Expert Opinion

The safety of disulfiram for the treatment of alcohol and cocaine dependence in randomized clinical trials: guidance for clinical practice

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Background: Disulfiram has demonstrated efficacy in six randomized clinical trials for the treatment of cocaine dependence, but is rarely used in clinical settings because of safety concerns. *Objective*: What are the common and serious side effects of disulfiram in cocaine-dependent individuals with and without alcohol dependence in randomized clinical trials? *Methods*: We located Phase I and II randomized trials that discussed the safety of disulfiram. *Results/conclusions*: In randomized clinical trials that eliminated subjects with serious cardiovascular, hepatic, and psychiatric disorders, the most frequent side effects of disulfiram over placebo or index groups include headaches, fatigue, sleepiness, and anxiety. Disulfiram in a dose of ≤ 250 mg/day led to only mild interactions with alcohol. When patients are screened for medical and psychiatric stability, and are evaluated for drug interactions, disulfiram has an acceptable side-effect profile for the treatment of cocaine dependence with or without alcohol dependence.

Keywords: alcohol dependence, cocaine dependence, disulfiram, randomized clinical trials, RCTs, safety

Expert Opin. Drug Saf. (2008) 7(4):459-472

1. Introduction

Disulfiram was synthesized in the early 1880s and used in industry to vulcanize rubber for 60 years prior to medical application. By 1910, observations were made that workers producing rubber had alcohol intolerance, and in 1937, EE Williams, a plant physician, suggested that '[i]f the chemical compound [disulfiram] is not harmful to man, one wonders if one has discovered a cure for alcoholism' [1]. In the mid 1940s, two scientists working on antiparasitic therapies, Hald and Jacobsen, made the previously ignored rediscovery that taking disulfiram with alcohol induced aversive reactions [2]. The use of disulfiram for the treatment of alcohol dependence has diminished in the last decade with the US FDA's approval of naltrexone and acamprosate for the treatment of alcohol dependence [3]. However, in the last decade, interest in disulfiram to treat cocaine dependence has increased because of clinically significant findings of efficacy in six randomized clinical trials [4-9]. Recently, disulfiram was identified as having pro-apoptotic properties in *in vitro* studies of human tumor cells [10], and therefore may have potential for use as a chemotherapeutic agent. Thus, the safety of disulfiram, particularly in the treatment of addictive disorders, continues to be contemporary and clinically relevant.

Reviews and case reports of disulfiram safety and adverse events span over 50 years [11-14]. Some safety reviews have focused on hepatoxicity and other

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hepatic side effects [15-17]. These reviews have focused primarily on the safety and adverse events of disulfiram in the treatment of alcohol dependence. They have concluded that, with adequate clinical vigilance, the uncommon but serious effects can be avoided or managed in alcoholics. Two other recent reviews have examined the efficacy of disulfiram in the treatment of cocaine dependence [18,19] and have endorsed its use.

In this review, we focus on the safety and adverse events as noted in Phase I randomized safety and pharmacokinetic studies, as well as Phase II randomized clinical trials that evaluated efficacy and safety of disulfiram in both alcohol-dependent populations and populations that were cocaine-dependent, with or without comorbid alcohol dependence. Aside from the sheer volume of literature occurring over 60 years with the clinical use of disulfiram, a major challenge is attempting to separate the complications and comorbidities occurring with alcohol and cocaine dependence from true disulfiram adverse events. Early [20] and more recent [21] case reports have recorded serious adverse reactions to disulfiram, but it is difficult to judge whether these are related to disulfiram itself; to disulfiram and alcohol interactions; or to the comorbid medical and psychiatric consequences of alcohol and/or cocaine use.

Our review begins with the discussion of the relevant clinical pharmacology of disulfiram as it pertains to safety. We then move to a discussion of the clinical parameters of the disulfiram–ethanol interaction. Next, we take up the safety and adverse events of disulfiram in the context of Phase I and II randomized studies, first for alcohol and then for cocaine dependence. We conclude with information extrapolated from these trials that can guide safe practices with disulfiram in the future, particularly in cocaine-dependent alcohol-using patients.

2. Mechanism of action, metabolism, and pharmacokinetics of disulfiram

In humans, alcohol is primarily metabolized in the liver by alcohol dehydrogenases to acetaldehyde and rapidly converted to acetate [22]. Disulfiram and several of its metabolic derivatives irreversibly block the conversion of acetaldehyde to acetate by disabling both cytoplasmic and mitochondrial forms of aldehyde dehydrogenase (ALDH1 and 2). It is this elevation and prolongation of acetaldehyde levels that is believed to be the basis for the disulfiram–ethanol interaction [23].

Disulfiram and its active metabolites reduce the activity of many other enzymatic reactions that are relevant to its safety in the treatment of alcohol and cocaine dependence. Disulfiram and its metabolites inhibit microsomal carboxylesterases and plasma cholinesterases [24]. McCance-Katz and colleagues [25] have suggested that the pharmacokinetic increases in plasma cocaine levels caused by disulfiram may be related to this mechanism of action. Pharmaceutical agents metabolized by CYP450 CYP2E1 for oxidative pathways have been shown to have increased plasma concentrations and to prolong half-lives in patients taking disulfiram [26]. This is believed to be the reason why plasma levels of amitriptyline, warfarin, phenytoin, and some benzodiazepines (such as chlordiazepoxide and diazepam) are elevated in the presence of disulfiram. An important potential therapeutic benefit of disulfiram is its inhibition of conversion of dopamine to noradrenaline by dopamine beta-hydroxylase (DBH) [27,28]. Increased brain and peripheral levels of dopamine, with concomitant decreases in noradrenaline and adrenaline levels, may account for the therapeutic benefit in cocaine dependence and the hypotension seen in the disulfiram–ethanol interaction.

In the presence of gastric acid, disulfiram is quickly converted to diethyldithiocarbamate, followed by rapid conversion to carbon disulfide and diethyl amine [29]. It is difficult to detect the parent drug in the bloodstream; but other products from diethyldithiocarbamate, such as carbon disulfide and diethylamine, can be detected in blood. Diethyldithiocarbamic acid is a strong metal-chelating agent, hence its use in treating nickel sensitivity; but it also binds to copper, lead, and other metals. This chelation may have a relationship to some of the side effects seen with disulfiram in long-term use in some patient populations [30]. After some intermediate steps, diethyldithiocarbamic acid undergoes oxidative biotransformation to diethylthiomethylcarbomate, which itself undergoes further oxidation to sulphoxide and sulphone metabolites. Diethylthiocarbomate inhibits DBH, limiting noradrenaline synthesis and increasing synaptic dopamine. Faiman and colleagues reported that levels of all of the major metabolites of disulfiram vary greatly between individuals [29]. Diethyldicarbomate is estimated to have a half-life of 15 h, while diethylamine has a half-life of 13.9 h and carbon disulfide 8.9 h [29]. After glucuronidation, many of these metabolites undergo renal excretion, but other excretion may include unchanged disulfiram (up to 20%) in the feces, and excretion of carbon disulfide through the lungs, particularly with chronic dosing [29]. This latter route may account for the side effect of metallic taste by the patient and halitosis as reported by others. In addition to considerations of half-life and modes of metabolism and excretion, it should be noted that the metabolites of disulfiram irreversibly block and destroy aldehyde dehydrogenases, resulting in a prolonged effect lasting up to 14 days due to the slow restoration rate of these enzymes [30].

Thus, the variable side-effect profile and the differential intensity of the disulfiram–ethanol interaction can be seen to be dependent upon alcohol-related liver disease, decreased concentrations of serum albumin leading to higher levels of free drug metabolites, and to some extent lower rates of renal excretion. Therefore, prior to starting therapy with disulfiram, an assessment of liver function, renal function, and serum albumin is recommended [31].

3. Disulfiram–ethanol interaction

Many textbooks cover the disulfiram–ethanol interaction [22,32-34]. EE Williams' description of rubber plant workers is vivid: 'After a glass of beer (6 ounces) the blood pressure falls about 10 points, the pulse is slightly accelerated, and skin becomes flushed in the face and wrists. In fifteen minutes the blood pressure falls another 10 points, the heart is more rapid, and the patient complains of fullness in the head. There doesn't seem to be any other effect of the chemical; men have worked here for years without any complaint other than their inability to drink.'

Systematic, blinded, randomized studies of the dose–response effects of disulfiram and ethanol are not common [35]. Brewer [36] did a retrospective clinical review of alcoholic patients taking disulfiram who were challenged with alcohol (n = 33) and individuals who spontaneously drank despite warnings of the disulfiram–ethanol interaction (n = 30). The average age of this population was 43 (range 25 – 74). All patients were on liquid forms of disulfiram and stated to have reliable witnessed supervision of disulfiram ingestion. Time on disulfiram was variable, but was generally for a minimum of 1 – 2 weeks. Disulfiram doses were 200 – 300 mg/day. Alcohol ingested was estimated at 10 – 12 g in one sitting. Of the 63 subjects on disulfiram 200 – 300 mg daily, 33% had a significant response of flushing, tachycardia, and a drop in blood pressure. Quantification of the tachycardia and hypotension was not reported. Thirty of the 63 individuals had no response at these doses of ethanol and disulfiram. Of these low-dose non-responders, 17 individuals required 400 – 500 mg/day of disulfiram to respond with flushing, tachycardia, and a drop in blood pressure. Another six required 600 – 700 mg/day, and an additional seven individuals required 800 – 1500 mg/day to demonstrate a response. None of the individuals required treatment or hospitalization for the disulfiram–ethanol interaction. Three individuals were described as having a mild confusional state, which disappeared spontaneously within 1 – 3 days of disulfiram discontinuation or reduction in dosage.

Christensen and colleagues [37] conducted a prospective open-label laboratory study evaluating the disulfiram–alcohol interaction. Fifty-two social drinkers and abstainers (29 men and 23 women with an age range of 20 – 61 years) were treated as outpatients with increasing doses of disulfiram 100, 200, and 300 mg for 14 days each. At the end of each 14-day block, volunteers were challenged with 0.15 g of ethanol per kilogram of body weight. Mean weight of subjects was 69 kg, so most subjects received around 10 g of ethanol for their challenge. Subjects rated flushing, heat sensation, nausea, vomiting, palpitations, breathlessness, and headaches on a subjective scale of 0 – 3, for the next 50 min. Objective measures in diastolic blood pressure, respiration, and pulse were evaluated by the investigators. A disulfiram–ethanol interaction was operationally defined as either a sum of the subjective scores (excluding flushing) of ≥ 6 plus the appearance of flushing, an increased respiration rate by 5/min, a decrease of diastolic blood pressure by 20 mmHg, and/or an increase of pulse rate by 26 bpm. None of the subjects had a disulfiram–ethanol interaction after 1 mg of disulfiram; 21 subjects had a interaction after 100 mg; 27 subjects had an interaction after 200 mg; and 4 subjects required 300 mg to have an effect. With one exception, the subjects all had reductions in blood pressure. Two subjects at 300 mg disulfiram had highly significant diastolic blood pressure changes, placing them in the range of hypotensive shock: one subject exhibited a 46-mmHg decrease, and the other a 66-mmHg decrease, in blood pressure. Specific defining characteristics of these two subjects were not reported. In addition, during the study eight individuals reported tiredness, three reported diarrhea, and four reported headaches, all of which were not necessarily associated with the ethanol challenge. This study is limited by its open-label design, lack of measures to assure compliance, and the lack of an alcohol-dependent group. In the same population of non-alcoholics, but published separately [38], these investigators evaluated the pharmacokinetics of disulfiram, diethylthiomethylcarbamate, plasma acetaldehyde, and erythrocyte dealdehyde hydrogenase activity. A correlation between levels of diethylthiomethylcarbamate and acetaldehyde was noted, but was not related to the subjective and objective adverse effects in the subjects.

Aldehyde dehydrogenase exists in several isoforms that differ in their abilities to metabolize acetaldehyde. These isoforms are encoded by different genetic alleles. The distribution of these alleles differs greatly among ethnic groups, producing various degrees of aversion to alcohol, presumably by the acetaldehyde–ethanol reaction [39]. The clinical observational report [36] and the laboratory study on disulfiram–ethanol interaction [37] were conducted in a relatively homogenous population of Scandinavians. The effects of the disulfiram–ethanol interaction in more diverse ethnic groups such as Hispanics and African Americans have received less attention. However, approximately 15 – 40% of Southeast Asians carry an allele encoding an inactive form of type 2 aldehyde dehydrogenase due to an E487K mutation, and people heterozygous for this mutation drink less alcohol, while homozygotes virtually never develop alcoholism [40].

Another genetic effect that is intriguing is the potential effect of DBH inhibition by disulfiram and its effect in the hypotensive and tachycardic components of the disulfiram–ethanol interaction. Preclinical studies in mice indicate interactions between different allelic genotypes of DBH, disulfiram inhibition and regulation of catecholamine levels and distribution of noradrenaline and dopamine in the brain [41]. These studies indicate higher CNS levels of dopamine and relatively lower levels of noradrenaline and adrenaline in the periphery in mice. Variations in the gene

that codes for DBH, such as single-nucleotide polymorphisms (i.e., 444A→G and 1021C→T) and short-nucleotide sequence deletions (i.e., 4784–4803del) alter DBH activity, and low DBH activity in cocaine users on disulfiram is correlated with cocaine-induced psychosis [42]. In the future, screening cocaine-dependent patients for these genetic variations in the DBH gene prior to disulfiram treatment could potentially avoid inducing psychotic symptoms.

In summary, information on the disulfiram–ethanol interaction is restricted to two reports and limited by the homogenous populations studied. Other enzymatic effects of disulfiram, such as its ability to reduce DBH activity, which leads to inodilation effects (tachycardia and vasodilation) due to the increased levels of circulating dopamine, is a possible contributing factor to the disulfiram–ethanol hypotension and tachycardia and requires further investigation in humans. Genetically induced low DBH activity lowered further by disulfiram probably predisposes for psychotic symptoms by increasing dopamine, and for greater hypotension by lowering noradrenaline and adrenaline.

4. Disulfiram safety and adverse events in randomized clinical trials for the treatment of alcohol dependence

Although disulfiram came into wide use prior to 1950, the first randomized clinical trials of its efficacy and safety for the treatment of alcohol dependence did not occur until the 1980s. Christensen and colleagues [2] studied 241 individuals randomized to 400 mg of disulfiram or placebo in a five-site multicenter study. A total of 158 subjects completed the study, and completers did not differ demographically between groups. Eighty-three individuals took disulfiram. All individuals started the trial on a placebo washout for 2 weeks with careful assessment of side effects at the end of the first 2 weeks. Individuals were then randomized to disulfiram or placebo for 6 weeks. All individuals were alcohol-dependent and aged 18 – 70 years. Individuals who were pregnant or who had severe liver or cardiovascular disease were excluded. Individuals received a self-report structured side-effect questionnaire each week of the study, which rated intensity and frequency of side effects. A composite score of frequency and intensity of side effects was derived. All individuals in the study had been on clinical disulfiram treatment for several months prior to the trial. Since this was an in-patient study with observed administration of disulfiram, compliance was not in question. During treatment, only one significant difference emerged. There was more sexual dysfunction in the placebo group ($p = 0.037$), while there was a trend for unpleasant taste being more common in the disulfiram group ($p = 0.09$). Since all subjects were in-patients, there was a low likelihood of any disulfiram–ethanol interactions and none were reported. A third of subjects in both groups dropped out during the trial. The investigators concluded that the numerous side effects generally mentioned in disulfiram labeling (including tiredness, sleepiness, dizziness, cognitive changes, headaches, unpleasant taste, halitosis, unpleasant body odor, nonspecific GI symptoms, and rash) either occur very infrequently in patients on disulfiram as true adverse events or they could be attributed as comorbid disorders arising in the natural history of alcohol dependence.

Fuller and colleagues [43] conducted a large, multicenter trial of 605 alcohol-dependent patients who were randomized to disulfiram (1 or 250 mg) or placebo. This was an outpatient trial that excluded individuals living alone, individuals with heart disease, organic brain syndrome, schizophrenia, bipolar disorder, seizure disorder, cirrhosis of the liver, or diabetes mellitus Type 1, individuals taking anticonvulsant medications, or individuals who had been abstinent from alcohol for > 1 month. Administration of the medication was in the hands of the subjects. Riboflavin 50 mg was added to each of the three treatment preparations to serve as a measure of compliance in urine and measured photometrically. The mean age of the subjects was 41.3 years, and their ethnicity was 53% Caucasian and 47% African–American. Good compliance was defined as ≥ 15 urine specimens positive for riboflavin during the year of treatment. Twenty per cent of subjects were judged compliant by riboflavin measures, and compliance rates did not differ among the three treatment groups ($p = 0.46$). Psychiatric problems, otherwise undefined, were seen in 11 patients and were distributed evenly among the three treatment groups. Drowsiness occurred in 8% of the subjects on 250 mg of disulfiram and was significantly higher than the other two groups ($p = 0.03$). There was no evidence of neuropathy or hepatitis in any of the groups. Out of 605 ndividuals, 438 reported drinking during the study. No disulfiram–ethanol interactions were reported in this study. Due to the overall poor compliance rate with disulfiram use throughout the 12 months, it is not possible to evaluate the lack of disulfiram–ethanol interactions in this study.

Chick and colleagues [44] studied 126 individuals in a randomized clinical trial in which subjects received in double-blind fashion either 200 mg of disulfiram or placebo. This was a 6-month multicenter study conducted in outpatients who had daily supervision by a spouse, other relative, friend, or clinic staff at least once per week. Subjects who were pregnant or who had cardiac disease, a history of psychosis, polydrug abuse, or serious hepatic disease were excluded. The placebo was an active one, given as 100 mg vitamin C tablet taken daily. Dropout was the same for both groups, at approximately 20%. Eleven subjects in the disulfiram group reported headaches, versus six in the vitamin C placebo group. Fatigue occurred in twelve disulfiram subjects versus six in the vitamin C placebo group. A disulfiram–alcohol interaction was reported 29 times. None led to a hospitalization, a reduction in dose, or other serious outcomes. Reported side effects included

depression in four disulfiram subjects and five vitamin C subjects, and nausea was equally common in both groups. No hepatitis occurred in either group.

In another large trial (n = 100), male alcohol-dependent patients (mean age 41.7) were randomized to disulfiram 250 mg daily or acamprosate 1998 mg daily for up to 8 months [45]. Therapy was witnessed. Dropout rates were equivalent. Three patients in the disulfiram group were removed due to neuropathy; none in the acamprosate group. Insomnia was common (30 – 32%) and equal in groups. Nausea was uncommon (3 – 4%) and equal in groups. Drinking occurred with acamprosate (54%) and disulfiram (12%), but no disulfiram–alcohol interaction was reported.

Laaksonen and colleagues [46] conducted a large randomized, multicenter, open-label comparison trial of disulfiram, naltrexone, and acamprosate in alcohol-dependent men and women 25 – 65 years of age in Finland. Subjects (n = 243) were randomized equally to receive naltrexone 50 mg, acamprosate 1998, (2 grams) or disulfiram 200 mg in witnessed therapy for 12 weeks. For weeks 13 – 52, medication administration was unwitnessed and intermittently triggered by 'high craving situations.' About a third of the subjects in all groups had at least one adverse event. There were no significant differences between any of the three treatment groups in reporting adverse events. The most common adverse events for acamprosate were diarrhea and dermatologic conditions, occurring in about 25% of subjects. Headache and dizziness occurred about 25% of the disulfiram subjects and in about 23% of the naltrexone subjects. Alanine transaminase elevations > 200 occurred in six disulfiram subjects and in no acamprosate or naltrexone subjects. Dose was cut to 100 mg for three of these subjects, while in the other three cases it was discontinued. In all six subjects, values returned to normal in 2 – 3 weeks. Interestingly, in terms of time to first drink and heavy drinking days, disulfiram was more effective than either of the other two medications, especially in the continuous witness medication period.

In summary, adverse reactions in the disulfiram randomized double-blind clinical trials appear far less serious and less frequent than adverse events reported post-marketing in textbooks or the package insert. This can, in part, be accounted for by relatively small sample sizes in clinical trials, as well as rigorous screening to rule out serious psychiatric illnesses, serious liver disease, and unstable cardiovascular conditions. In the absence of such conditions, disulfiram–alcohol interactions appear to be mild when they occur with doses of disulfiram < 500 mg daily.

5. Disulfiram–alcohol–cocaine interactions

Three laboratory studies have examined safety, pharmacokinetic interactions, and subjective responses to disulfiram administration in individuals taking cocaine through nasal and intravenous routes of administration. McCance-Katz and colleagues [25], in a randomized, double-blind, placebo-controlled trial, studied chronic disulfiram treatment effects on intranasal cocaine administration in six non-treatment-seeking cocaine-dependent individuals. Two were Caucasian, two were women and four were African–American, with a mean age of 31.8. Subjects were randomly assigned to disulfiram 250 or 500 mg, or identical placebo, for 3 days, and then underwent nasal cocaine administration. Due to subject dropout, the study reported only on the 250 mg dose of disulfiram. Following 3 days of disulfiram treatment, on the fourth day subjects received cocaine 1 mg/kg, 2 mg/kg, or placebo administration in daily sessions for three days. Subjects were given the low dose of cocaine first for safety reasons. Heart rate and diastolic and systolic blood pressures were monitored, and blood sampling for disulfiram and cocaine levels were taken at baseline and several time points up to 480 min. Disulfiram 250 mg/day for 3 days significantly increased plasma cocaine concentrations relative to placebo. Cocaine levels were roughly three times higher compared to the cocaine group alone. Likewise, the elimination half-life of cocaine was increased by disulfiram treatment over cocaine alone from 83 to 135 min. Disulfiram plus cocaine increased heart rate to about 92 – 95 bpm at 30 – 60 min following cocaine administration. Systolic and diastolic blood pressures also significantly increased, but values were not given. Disulfiram did increase the subjective ratings of 'high' for both cocaine doses, but this was only statistically significant for the 2 mg/kg dose ($p = 0.058$). The investigators suggested that disulfiram was inhibiting both microsomal and plasma carboxylesterases and plasma cholinesterase, which are the major cocaine metabolic pathways [47].

The same group [48], using the same study population as in the first study with the addition of one more African–American subject, published a more detailed account of the interaction, and included the data from the 500 mg/day disulfiram condition. Subjects were stable medically and psychiatrically and had no significant psychiatric or medical disorders. Four subjects used occasional marijuana (1 – 2 joints per month), but did not meet criteria for other illicit drug use. The AUC for the 500 mg disulfiram and intranasal cocaine 1 or 2 mg/kg group appeared to increase sixfold over cocaine conditions alone, and peak concentrations increased two- to threefold. However, in terms of cardiovascular effects, heart rate was significantly increased by the disulfiram 250 mg dose for both doses of intranasal cocaine; but there was no significant difference between disulfiram 250 and 500 mg treatments. Both 250 and 500 mg of disulfiram under 1 and 2 mg/kg cocaine conditions increased peak heart rate by about 20 bpm, from 80 to approximately 100 bpm. Peak systolic blood pressures were increased from about 120 to approximately 140 mmHg, with a peak effect time at about 180 min for the cocaine 2 mg/kg condition. For the 1 mg/kg cocaine condition, systolic blood pressure increases were about 15 mmHg, and diastolic blood pressure

increased from approximately 65 to about 78 mmHg. No arrhythmias were reported under any conditions. Visual analog scale items of feeling 'high,' 'rush,' 'sleep,' 'pleasant,' 'nervous,' 'paranoia,' 'sad,' 'depressed,' 'crash,' 'cocaine craving,' 'good effects' and 'bad effects' revealed no significant differences in subjects treated with disulfiram 250 or 500 mg versus placebo for either of the cocaine conditions. Some adverse effects were reported by subjects, including dyspepsia/nausea in three subjects, palpitations in two subjects, anxiety in five subjects and restlessness in two subjects.

In a more recent study [49], disulfiram was studied with intravenous cocaine administration. Subjects were nine non-treatment-seeking cocaine-dependent individuals: seven were African–American, one was Caucasian, and one was Hispanic. Six subjects were male and three were female, with a mean age of 40. Six participants had a history of alcohol abuse, and one had a history of alcohol dependence not requiring detoxification. The study was a randomized, double-blind, counterbalanced, placebo-controlled within-subjects design for both disulfiram and cocaine conditions. Subjects were first given, on a random basis, one of two disulfiram doses (62.5 or 250 mg) or placebo daily, each for 6 days. Cocaine intravenous doses were 0.25 and 0.5 mg/kg for three subjects; nine subjects completed only the 0.25 mg/kg dose. Cocaine and disulfiram pharmacokinetics were studied, as well as cardiovascular responses and subjective effects of the combination. AUC for cocaine after disulfiram pretreatment again indicated a substantial increase in AUC from 30 to 140%, although this was variable among subjects. Disulfiram administration was associated with an increase in cocaine half-life from 112 to 193 min. Mean peak heart rates for the high dose of cocaine and the high dose of disulfiram rose from about 75 bpm under resting conditions to slightly over 90 bpm, with the peak observed about 10 – 15 min following administration of intravenous cocaine. The 0.25 mg dose of cocaine yielded similar increases in heart rate. There was no difference in heart rate increases between the 62.5 and 250 mg doses of disulfiram. Under the high dose of cocaine and the 250 mg of disulfiram, peak rises in systolic blood pressure were from 115 to approximately 148 mmHg. Similar rises were seen for the low dose of cocaine, 0.25 mg/kg. Diastolic blood pressures in the 250 mg disulfiram and 0.5 mg/kg cocaine increased from about 68 to 85 mmHg. Blood pressure elevations and pulse rises appeared to be within the parameters seen in healthy adults undergoing modest exercise. The same Visual Analog Scale items were used as mentioned in the previous study. For most subjective responses, there was no significant difference across all conditions. However, there was an approximate 50% reduction in any 'high,' 'cocaine high' and 'rush' ratings following the 0.25 mg/kg cocaine dose administered with disulfiram 62.5 or 250 mg per day. The mean 'rush' scores decreased about 60% on 62.5 mg disulfiram per day and 46% with the 250 mg dose of disulfiram per day. All of these effects were significant, with p values of 0.02 – 0.03.

To the best of our knowledge, only one study has investigated the interaction between disulfiram, alcohol, and cocaine in a systematic blinded trial [35,50]. Although some of the results have been presented, the final study has not yet been published. This study was a two-site, double-blind, placebo-controlled in-patient study to determine the psychiatric and cardiovascular safety of alcohol use in cocaine-dependent subjects who used cocaine after chronic treatment with disulfiram. The study first established subjects' reaction to cocaine after disulfiram pre-treatment, and then to ethanol after disulfiram pretreatment. The third condition included the three-way interaction among the drugs. The disulfiram doses used were 250 or 500 mg. The intravenous cocaine dose was 30 mg cocaine hydrochloride, and the ethanol dose was 10% ethanol in 5% dextrose. The maximum doses of ethanol were 0.4 g/kg for males and 0.34 g/kg for females. Outcome measures included systolic and diastolic blood pressures, heart rate, and electrocardiograph measures. Subjective measures of craving and euphoria were assessed by standardized rating scales. Disulfiram treatment was 250 mg once a day, 500 mg once a day or placebo once a day, for 7 days each. Cocaine and ethanol in combination with disulfiram were first tested separately; then, on day 7, the three-drug interaction was tested.

Data arbitrarily defined as groups 1, 2 and 3 based on preliminary analysis suggested that ethanol produced a decrease in blood pressure and a compensatory increase in heart rate for treatment group 1. In group 2 (presumably the 250 mg of disulfiram), diastolic blood pressures dropped from about 80 mmHg pre-ethanol infusion to about 65 mmHg for the six subjects. Cocaine added to the ethanol tended to ameliorate the modest drops in diastolic blood pressure. Pulse rates for this group went from about 70 bpm to a maximum of 100 bpm, both for the presumed ethanol disulfiram condition and for the triple condition of disulfiram, ethanol, and cocaine. In the presumed 500 mg disulfiram group (group 3), only one subject completed that arm of the study, and two subjects were discontinued from the study because of marked hypotension under the disulfiram and ethanol condition without cocaine. One subject in group 3 completed all 7 days of the study and the final interaction among all three drugs. This subject, under disulfiram and ethanol condition alone, demonstrated reductions in diastolic blood pressures from around 84 mmHg to around 56 mmHg. On day 7, when cocaine + ethanol under the disulfiram condition was administered, blood pressure was protected by the cocaine, in that blood pressure did not drop significantly. For two other subjects, however, under presumed ethanol + 500 mg disulfiram conditions without cocaine, diastolic blood pressures dropped for one subject from around 70 mmHg to 50 mmHg, and this low blood pressure was sustained for at least 1 h. For the other subject, diastolic blood pressures were in the low 70s and

dropped to almost 40, and were sustained > 1 h. Both of these subjects exhibited a compensatory rise in pulse, from 70 to 110 bpm for one subject and from 70 to 130 bpm in the second subject, and this elevation was sustained for > 1 h. Because of the marked drop in diastolic blood pressure, neither subject was allowed to continue to receive the final condition with cocaine.

All conclusions must be very tentative at this point. For the 250 mg dose of disulfiram, both cocaine and ethanol were tolerated together in this short study. At 500 mg of disulfiram, the disulfiram + ethanol reaction led to significant hypotension in two subjects. The third subject had only modest blood pressure reduction, which was due to the ameliorating effects of the cocaine in that condition. Diastolic pressure did not fall, nor did compensatory rises in pulse rate occur. In summary, in this study it is likely that the major safety problem was the 500 mg dose of disulfiram with ethanol. The three-way interaction of cocaine, 250 mg of disulfiram and ethanol was tolerated safely, and cocaine may have protected against hypotension.

In summary, the three-way interaction of disulfiram, alcohol and cocaine has few subjects and studies. The most serious interaction appears to be disulfiram in doses of 500 mg with alcohol. Disulfiram slows the metabolism of cocaine; no study has demonstrated deleterious clinical effects of this interaction.

6. Disulfiram safety and adverse events in randomized clinical trials for the treatment of cocaine dependence

To date, there have been six randomized clinical trials using disulfiram to treat cocaine- and alcohol-abusing individuals (**Table 1**). The first was a study conducted by Carroll and colleagues [4] in which subjects were randomly assigned to disulfiram or naltrexone. The disulfiram dose was 250 mg per day for 12 weeks. Ingestion of disulfiram and naltrexone was observed once weekly by the project nurse. No side effects for either group were described. Subjects were 18 outpatients who had been screened to have no substance dependence other than alcohol and were medically stable and free of psychotic, bipolar, and other major psychiatric disorders. Seventeen men and seven non-Caucasians were included in the sample, with a mean age of 32. Attrition for both groups was high, with less than half the sample in each group completing the study.

The second randomized clinical trial of disulfiram for the treatment of cocaine dependence was conducted by the same group [5]. This was a larger trial with 122 subjects, with 73% males and 61% African–American or Hispanic. Subjects were excluded if they were dependent upon opiates or sedative hypnotics, had suicidal ideation, homicidal ideation, psychotic symptoms, or medical instability. Individuals could take 250 – 500 mg in flexible dosing. The mean dose was 261.5 mg in this 12-week clinical trial. Riboflavin was used to monitor disulfiram compliance by urinary screens, and compliance was high, with riboflavin confirming self-report 88% of the time. There was no mention of adverse events nor any mention of disulfiram–alcohol interactions in this comorbid alcohol/cocaine population.

Petrakis and colleagues [7] conducted a randomized clinical trial in opiate-dependent, methadone-maintained cocaine-dependent outpatients. Sixty-seven subjects participated in the trial, with 34 individuals randomized to disulfiram for 12 weeks. The sample consisted of 48% males, 51% being Caucasian. Along with their methadone, disulfiram ingestion was witnessed in therapy for the duration of the study. Exclusions included homicidal ideation, suicidal ideation, and medical instability. Thirty-six subjects took disulfiram at a dose of 250 mg/day. The mean methadone dose was 88.6 mg/day. Sixty-two per cent of the sample used crack cocaine, and 27% of the sample used intravenous cocaine. Eleven per cent were nasal insufflators. Subjects were breathalyzed prior to methadone dosing daily, and if they had a positive breathalyzer reading > 0.02 g/ml of alcohol, methadone or disulfiram was not administered that day. In the disulfiram group, two individuals developed a rash and were discontinued from the trial. One disulfiram subject had a seizure, one experienced depression, one had suicidal ideation, and one subject had psychotic symptoms. Five subjects reported drinking during the study, but none of these subjects had a disulfiram–ethanol interaction.

In a small, randomized clinical trial, George and colleagues [6] randomized 20 individuals to receive disulfiram or placebo. All subjects had a history of both opiate and cocaine dependence, and were taking buprenorphine therapy daily. Subjects with psychotic disorders, suicidality, pregnancy, and medical disorders were excluded. The authors also noted that they excluded subjects taking metronidazole (Flagyl) and other medicines that could produce disulfiram–ethanol interactions. Subjects were treated for 12 weeks. Buprenorphine and disulfiram ingestion was witnessed daily. Two subjects in the disulfiram group reported alcohol use during the study, but no disulfiram–ethanol interactions occurred in either subject. No other adverse events were reported.

In another large randomized clinical trial, Carroll and colleagues [8] randomized to disulfiram 250 mg/day or placebo for 12 weeks with a total number of subjects of 121, with 60 individuals taking disulfiram. The population was 26% female, 63% Caucasian, 31% African–American, and 6% Hispanic; the mean age was 34.6. Those cocaine-dependent individuals reported just over 9 drinking days in the 28 days prior to the study. Fifty-four met diagnostic criteria for alcohol dependence. Riboflavin markers were used to measure disulfiram compliance and 84% of the time riboflavin markers were consistent with self-report for taking disulfiram or placebo. The study excluded individuals with psychotic disorders and medically unstable individuals. During the study, 35 subjects drank on one or more days,

Table 1. Summary of randomized clinical trials using disulfiram to treat cocaine- and alcohol-abusing individuals.

	Petrakis (2000)	Carroll (2004)	Carroll (1998)	Carroll (1993)	George (2000)	Pettinati (2008)
N	67	121	122	18	20	208
Male	48%	74%	73%	72%	60%	70%
Race	51% Caucasian	63% Caucasian 31% African–American 6% Hispanic	39% Caucasian 56% African–American 3% Hispanic 2% Other	61.1% Caucasian	75% Caucasian	88.9% African–American
Age (years)	Not reported	34.6 (SD = 7)	30.8 (SD = 5.5)	32	Disulfiram = 36.8 (SD = 6.9) Placebo = 39.3 (SD = 5.1)	41
Ethanol use	4.1/30 days (SD = 7.6)	9.4/28 days (SD = 7.6)	17.2/30 days (SD = 7.9)	5.3 SD per day	Disulfiram = 0.6 SD per week (SD = 0.13) Placebo = 0.18 SD per week (SD = 0.58)	~ 14/30 days
Cocaine use	18.4/30 days (SD = 9.8)	13/28 days (SD = 8.7)	14.1/30 days (SD = 8.3)	3.7 g/week	Not reported	~ 17/30 days
Disulfiram exposure	250 mg q.d. × 12 weeks	250 mg q.d. × 12 weeks	250 – 500 mg q.d. × 12 weeks	250 mg q.d. × 12 weeks	250 mg q.d. × 12 weeks	250 mg q.d. × 12 wks
Compliance check	Witnessed ingestion	Riboflavin marker	Riboflavin marker	Witnessed ingestion	Witnessed ingestion	Pill counts
Disulfiram efficacy	Yes	Yes	Yes	Yes	Yes	Yes
Adverse events	Rash (n = 3) Chest pain (n = 1) MDE (n = 1) Suicidal ideation (n = 1) Psychotic symptoms (n = 1)	Headache Fatigue Nausea Diarrhea	Rash (n = 1) CD (n = 4)	Not mentioned	Not mentioned	Headache Drowsiness Anxiety Nausea

MDE: Major depressive disorder; SD: Standard deviation.

Table 1. Summary of randomized clinical trials using disulfiram to treat cocaine- and alcohol-abusing individuals (continued).

	Petrakis (2000)	Carroll (2004)	Carroll (1998)	Carroll (1993)	George (2000)	Pettinati (2008)
Disulfiram–ethanol interaction	0 reports	0 reports	0 reports	0 reports	0 reports	0 reports
Disulfiram–cocaine interaction	Self-reported seizure after using cocaine	0 reports	0 reports	0 reports	0 reports	0 reports
Major exclusions	Serious medical diagnoses Serious psychiatric disorder	Serious medical diagnoses Suicidal ideation Severe polysubstance dependence	Serious medical diagnoses Opiate or barbiturate dependence Psychotic or bipolar disorder Suicidal ideation	Psychotic or bipolar disorder	Serious medical diagnoses Use of metronidazole Current psychosis or suicidal ideation Pregnancy	Serious medical diagnoses Psychosis Mania Dementia Pregnancy Breast feeding
Subjective effects of cocaine	Craving decreased No effect on subjective 'high'	Not mentioned	Not mentioned	Lowered expectation of cocaine high without ethanol	Not mentioned	Not mentioned

MDE: Major depressive disorder; SD: Standard deviation.

but there was no disulfiram–ethanol interaction reported. The authors found that individuals needed to be on disulfiram for ≥ 3 weeks in order to show a significant reduction in drinking. Adverse events were in general mild, and there were nonsignificant differences in frequency of side effects for placebo versus disulfiram. Side effects noted in both groups were 33% headaches for placebo and 34% headaches for disulfiram; nausea was 26% for both groups; and fatigue occurred in 28% of placebo subjects and 34% of disulfiram subjects. No differences in adverse experiences occurred in those individuals who used alcohol or cocaine during the study. There were no deaths and no serious adverse events reported.

Pettinati and colleagues [9] conducted a double-blind, placebo-controlled trial that evaluated the safety of disulfiram, naltrexone, the combination of the two, and placebo in patients with comorbid cocaine and alcohol dependence. Two hundred and eight subjects were randomized to disulfiram 250 mg/day, naltrexone 100 mg/day, a combination, or placebo for 11 weeks. The most effective treatment arm was the combination of naltrexone and disulfiram in reducing both alcohol and cocaine use. Medication adherence in this trial was not high, in that slightly less than 50% of patients took 80% of their medications while in treatment, and this rate did not differ for any of the four treatment groups. Headache, drowsiness, anxiety, irritability, and nausea were the most frequent side effects recorded by the disulfiram and the disulfiram-naltrexone group. These side effects were consistently higher than the same side-effect frequency in the placebo group. There were no patient deaths or serious adverse events reported during this trial. Although patients drank during the trial, no disulfiram–ethanol interactions were reported.

In summary, over a 10-year period, approximately 258 subjects have taken disulfiram in randomized controlled trials for cocaine dependence for periods of 1 – 12 weeks, primarily at a dose of 250 mg daily. Side effects reported were similar to those observed in disulfiram alcohol dependence trials. About 40% of subjects reported some ethanol use in the disulfiram cocaine trials, and none of these reported any disulfiram–ethanol interactions.

7. Clinical lessons from randomized clinical trials

There are no pharmacotherapies approved by the FDA for treatment of cocaine dependence. The devastating medical, psychiatric, legal, social, and societal damage of cocaine dependence weighs heavily in the risk:benefit ratio of evaluating the safety of disulfiram for the treatment of cocaine dependence. Based on the systematic Phase I studies and the randomized Phase II studies, one has to conclude that the interaction of the three agents appears to be no greater, and perhaps less, than the interaction of disulfiram and alcohol alone. Information from the Phase I and II trials

on disulfiram are informative as to maintaining an 'envelope' of safety for clinical patients taking disulfiram. These issues are briefly summarized below.

7.1 Informed consent

By obtaining both written and oral informed consent for disulfiram in a standardized fashion, the clinician can accomplish a balanced and detailed accounting of disulfiram side effects and of the consequences of cocaine and alcohol abuse. Patients can make an informed decision with clear expectancies. Common and serious adverse events should be covered. In addition, handouts listing interactions of medicines with alcohol, cocaine, and disulfiram should be provided to patients and to their significant others and family. Obtaining informed consent implies the capacity to give it; if this is in doubt, assess and document cognitive capacity.

7.2 Patient characteristics

Controlled studies of disulfiram have primarily occurred in males and females of Caucasian (particularly Scandinavian), African–American and Hispanic ethnicities. Asians have not been reported in these studies. Because of this and the theoretical potential for an unusually severe disulfiram–ethanol reaction, disulfiram cannot be recommended for treatment in this group. Most studies have been conducted in individuals aged 20 – 50 years, and mean ages have been around 40 years. Since risk of cardiovascular diseases, including stroke, increase greatly from the age of 50 onward, this helps, but does not eliminate, possible cardiovascular complications in patients using disulfiram, alcohol, and cocaine. Women who are pregnant or at risk for becoming pregnant, or nursing mothers, should not use disulfiram.

7.3 Comorbid disorders

Randomized clinical trials using disulfiram for treating cocaine dependence have done an excellent job of screening out patients with comorbid disorders that might lead to significant adverse events (**Table 1**). This is a factor that helps to explain why the frequency of adverse events seen in randomized clinical trials is less than that seen in the clinical use of disulfiram. A history of cardiovascular disease and serious Axis I disorders that can have psychotic consequences come at the top of the exclusionary criteria for using disulfiram to treat comorbid alcohol and cocaine dependence. Patients with cardiovascular disorders, including recent myocardial infarctions, arrhythmias, angina, previous strokes or transient ischemic attacks, in which hypotension and tachycardia could lead to grave, if not lethal consequences, should be excluded.

The question arises as to whether patients who have none of these conditions, but who have risk factors for cardiovascular disease, should be seen for a cardiovascular evaluation prior to disulfiram therapy. Here the randomized clinical trials are silent and provide us with no guidance. Many cocaine-dependent alcoholics in their 30s and 40s smoke, have untreated hypertension, and may or may not have familial risk factors and elevated lipids. One way to think clinically about this is that every time they use cocaine, they undergo stress testing with hypertension, tachycardia, and generalized manifestations of vasoconstriction [22]. Therefore, if the patient reports chest discomfort, shortness of breath, palpitations or visits to the emergency room during cocaine use, then one would be wise to avoid disulfiram therapy and refer the patient for further cardiovascular evaluation. Because of the downregulation of DBH by disulfiram, screen for and exclude patients with schizophreniform disorders, bipolar disorder or a history of cocaine-induced psychosis. Brief suspiciousness during acute cocaine use is not considered to be a symptom of psychosis.

Acutely suicidal patients have been excluded from randomized clinical trials, and that is sound guidance. As discussed below in the disulfiram dosing section (see Section 7.5), witnessed administration of disulfiram, coupled with keeping the disulfiram in a secure place away from the patient, will decrease the odds of the patient taking an overdose of disulfiram or stockpiling the disulfiram for the possibility of a future overdose.

7.4 Drug interactions

In any patient with cocaine dependence, it is important to assess the extent of alcohol consumption. Alcohol interacts with many classes of medications, and regular high-dose alcohol intake is probably the most significant interaction to consider in a patient who is taking disulfiram for the treatment of cocaine dependence. Several websites update ethanol-related interactions regularly (Micromedex, 2008; Prescribers Letter, 2008). Depending on the extent of the dose, duration of alcohol use, wide classes of medicine can interact adversely with alcohol, including analgesics, antidepressants (including monoamine oxidase inhibitors), antithrombosis and antidiabetic medications. Anti-infectives (cephalosporins such as cefoperazone, cefotetan, ketoconazole and metronidazole) can have disulfiram-like interactions with alcohol, and can be additive with disulfiram. Patients who are hypotensive due to medications or disease states may be relatively poor candidates for disulfiram therapy.

Disulfiram has effects on the P450 system, principally inhibiting CPY2E1, at doses of ≤ 250 mg daily [26]. Disulfiram elevates levels of phenytoin and increases warfarin activity. It can interact with certain benzodiazepines to slow their metabolism, including chlordiazepoxide and diazepam. Disulfiram does not interact with oxazepam to a significant degree [51]. Since interactions are updated frequently, the practitioner should consult an online interaction website for current updates. Examples of common medications that interact with disulfiram (pharmacokinetically or pharmacodynamically) include omeprazole, isoniazid, imipramine and amprenavir [52].

Table 2. A safety checklist for disulfiram for the treatment of cocaine dependence (based on inclusion/exclusion criteria found in randomized clinical trials of disulfiram for cocaine dependence).

Oral and written informed consent
Risks/benefits of disulfiram
Risks of continued use of alcohol/cocaine
Patient characteristics
Under 50, white, African–American and Hispanic males and females not at risk of pregnancy
Comorbid disorders screen
No cardiovascular disease
No severe liver disease
No neuropathy
No history of cocaine-induced psychosis or other psychotic disorder
Medication interactions
Caution with:
Long-acting benzodiazepines
Some anti-infective medications that have 'disulfiram-like' interactions with alcohol (e.g., metronidazole)
Some cephalosporins (see Section 7.4)
Disulfiram dosing
Up to 250 mg/day: is witnessed therapy safe and practical? If not, how will disulfiram adherence be measured?

7.5 Dosing of disulfiram

Here the literature provides firm guidance for the treatment of cocaine dependence with or without alcohol use. The 250 mg dose in the five randomized clinical trials was safe and efficacious for the treatment of cocaine dependence. This is also the dose in the study by Christensen and colleagues [37] and in the Brewer clinical report [36], which evoked a mild warning reaction to the use of alcohol with disulfiram without severe hypotension and tachycardia. Patients, and those observing administration, should be instructed that the patient must not take extra doses to make up for missed doses. Without witnessed therapy several times a week, disulfiram is likely to be ineffective in altering alcohol use and decreasing cocaine use. Martin and Beresford [53] have emphasized the need for witnessed disulfiram administration to provide maximum efficacy. They point out that there is a literature on court-mandated supervised disulfiram adherence. In their work in this area, court-mandated disulfiram adherence doubled clinic attendance to 87% of visits as compared to 42% of visits to the group without court-ordered appearance ($p = 0.0001$). Follow-up at 15 months indicated even a greater difference with clinic visits, with 61% of court-mandated group attending clinics versus 18% in the voluntary group.

In this same paper, the authors retrospectively reviewed hepatic safety in individuals who were hepatitis virus C (HVC)-negative ($n = 20$) and in HVC-positive individuals ($n = 26$) at 3, 6, 9 and 12 months of disulfirm treatment. There were no significant statistical or clinical elevations for either group at any time point. Although this is a small sample, lack of hepatic toxicity while on disulfiram in the HVC-positive group is reassuring, since HVC infectivity is common among cocaine-dependent individuals. Patients and medication observers need to be reminded that there is a 2- to 3-day window at the start of disulfiram therapy, before it becomes efficacious in producing the disulfiram–ethanol reaction. Of great importance is the notification of the patient and significant others that there needs to be a 2-week washout period after disulfiram is ended before any ethanol ingestion occurs, to rule out the possibility of the disulfiram–ethanol reaction. The medication should be kept in a secure environment where it is safe from children and potentially impulsive, self-destructive patients.

7.6 Clinician education

As this paper documents, prescribing disulfiram for cocaine-dependent, alcohol-using patients requires diligence on the part of both patient and physician. The patient must have sufficient information to agree to disulfiram therapy, avoid harmful interactions, and promptly report side effects. The physician must rule out dangerous comorbid disorders, avoid drug interactions, and know the psychiatric status of the individual patient. **Table 2** provides a checklist that offers a guide to safe clinical management, but is not comprehensive of all factors to be considered for the clinician prescribing disulfiram in a specific patient.

8. Expert opinion

Six randomized clinical trials of disulfiram to treat cocaine dependence with or without alcohol dependence have found both efficacy and safety. Side effects rarely lead to discontinuation of medication; there have been no deaths reported in this population; and the disulfiram–ethanol interaction has not been reported in these trials. Although speculative, an explanation for this lack of serious interaction between disulfiram and ethanol is undoubtedly in part due to the restriction of dose of disulfiram to ≤ 250 mg; the exclusion of medical, psychiatric, and neurologic disorders that could worsen this reaction; the exclusion of individuals who have poor metabolism of alcohol and acetaldehyde (primarily Asians); and the limited evidence that cocaine in the presence of alcohol and disulfiram may reverse some of the effects of disulfiram and alcohol alone.

Numerous medications for the treatment of cocaine dependence have been studied and are currently being studied [18]. Modafinil has emerged as a drug with some promise for the treatment of cocaine dependence, but has not shown any efficacy for the treatment of comorbid

alcohol dependence. Although medications that diminish the activity of DBH without altering aldehyde dehydrogenase activity are under development, it is unclear whether any of these medications would effect a significant reduction in alcohol use. Therefore, disulfiram stands alone as an agent that effectively and safely treats comorbid cocaine and alcohol dependence.

Could disulfiram be approved by the FDA for the treatment of cocaine dependence with or without alcohol dependence? The short answer is that only the FDA could make this decision. The more complex answer is that there is an interesting precedent in this area that demonstrates parallels between naltrexone and disulfiram. Naltrexone had been marketed, beginning in the 1970s, as a fairly expensive treatment for opiate dependence. Two small trials published in the early 1990s showed modest efficacy and good safety of naltrexone in the treatment of alcohol dependence. Shortly thereafter, in a collaboration between a private pharmaceutical firm and the National Institute of Alcohol Abuse and Alcoholism (NIAAA), naltrexone won approval as the second drug to receive FDA approval for the treatment of alcohol dependence. Remarkably, efficacy was established in two combined studies that had approximately 200 subjects randomized to naltrexone or placebo. However, as with disulfiram, there were some controversies over serious medical side effects, including hepatotoxicity. In clinical practice, these side effects for naltrexone have not proven to be of major concern as long as there is adequate medical screening and monitoring.

Similarly, in the six randomized clinical trials of disulfiram for the treatment of cocaine dependence, safety has been established primarily because of adequate medical monitoring. Patient information, in the form of oral and written informed consent, has been sound; patient populations have been limited to Caucasians, African–Americans, and Hispanics; Asians and pregnant females have been excluded. Patients with comorbid medical, psychiatric, and neurologic disorders have been excluded, and side effects in these areas have been monitored. Patients who might have pharmacokinetic and pharmacodynamic interactions from other medicines interacting with disulfiram have also been excluded. Disulfiram dose has been limited to ≤ 250 mg. A system of witnessed therapy or a system of medication adherence monitoring is essential.

It is likely that the indiscriminate wide use of disulfiram to treat cocaine dependence would lead to some severe medical complications. Thus, physicians and other prescribing practitioners need to have sound knowledge for their prescribing practices of disulfiram and cocaine- or alcohol-dependent patients. Again, there is an interesting precedent here from the field of addictions. Physicians who wish to prescribe a buprenorphine–naloxone combination must take a course and receive a special license to prescribe buprenorphine. Perhaps one solution to assuring adequate safety and monitoring on the part of practitioners would be have a similar course with a special license to prescribe disulfiram for the use of cocaine dependence.

There are > 50 million stimulant abusers worldwide, with about 14 million of these being cocaine abusers [54]. Although various forms of psychotherapies have demonstrable benefit for cocaine dependence, such therapies are expensive and not widely available. Disulfiram offers an intriguing and compelling treatment for cocaine dependence. It has not been studied in amfetamine and methamfetamine dependence, but could also be beneficial in these areas.

Disulfiram has been established to be efficacious in the treatment of cocaine dependence with or without alcohol use or dependence. Both Phase II randomized clinical trials and Phase I human laboratory studies of safety and pharmacokinetics indicate that – with appropriate dosage, appropriate patient instructions, witnessed therapy, and attention to comorbid disorders and drug interactions – disulfiram therapy can be safe and of therapeutic benefit to patients with cocaine addiction. Medications that downregulate DBH without affecting aldehyde dehydrogenase are under investigation [55] and may provide a safer alternative to disulfiram in the future.

Declaration of interest

The authors declare that they have no conflicts of interests concerning the preparation of this manuscript.

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