not produce histological liver damage [10], nor did animals enzyme-

Table 1. Number of Adverse Drug Reactions (ADR) and Reports in Denmark 1968–1991

	1968–73	1974–80	1981–85	1986–91	Total
ADRs	6	48	68	33	155
Reports	4	38	55	27	124

induced with phenobarbital show evidence of hepatotoxicity.

Several hypotheses have been put forward as to the mechanism of hepatitis, of which the most plausible seem to be: 1: hypersensitivity; 2: effect of toxic metabolites, e.g. free sulphur radicals; 3: unknown characteristics occurring predominantly or solely in patients with undiagnosed, as well as proven, nickel allergy.

Peripheral neuropathy has been reported as a disabling adverse reaction to disulfiram. From a diagnostic point of view, the symptoms of alcohol-induced and disulfiram-induced peripheral neuropathy are similar, and the two aetiologies are difficult to differentiate. The symptoms and findings of disulfiram-induced neuropathy are subacute or chronic, somewhat motor predominant, worse peripheral, bilateral and involve also sensory and autonomic nerve fibres. Thus, generalized weakness, paraesthesia and vasomotor instabilities cause symptoms specific to the tissue-end organ involved. However, optic neuritis and clonic blepharospasm are encountered more frequently in disulfiram neuropathy than in alcoholic neuropathy, unless unusually heavy smoking accompanies the alcohol consumption [11]. There is disagreement on the reversibility of the neuropathy after discontinuation of disulfiram.

The pathophysiological documentation of disulfiram neuropathy is restricted to a few systematic investigations. Nerve conduction studies were performed bilaterally on the peroneal and sural nerves and unilaterally on the median and ulnar motor and sensory nerves before and 1 and 3 months after the start of disulfiram therapy [12]. All the patients were male alcoholics with no sign of alcohol-related organ damage, and no signs of malnutrition. The treatment dose was disulfiram 250 mg daily. None of the patients developed symptoms related to peripheral neuropathy during the study period, and no abnormalities were found at repeated clinical examinations of stretch reflexes, muscle strength, or sensory functions. The analyses revealed significant changes in peroneal distal latency, conduction velocity, and compound muscle action potential. The sensory studies disclosed that only the median nerve showed significant change in the compound nerve action potential. These results indicated a progressive subclinical dysfunction of peripheral nerves at 1 and 3 months after the start of disulfiram treatment. The same group of scientists using an ex-

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Table 2. Documentation regarding drug interactions with disulfiram in man.

Drug	Finding	Assumed clinical importance	Reference
<i>Interactions found</i>			
Antipyrine	decreased clearance	—	[18,19]
Chlordiazepoxide	decreased clearance	++	[36]
Caffeine	decreased clearance	+	[37]
Diazepam	decreased clearance	++	[36]
Phenytoin	decreased clearance	+++	[38]
Theophylline	decreased clearance	+++	[39]
Warfarin	unchanged elimination; increased effect	+++	[22]
Metronidazole	confusion and psychosis	+++	[23]
Isoniazid	confusion and psychosis	+++	[24]
Amitriptylin	psychosis	+++	[25]
Perphenazine	increased perphenazine first pass metabolism	++	[26]
<i>Interactions not found</i>			
Alprazolam	unchanged clearance	—	[40]
Carbamazepine	unchanged steady state concentrations	—	[41]
Metadone	unchanged through concentrations and half-life	—	[42]
Oxazepam*	unchanged clearance	—	[36]
Paracetamol †	unchanged rates of metabolite formation	—	[29]
Tolbutamide	unchanged clearance	—	[38]

\* solely eliminated by glucuronidation; † mainly eliminated by glucuronidation and sulphation.

— indicates no clinical importance

+, ++, +++ indicate increasing clinical importance

tended methodology later investigated 33 alcoholics treated with 250 mg disulfiram/day, 9 patients with 125 mg/day, and 24 alcoholics treated without disulfiram. Measurements were performed for 6 months. The patients on 250 mg daily showed the neurophysiological results described above (motor conduction velocity, motor latency, peroneal conduction velocity, sensory velocity and amplitude, as well as sural sensory conduction velocity), whereas no changes were observed in patients on 125 mg/day, and the control group showed a significant electrophysiological improvement during the same period of observation. Three patients on 250 mg/day developed abnormal EMG. None of the patients developed symptoms [13]. These results indicate that the risk of developing peripheral neuropathy might be dose-related. This is further supported by the fact that all the patients reported to have severe neuropathy were receiving 250 mg/day or higher doses [14]. The same review of 37 cases of neuropathy between 1971 and 1988 reported some other common characteristics. The incidence rate of neuropathy is probably disproportionately high in women, the latency period for the onset of symptoms is longer with a low dose, and the symptoms are less severe with doses below 250 mg/day. The authors also found indications of dose-dependency, and that the course of recovery depends primarily on the initial degree of impairment. Furthermore, in most of the case reports the patients developed neuropathic symptoms within 2 to 3 months of starting disulfiram treatment. In the carefully performed studies mentioned above no symptoms appeared during 3 and 6 months, respectively. This sug-

gests that electro-physiological measurements are of no value in predicting the appearance of clinically manifested neuropathy. Pathologically, it is generally agreed that the electron microscopic changes are axonal degeneration, loss of myelinated fibres, and neurofilament accumulation in enlarged axons [14].

Several mechanisms have been suggested for the nerve damage. The most plausible seem to be: 1: neurotoxic effect of the putative disulfiram metabolite CS<sub>2</sub>; 2: DDC-chelation of copper-containing enzymes in the synthesis of adrenaline, dopamine, and beta-hydroxylase bringing about primary axonal degeneration; 3: concomitantly administered, chloral hydrate-like drug competitively inhibits glucuronidation of DDC with a secondary enhancement of the production of CS<sub>2</sub>; 4: nerve damage is always present, but another factor is responsible for the degree of damage.

The skin reactions are related to the development of urticaria, acneiform eruptions, and allergic dermatitis. In nickel-allergic patients [2] severe episodes of dermatitis, and, in some instances, cutaneous vasculitis were seen during the initial one to three weeks of therapy. This phenomenon was only observed with initial doses of 200—400 mg disulfiram daily, not with initial doses of 50 mg daily. A low initial dose, and a rise in dose over 2 weeks was recommended by the authors, from 50 mg/day to 100—200 mg/day. The authors hypothesize that some of the rashes observed during the initial phase of disulfiram therapy in alcoholics might be due to unrecognized nickel allergy and not to disulfiram allergy. The same group has published 2 cases [15]. This might be a special risk in adult females,



as 10% can be expected to have nickel allergy. The prevalence rate in men is estimated to about 1%.

### Disulfiram drug interactions

The ethanol-sensitizing effect of disulfiram was described by Hald, Jacobsen and Larsen [16]. The possible underlying mechanism is the increase in the blood concentration of acetaldehyde, which is consistent with inhibition of liver aldehyde dehydrogenase, presumably by its metabolite diethylthiomethylcarbamate (Me-DTC) [17, 43]. Initially, the disulfiram enzyme inhibition was considered specific and selective, but today a variety of identified and unidentified enzymes have been demonstrated to be inhibited.

Disulfiram may cause clinically important drug interactions by different mechanisms (Table 2). Chemical compounds that contain a free  $S=C<$  grouping have been identified as inhibitors of microsomal mixed-function oxygenases, i.e. cytochrome P450s. In the case of disulfiram an inhibitory effect on the elimination of the model drug antipyrine has been shown to require several days of treatment to be maximal [18,19]. The elimination of many other, but not all, oxidatively metabolized drugs is retarded by concomitant disulfiram administration, whereas glucuronidation appears to be spared (Table 2). However, the disulfiram-related augmentation of the anticoagulant effect of S-warfarin, originally ascribed inhibition of the oxidative S-warfarin metabolism [20,21], was later shown to be pharmacodynamic [22]. Moreover, concurrent administration of disulfiram and metronidazole [23] or isoniazid [24] may lead to confusion and/or psychosis possibly by altered catecholamine metabolism in the brain. Similarly, co-administration of disulfiram and amitriptylin may lead to psychosis, probably by increasing monoamine concentrations in the brain [25]. A case report has also suggested that concomitant disulfiram administration may increase the first pass metabolism of perphenazine by sulphoxidation, thus decreasing oral bioavailability and efficacy significantly [26]. Disulfiram also has some unexplained effects on the intermediary energy metabolism as indicated by considerably elevated acetone concentrations in blood [27]. The clinical implications are unknown.

On the possible beneficial side of drug interactions, disulfiram has been shown to prevent acetaminophen hepatotoxicity in rats [28,29], and in conventional therapeutic doses of 200 mg a day for 5 days to humans a 10% decrease in acetaminophen clearance resulted [30]. In that study it could not be determined for certain whether the formation of acetaminophen sulphhydryl metabolites representing the acetaminophen metabolism by cytochrome P450s was reduced. However, two conclusions can be drawn from that study: disulfiram does not have a hazardous interaction with acetamino-

phen, and it might even reduce the risk from acetaminophen overdose.

Along these lines, it has recently been demonstrated that disulfiram, carbon disulfide, and diethyldithiocarbamate are inhibitors of cytochrome P4502E1 [17]. As P4502E1 activates acetaminophen to the toxic benzquinoneimine [31], such inhibition fits mechanistic considerations of a protective effect of disulfiram against acetaminophen-induced hepatic damage. Alcoholics are considered particularly susceptible to acetaminophen overdose [32]. Whether alcoholics treated with disulfiram have a normalized risk of liver damage from acetaminophen overdose has not been investigated. However, it is a possibility that the doses of disulfiram used are too low to produce significant cytochrome P4502E1 and P4501A2 inhibition [30]. This must be determined by specific *in vivo* probes. In animals, disulfiram inhibits N-nitrosodimethylamine-induced carcinogenesis, but, interestingly, shifted the site of tumour formation from the liver to the nasal cavity [33]. Whether disulfiram reduces the overall carcinogenic induced risk in humans, or whether it is shifted to another organ, as in the animals, has at present not been determined or inferred in man.

It has been suggested, and many studies indicate this, that disulfiram *per se* has no effect on enzyme activity, but rather the effect is mediated via its metabolites. Administration of both DDC and  $CS_2$  to rats decreased cytochrome P4502E1 concentration and activity in the liver [17]. In rat liver microsomes co-incubation and pre-incubation with DDC decreased P4502E1 activity by a time-dependent process requiring NADPH, which suggests metabolite-related suicide inactivation, as well as competitive inhibition.  $CS_2$  is also metabolized by P4502E1, with the possible result of enzyme inactivation, owing to binding of the reactive product, atomic sulphur [34]. Intriguingly, administration of disulfiram and DDC but not of  $CS_2$  induced the microsomal concentration and activity of cytochrome P450IIB1 in rats [17]. In that study the activity of other cytochrome P450s, i.e. IIA1/2 and IIIA1/2 showed only minor changes. It should be noted that the selectivity of the effects of disulfiram on the cytochrome P450s may be dose-dependent [35] and that the effects require some time to develop [19], probably because of the putative mechanisms involved, i.e. metabolic suicide inhibition *viz.* change in P450 gene transcription.

### Conclusion

The adverse reactions caused by disulfiram are mainly related to the liver, nervous system, and skin, and occur at an intermediate frequency (1 per 200–2000 treatment year). Disulfiram interacts with the elimination or pharmacodynamics of a number of important drugs. The mechanisms of both the adverse reaction and interactions remain to be finally clarified.

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## Discussion

Alcoholism and continued alcohol abuse carries a substantial health risk. The risk of any therapy should not inflict another and larger risk on any patient. The exact dose relationship between alcohol and adverse health effects is not estimated precisely. In the case of disulfiram treatment, the most serious adverse reaction is intermediate, approximately 1:25000 patients per year may die from disulfiram hepatitis, other side effects are not life threatening.

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The major types of side effects from disulfiram treatment, liver and peripheral nerve symptoms, are not easily distinguished from manifestations of alcohol abuse. An exact risk/benefit analysis is at present not feasible, but there are no indications that disulfiram treatment imposes a deleterious health impact, rather that data on adverse reactions put disulfiram in the company of many other drugs with an intermediate adverse drug reaction rate.