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DISULFIRAM: A REVIEW ARTICLE ON PHARMACOLOGICAL PROFILE AND ITS APPLICATIONS BEYOND ALCOHOL DEPENDENCE

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ABSTRACT

Disulfiram, an alcohol-aversive drug, has been approved by the U.S. Food and Drug Administration (FDA) for over 55 years and is widely used in the treatment of alcohol dependence. This review evaluates its clinical efficacy, risks, benefits, and indications while summarizing recent findings in its therapeutic applications. Disulfiram functions by inhibiting the enzyme aldehyde dehydrogenase, leading to unpleasant physiological reactions when alcohol is consumed. This deterrent effect has made it a useful component in alcohol use disorder treatment, particularly in supervised settings to ensure compliance. Clinical studies suggest that Disulfiram can be effective in reducing alcohol relapse when used alongside psychosocial interventions. Beyond alcohol dependency, emerging research has explored its potential in treating cocaine addiction and co-occurring alcohol-cocaine dependence by disrupting dopamine metabolism. Despite its benefits, Disulfiram therapy is associated with risks such as hepatotoxicity, cardiovascular complications, and patient non-adherence due to its aversive effects. Proper patient selection, monitoring, and a structured treatment plan are crucial to maximize its therapeutic potential. This review discusses the challenges clinicians face in managing alcoholism, including identifying alcohol-dependent individuals, implementing detoxification strategies, and incorporating pharmacotherapy into comprehensive treatment programs. Furthermore, it highlights alternative pharmacological interventions and the evolving role of Disulfiram in addiction medicine. The findings underscore the importance of individualized treatment approaches, considering both the pharmacological and psychosocial aspects of recovery.

KEYWORDS:DDC-Diethyldithiocarbamic acid, DSF-Disulfiram, DTC- Diethylthiocarbamic acid, DEA-Diethylamine, CS_2 -Carbon disulphide CYP-Cytochrome (enzyme), TM- tetrathiomolybdate.

INTRODUCTION

It has been more than 55 years, Disulfiram has been approved by US(FDA)[1] and used as an alcohol-aversivedrug recommended by physicians in the treatment of alcohol dependency or disorders. We reviewed the clinical literature regarding the risks, benefits, indications, and efficacy and summarized current knowledge of this therapy. Clinical trials using disulfiram for the treatment of alcohol, cocaine, or co-occurring alcohol + cocaine dependence were included in this review. Providing treatment that will end abusive drinking is a challenge for the clinician caring for the alcoholic patient. In order to administer this treatment, medical professionals need to recognize and deal with the active alcoholic in their practice, oversee the patient's alcohol detoxification, and give basic information about additional treatment options. Surveys indicate that approximately half of all practitioners who treat alcoholism employ alcohol aversive medications, which are accessible in addition to these fundamental therapies.

The History of Alcohol-Aversive Drugs

Aversion Therapy

Aversion therapy is a behavioral treatment technique in which a controlled drinking situation is linked to an electrical, chemical, or behavioral aversive stimulus administered by the therapist. It is an old technique that has been reviewed by Nathan, who describes the use of emetine, electric shock, succinylcholine induced paralysis, aversive images, and a host of other aversive events in a comprehensive review of the treatment of alcoholism by aversive therapy. Aversive conditioning can often be difficult to administer and is relatively uncommon in this country. Although classical aversive conditioning is restricted to a few centers that report a consistently moderate success rate another form of aversive therapy using alcohol aversive drugs has become quite common.[2]

Alcohol Aversive Drugs

Calcium Carbamide

Carbamide, another industrial compound with known alcohol aversive effects, was suggested for use in alcoholism treatment by Ferguson in 1956.[17] The citric acid salt (Citrated calcium carbamide, Temposil, Abstem) was introduced into Canadian and European practice following a series of reports demon-strating that the usual daily dose of 50 mg of this drug produced a milder aversive reaction than disulfiram, did not inhibit dopamine hydroxylase, produced less severe cardiovascular effects, and was clinically equivalent in trials in volunteers and in short-term trials in alcoholic patients. Continued work at the Addition Research Foundation has shown that the rapid onset and short duration of action of calcium carbamide may be important advantages of this drug in some clinical situations. Calcium carbamide is prescribed about half as frequently as Disulfiram.[2]

Metronidazole

In 1964[18], Taylor used the antitrichomonal drug metronidazole as an alcohol aversive and reported that the drug was effective not only in producing an aversive response, but also in reducing the craving for alcohol. Several authors attempted to replicate these results and were not able to demonstrate either an anticraving or a reliable aversive effect. Rothstein and Clancy initiated andthen abandoned a trial using a combination of disulfiram and metronidazole due to a greatly increased incidence of toxic psychosis (20%) in patients taking both drugs. The Food and Drug Administration has never approved the marketing of metronidazole as an alcohol-aversive drug.[2]

DISULFIRAM(ANTABUSE)

Discovery of Disulfiram

1800s, tetraethylthiuram disulfide (Disulfiram), a Since thiuram derivative has been used as a compounding agent to accelerate the manufacturing process of rubber. In 1937 Disulfiram was firstly discovered as a potential treatment for alcoholism when E. E. Williams, an American chemical plant physician, observed that a group of laborers exposed to Disulfiram experienced unpleasant physiological symptoms after drinking alcohol. These individuals became ‘‘involuntary total abstainers.’’ Williams speculated that disulfiram’s aversive properties to alcohol could perhaps lead to ‘‘the cure for alcoholism.’’ A decade later, 2 Danish researchers, Hald and Jacobsen, independently chanced upon the disulfiram-ethanol reaction during their investigation on disulfiram as vermicide and began collaborating with a clinician, Martensen-Larsen. In subsequent clinical trials, mainly by Hald and Jacobsen10 and Martensen-Larsen, disulfiram was found to be therapeutic for its deterrent effects, and the research findings provided early signs of optimism for a pharmacological treatment of alcoholism.[1]

Pharmacology

Faiman has extensively reviewed the pharmacology of disulfiram (Antabuse, Antabuse) in an excellent article. The drug is absorbed rapidly following an oral dose, attaches to visceral tissues within an hour (resulting in very low plasma levels), and is excreted as diethyldithiocarbamate and its conjugates, diethyl-amine and carbon disulfide. Disulfiram is a relatively non-specific irreversible inhibitor of sulfhydryl containing enzymes. The target enzyme for the pharmacologic effect of the drug is aldehyde dehydrogenase, an NAD requiring enzyme, which converts acetaldehyde to acetate in the metabolism of ethanol. Aldehyde dehydrogenase is not the only enzyme the drug affects; dopamine hydroxylase, superoxide dismutase, and some of the enzymes of intermediary metabolism are reduced in activity as well. Ingestion of a single dose of oral disulfiram will begin to affect ethanol metabolism within 1 to 2 hours, peak at 12 hours, and recede over 12 to 72 hours, depending on the rate of new enzyme synthesis.[2]

The ethanol-disulfiram reaction is presumed to be due to the combination of the effects of circulating acetaldehyde with an intrinsic host susceptibility; it consists of a highly aversive episode of flushing, weakness, nausea, as well as occasional hypotension. The drug is usually given in an oral form as a liquid or tablet, and a wide range of doses have been used in clinical practice. The medically supervised ethanol- disulfiram reaction was commonly performed in the years between 1949 and 1955.[7-13] This method consisted of detoxifying the patient from alcohol, loading them with several days of disulfiram therapy, and then having the patient drink alcohol under medical supervision. Following the reaction (which might be repeated several times), the dose of disulfiram was adjusted to the minimum individual dose that would produce an aversive response.[2]

MOA: Alcohol dehydrogenase breaks down ethanol when it enters our bodies to produce acetaldehyde, which is then further broken down into acetate by aldehyde dehydrogenase. Disulfiram suppresses acetaldehyde metabolism and the activity of aldehyde dehydrogenase.

The increased concentration of acetaldehyde causes Nausea, vomiting, palpitation, blurred vision, dyspnea (**Fig.1**).

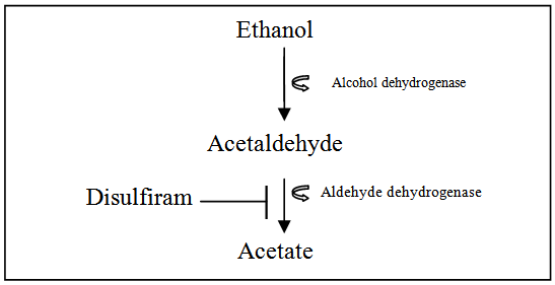

Fig. 1: Inhibition of Acetate by Disulfiram.

Disulfiram and its active metabolite have many other targets. DC is a potent metal-chelating agent, which explains its effectiveness in treating nickel sensitivity and its effects on the activity of copper-dependent enzymes such as microsomal carboxylesterases, plasma cholinesterase, and cytochrome oxidase, among others.[20-21] Microsomal carboxylesterases and plasma cholinesterase are theorized to play a role in the pharmacokinetic increases in plasma cocaine levels caused by disulfiram and drugs metabolized by the cytochrome oxidase systems CYP450 and CYP2E1 (such as amitriptyline, warfarin, phenytoin, and some benzodiazepines [chlordiazepoxide, diazepam]) have increased plasma levels and prolonged half-lives in patients taking disulfiram.[4]

DDC also inhibits dopamine beta hydroxylase (DBH), which converts dopamine to norepinephrine.[24-25] The inhibition of DBH leads to an increase in the level of dopamine in the brain and periphery and decreased level of norepinephrine and epinephrine. The increased level of dopamine in the brain and periphery from the disulfiram may explain its possible therapeutic benefits in cocaine dependence and the potentiation of psychosis norepinephrine and epinephrine may explain the side-effects of hypotension seen in the disulfiram-ethanol reaction (**Fig.3).**

Pharmacokinetics

Absorption of disulfiram

Disulfiram is administered orally with standard doses ranging from 250-500mg daily and maximum suggested daily dosage of 500mg.[74-75] DSF is reduced to diethyldithiocarbamic acid (DDC), about 80-90% of the dose is absorbed in the gastrointestinal tract.[76,77] In acidic conditions, DDC is highly unstable and quickly breaks down into carbon disulphide (CS_2) and diethylamine (DEA).[78]

Metabolism of Disulfiram

Distribution, Protein binding and metabolism:

DSF and its metabolites are uniformly distributed throughout the body in various tissues after absorption. DSF and DDC attach to proteins both in vitro and in vivo by forming mixed disulphides with the free thiol groups of various proteins.[79-80] In the bloodstream, both DSF and Me-DTC exhibit a high degree of binding primarily to albumin, with average binding percentages of 96.1 and 79.5, respectively.[81]

The percentage bindings were linear across the 345-2756 nM concentration range, with mean association constants at 7.4, of 7.1 x 10^4 for DSF and 6.1 x 10^3 for Me- DTC. Both drugs had an average of roughly one binding site per protein molecule, indicating a single kind of binding site. The mean number of binding sites per protein molecule was approximately 1 for both substances, which suggests a single type of binding site.

Upon ingestion, disulfiram is converted into diethyldithiocarbamic acid (DDC) under the acidic conditions of the stomach. Due to its instability, DDC can decompose into carbon disulphide and dimethylamine, or form a bis(diethyldithiocarbamate) copper complex (Cu(DDC)2) (**Fig.2**)

Clinical uses of disulfiram are due to its quick biotransformation into metabolic products and extensive in vivo metabolism.[82] Once disulfiram is reduced, all further metabolism takes place via DDTC, which has three possible metabolic fates.

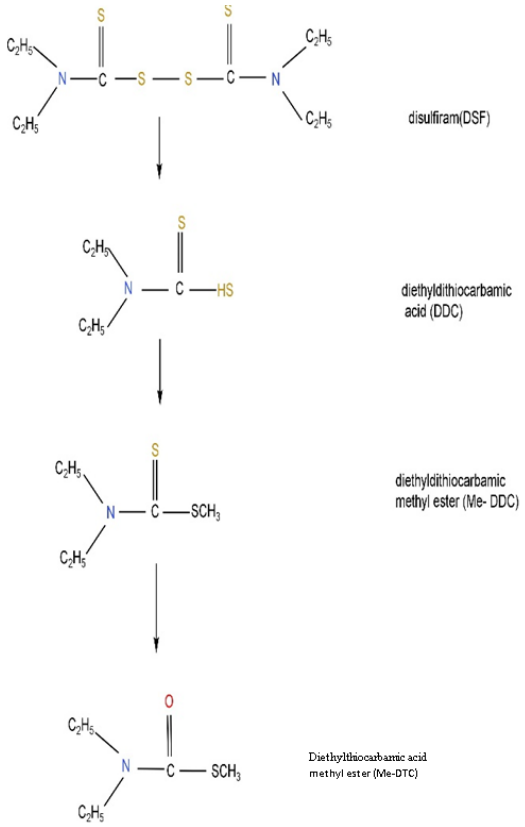

Fig. 2: Metabolism of disulfiram(DSF) into Diethylthiocarbamicb acid(Me-DTC)[6]

1. Spontaneous degradation: DDTC is acid liable and its half-life is a linear function of its pH. In an acidic environment, such as the stomach, DDTC is decomposed to diethylamine and carbon disulfide (CS2). The CS2 can be detected in the blood and of its pH.[83] In an acidic environment, such as the stomach, DDTC is decomposed to diethylamine and carbon disulfide (CS2).

The CS2 can be detected in the blood and breath of humans after the administration of disulfiram.[84-85] After the oral administration of 250 mg of disulfiram, the half-life of CS2 is roughly 12 h.[85] CS2 has been identified in the breath 72 h after administration.[86]

2. Formation of glucuronide: The formation of glucuronide is brought about by the enzyme

glucuronosyl transferase, which is highly expressed in the liver. The glucuronide of DDTC accounts for 2–11%of the administered disulfiram dose that is excreted in the urine.[86-87]

3. Formation of methyl esters: The enzymes thiols methyltransferase (microsomal) and possibly thiopurine methyltransferase (cytosolic), found in the liver and several other tissues including the GI tract, lungs, kidneys, catalyze the methylation of DDTC. The methylation reaction leads to the formation of the important lipophilic metabolite DDTC-Me (methyl diethyldithiocarbamate), which is then biotransformed into additional metabolites that aid in the irreversible inhibition of the ALDH enzyme.[82-88]

Elimination kinetics of disulfiram

The kidney, feces, and lung are the primary routes by which disulfiram metabolites are eliminated (89, 90, 91, 92). In the kidney, disulfiram is mainly excreted as a glucuronide of DDC or as inorganic sulphate. An oral dosage can be excreted in the feces as an intact medication for up to 20%.[90]

The kidneys remove around 65%, mostly as inorganic sulphate (up to 30% in animals) or the glucuronide of DDC (up to 53% in animals but much lower in humans).[93-94] DDC, Me-DDC, Me-DTC, CS2, and DEA, only minor amounts are recovered in urine. CS_2 is eliminated through the lungs, it is the major route of elimination.[95] where up to 53% of the dose is eliminated in some alcoholics[96], although only 12% was reported to be exhaled in another study.[97]

Studies have shown that disulfiram and DDTC have half-lives of approximately 7 hours and 15 hours, respectively, indicating significant inter-subject variability in their metabolism.

Pharmacodynamics

Alcohol dehydrogenase is an enzyme that breaks down ethanol in the liver by oxidizing it to acetaldehyde. Acetaldehyde is further metabolized to acetate by aldehyde dehydrogenase.[98] Acetate moves via various metabolic pathways, including the citric acid cycle (**Fig. 1**).

Acetaldehyde accumulation effects (Disulfiram-Ethanol reaction)

- Flushing, nausea, vomiting
- Tachycardia, hypotension, headache
- Dizziness, confusion, and sweating
- Severe cases may cause respiratory distress, cardiovascular collapse, or seizures.

The reaction begins almost instantly after consuming a single alcoholic drink and can persist for up to 30 minutes (if no further drinking occurs). As disulfiram and some of its metabolic derivatives irreversibly inhibit both the cytoplasmic and mitochondrial versions of aldehyde dehydrogenase, the restoration of enzyme activity depends on the synthesis of new proteins. Therefore, the effects can last several days after the last dose of disulfiram.[99-100]

Disulfiram and its active metabolites have many other actions. DC is a strong metal- chelating agent, which shows its effectiveness in treating nickel sensitivity and influencing the function of copper-dependent enzymes like microsomal carboxylesterases, plasma cholinesterases, and cytochrome oxidase, among others.[99-101]

DDC also inhibits dopamine β-hydroxylase (DBH), which converts dopamine to norepinephrine.[102,103] Blocking DBH results in higher dopamine concentrations in both the brain and peripheral areas, while norepinephrine and epinephrine levels decrease. The increased levels of dopamine in the brain and periphery from disulfiram may be useful as a treatment for cocaine dependence and the escalation of psychosis in psychotic people. The decreased levels of norepinephrine and epinephrine may explain the side-effect of hypotension seen in the disulfiram-ethanol reaction (**Fig.3**).

Catecholamine synthesis pathway

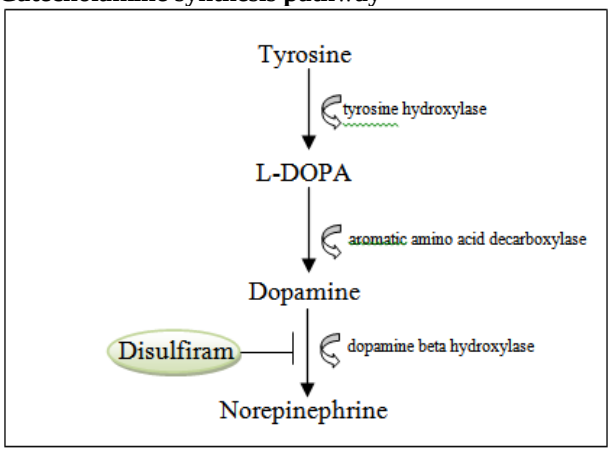

Fig. 3: Disulfiram inhibits dopamine -beta-hydroxylase in the catecholamine synthesis pathway.

Dosage

The minimal amount required to cause a reaction is unknown, even though very high doses of disulfiram are known to cause an ethanol-disulfiram reaction. Doses of 100 mg/day[26] to 250 mg/70 kg[27] have been demonstrated in experimental trials were conducted on volunteers to not consistently elicit a response. Brewer investigated alcoholic individuals who consumed alcohol while taking the medication or who had previously undergone a supervised ethanol-disulfiram challenge. After taking 200 mg/70 kg of disulfiram daily, 30 out of 63 alcoholic individuals in that research did not respond when challenged with alcohol.

Table I

It lists the loading doses, and the range of maintenance doses required to produce objective reactions in the early

studies of induced ethanol-disulfiram reactions.[7-13] As can be seen from the table, the maintenance dose of disulfiram required to elicit a supervised ethanol-disulfiram reaction is between 0.125 g/day and 1.00 g/day, with the median effective dose being about 300 rag/day to 500 rag/day. Since it is now possible to measure aldehyde dehydrogenase activity and to determine the degree of inhibition for an individual patient, such monitoring may allow more precise individualization of the dose in future research.[2]

Table I : Doses of Disulfiram used in Medically Supervised Ethanol-Disulfiram Reactions.

References	Day 1 (g)	Day 2 (g)	Day 3 (g)	Thereafter (g)
7	2.0	1.5	1.0	0.125-1.000
8	1-2	1.0	0.75	0.250-0.75
9	2.0	1.5	1.0	0.250-0.500
10	2.0	1.5	1.0	0.125-0.500
11	2.0	1.5	1.0	0.250-1.000
12	1.0	1.0	0.750	0.250-1.000
13	2.0	1.5	1.0	0.250

Toxicity

Numerous patients report a range of subjective adverse effects from disulfiram; nevertheless,[14] carefully planned, double-blind, randomised clinical trial of 241 participantsfailed to show any more subjective or any other side effects in people taking 200 mg/70 kg of disulfiram daily than with a placebo. Disulfiram may change the metabolism of endogenous amines and does change the metabolism of numerous medications that depend on hepatic metabolism.[15–28] In individuals using the medication, inhibition of dopamine hydroxylase and other monoamine enzyme systems has been linked to the development of hypertension[29], changed serotonin metabolism[30], and changed sympathetic tone of the patients.[31]

EFFECTIVENESS Of DISULFIRAM

Controlled studies

Disulfiram was introduced for the treatment and clinical use on the basic of unscientific and uncontrolled trials. Disulfiram was first used on a big scale withoutsupervise on done by Hoff[32] reported this in 1955. Hoff reported a case series of 1,020alcoholics[2] who choose to take disulfiram and 484 refused to take the drug, a significant improvement was see in those who chose the drug therapy.

In one of the largest surveys of the effectiveness of the disulfiram and such therapy Armor et al[33] published the outcome of patients that have selected disulfiram in number of treatments setting in the Rand report. According to these reports there was a better short term (6 months) result among those who had been consuming the disulfiram, but according to this report the effect was lost at 12 months and there is no way to determine whether the improvement was due to the selection bias or due to the Disulfiram.

Other studies on the possible bias introduced by the self-selection of the disulfiram treatment[34-35] suggested that those patients who accepted the disulfiram did differ from those who refused the drug. From these reports we can't conclude that if an improved outcome with the disulfiram was due to the drug or other factors such as patients' motivation or some type of selection bias.

Randomized clinical trials

There have been only two randomized clinical trials of disulfiram of adequate data and results that have addressed the pharmacologic and psychologic effects of disulfiram.

Fuller and Roth[39] approached the problem disentangling the pharmacologic and psychologic effects of the disulfiram in 1979.

Compliance with Disulfiram Therapy

Jacobson and Martinsen-Larsen[36], in their one of the earliest reports in English regarding the disulfiram made a remark that "as long as the patients take the tablets (Disulfiram) they will not drink."

Fuller and Neiderhiser[37] reported the compliance with the therapy in the group of 21 patients taking disulfiram for 1 year as the part of clinical trial of disulfiram efficacy.

Fuller et al reported a significant relationship between disulfiram compliance and treatment outcome. Of those patients who were found to be compliant with drug or placebo, 43% were abstinent in contrast with an 8% abstinence rate among noncompliant patients. From.[38]

This relationship was stable across all treatment groups regardless of the drug condition (**Table II**).

Table II: Relationship of Drug Compliance to Abstinence compared across drug treatment classes.

Treatment class	Percentage Abstinence	
	Compliant (20% of total)	Non-Compliant (80% of total)
250mg Disulfiram	38	10
1mg Disulfiram	50	9
Placebo	43	6
Across all classes	43	8

Fuller's work with riboflavin markers has not yet been fully replicated, and it is not known how accurate this method is in measuring compliance. In a similar study of lithium use in alcoholic populations (where compliance could be very accurately determined by serum lithium levels), medication compliance was a more powerful predictor of outcome than the drug effect being studied.[40]

Although the results were positive, these results are not definitive. Compliance and efficacy of the disulfiram is not definitive so to overcome this issue Surgical implanted tablets were introduced.

Disulfiram Implants

Kellan and Wesolkowski[41] described a technique of disulfiram implantation in a 1968 case report in Lancet. Two reports suggested that the implants resulted in a significant improvement in abstention[42,43] and in marriage, job, and social functioning.[42] These were promising results, but further studies indicated that patients were returning to drinking after implant without an ethanol-disulfiram reaction.[44-45]

These findings led Wilson et al[46] to study the 2- year post-implantation sobriety of 10 patients who had disulfiram implanted and 10 randomized control subjects who had sham operations. These investigators reported that there was no significant difference between the two groups in the first 6 months of followup, but that there was a small effect at 1 to 2 years. These authors[47] later added more cases to their series by randomizing additional patients until 3-5 they had a total of 40 patients who had accepted disulfiram and who received an implant, 40 patients who had accepted disulfiram and had received a placebo implant, 10 patients who had accepted disulfiram and had the operation delayed, and 10 disulfiram refusers. The major outcome in this study was days of abstinence from alcohol. In a 365-day follow-up, patients with implants had an average of 307 to 331 days of abstinence, compared to 24 to 31 days for those without implants. There was no significant difference between patients with disulfiram implants and those who received a placebo.

Implants improved performance, while individuals without implants performed worse, regardless of incentive {2}.

Contraindications, Precautions and Adverse effect and Monitoring

Contraindications/Precautions

The intensity of disulfiram ethanol reaction varies with each patients. Severe reactions which include Respiratory depression, Myocardial infarction, Cardiac arrhythmia, Convulsions, Congestive heart failure and death in severe cases if the patient is suffering from heart diseases or Respiratory problems. Therefore, the Disulfiram is contraindicated for patients with Cardiovascular or pulmonary diseases. Severe liver and kidney illness can reduce the excretion of disulfiram and its metabolites, leading to lower serum albumin levels and potentially higher amounts of free disulfiram metabolites. Before initiating disulfiram medication, it is recommended to check renal and hepatic function, including serum albumin.[48] Disulfiram should be taken with caution in patients with nephritis, brain injury, hypothyroidism, diabetes, hepatic illness, seizures, polydrug dependence, or an abnormal electroencephalogram.[49] Patients using above 500 mg of disulfiram per day and consuming more than 28 grams of alcohol are more likely to experience fatal responses.[49]

Adverse Effect

Disulfiram when taken in absence of alcohol can cause various adverse effects which include Dermatitis, fatigue, impotence, optic neuritis, peripheral neuropathy, hepatic damage and sometime psychosis. Drowsiness is also seen very commonly in patients taking disulfiram in the absence of alcohol.

Over a 23-year period (1968-19991), 155 aversive drug reactions reported for disulfiram, giving it an ADR report of 1 per 200-2000 per year.

Hepatic reactions were the most frequent ADR (34%), followed by the Neurologic (21%), Cutaneous (15%), Psychiatric (4%) and other (26%).[50]

Hepatotoxicity

Disulfiram may cause idiosyncratic hepatotoxicity, which can be fatal. Danish research on disulfiram for alcoholism reported 14 deaths, 11 of which were related to liver failure. The rate of fatal disulfiram-induced hepatitis is 1 per 25,000 individuals treated per year.[51] Current disulfiram doses (250-500 mg) are far lower than those used in early research (1-3 g). While there is still a danger, there are significantly fewer deaths from

disulfiram use in clinical practice. The peak of hepatotoxicity (fatal or nonfatal) occurs 60 days after starting disulfiram medication. Hepatotoxicity is typically reversible if stopped before clinically obvious liver damage develops.

Limitations of Disulfiram

Disulfiram when used has an avoidant action and used for aversive treatment of alcohol dependence. The fear or recollection of a disulfiram-ethanol interaction is one kind.

Conditioned avoidance aims to prevent patients from consuming alcohol. Efficacy studies on disulfiram over the past 60 years have yielded conflicting results due to small sample sizes, non-randomization, unblinded settings, short follow-up periods, and lack of treatment adherence measurements.

Early investigations were generally small and poorly controlled. Later trials appear to be divided in outcome based on whether disulfiram was administered supervised or unsupervised, with more favourable findings in studies with supervised disulfiram administration.[52] Review of disulfiram outcome studies have found out that only one of more than 40 clinical trials have met adequate research criteria and only five of 135 clinical trials have had a controlled design.[4]

Other Pharmacological effects of Disulfiram (DSF)

Anticancer activity of Disulfiram

The earliest clinical evidence shows that DSF has anticancer activity which can be traced back to the 1970s.[53] It was reported that DSF can induce apoptosis, reduce angiogenesis, and show metal ion-dependent antineoplastic activity. Researchers reported that DSF has anticancer effects in both human tumor cell lines and tumor cells from patients. Several effects of disulfiram, such as altering the intracellular Reactive oxygen species (ROS) level[54], inhibiting the Ubiquitin proteasome system (UPS)[55,56], and reducing the stemness of cancer cells.

- ***Reactive oxygen species***

ROS are produced by ordinary cellular metabolism. The elevated ROS level can change the oxidative mechanisms of cells which can deplete the antioxidant capacity of cellsultimately destroying the cellular structures and induce cell apoptosis in tumor tissues.

DSF and its major metabolite (diethyldithiocarbamate, DDC) bind to Cu, chelation triggers the production of ROS.[58,59] Another report indicates that DSF administered to the breast cancer cell lines at a concentration of 1 mM enhanced the cytotoxic effect of cisplatin by increasing the accumulation of ROS.[60] Thus, upregulating the ROS level might be a crucial underlying mechanism for the antitumor effects of DSF.

- ***Ubiquitin proteasome system***

UPS has a major role in maintaining the balance of protein metabolism and the normal function of cells. DSF contains active sulfhydryl groups, mechanistic studies have shown that it has a high affinity for thiol-containing proteins and can chelate some biological metals, which makes it possible to inhibit the 26S proteasome.[55] Such inhibition is related to the antitumor activity of DSF and this action is Cu dependent.

Notably, in breast cancer cell cultures and xenografts, DSF combined with Cu potently inhibited the proteasome in cancer cells, but not in normal or immortalized breast cells.[55] Recently, it was shown that the DDC/Cu complex CuET inhibits p97 binding to the proteasome substrate adapter NPL4, blocking substrate degradation and inducing cancer cell death.[61] The UPS is considered to be an essential target of DSF.

- ***Cancer stem cells (CSCs)***

Data from several studies showed that DSF can potently inhibit CSCs in different cancers, including breast cancer, lung cancer, and brain tumors, attenuating self-renewal ability, metastatic potential and cell growth, and augmentingcell apoptosis.[57,60,62]

- ***Oncogenetic signaling pathways***

Ying et al. confirmed that DSF can potently inhibit osteoclast differentiation by attenuating NF-kB activity in vitro.[63] Chiba et al. found that 90 % of cells showed an increase in phosphorylated p38 level when tumorinitiating hepatocellular carcinoma (HCC) was treated with DSF. This indicates that p38 MAPK is activated in HCC cells, and DSF inhibits tumor-initiating HCC cells in a p38-dependent manner.[64] Therefore, DSF could exert antitumor effects in part by downregulating the NF-kB and MAPK signaling pathways.

- ***Apoptosis***

Research showed that DSF induced apoptosis in human melanoma cell lines by decreasing the mitochondrial membrane potential.[65] In addition, studies of molecular targets indicated that, in the presence of Cu, DSF might take part in the intrinsic apoptotic pathway by increasing the expression ratio of Bax/Bcl-2 protein, leading to the promotion of apoptosis in human breast cancer cells.[66]

In malignant pleural mesothelioma (MPM) cells, DSF with Cu stimulated apoptosis by activating proapoptotic stress-activated protein kinases (SAPKs) p38 and JNK1/2, caspase-3 and -9, as well as increasing the expression of sulfatase 1 (SULF1) and apoptosis transducer CARP-1/CCAR1.[67] Other mechanisms of DSF actions are still being explored.

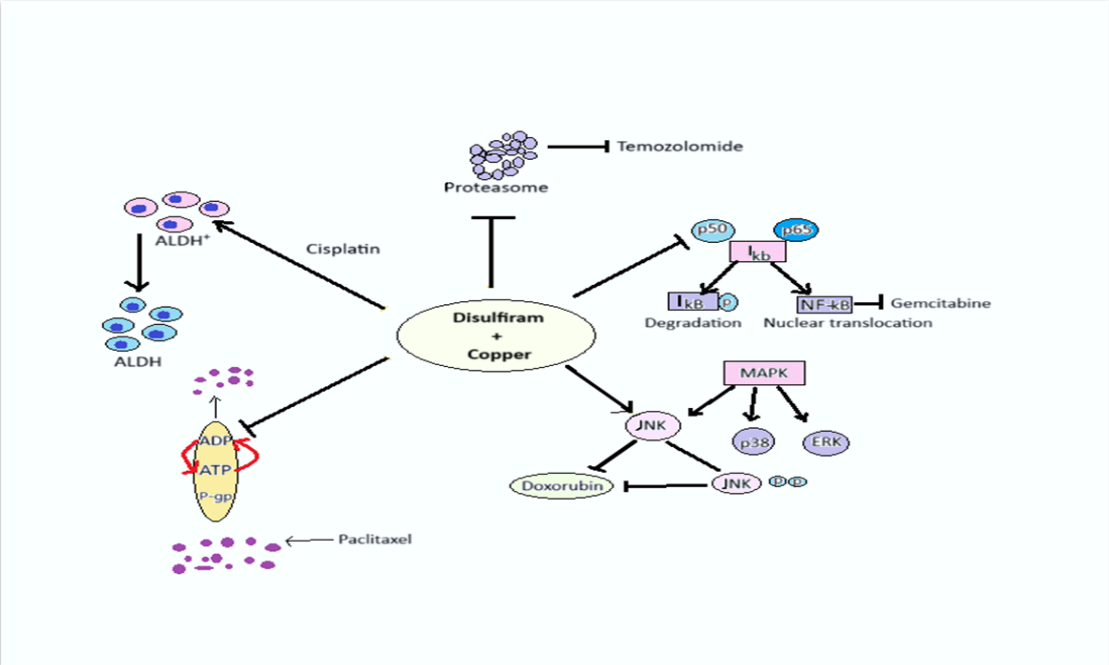

Figure 4: The mechanism of reversing drug resistance by disulfiram (DSF)/Copper (Cu). DSF in combination with Cu sensitizes cisplatin by targeting acetaldehyde dehydrogenase (ALDH)+cells. In addition, DSF/Cu inhibits the hydrolysis of ATP and, thus, the drug efflux pump. Furthermore, DSF/Cu can inhibit the proteasome and enhance the sensitivity of cells to temozolomide. Additionally, DSF/Cu can reduce nuclear factor kappa B (NF-kB) activity, retard IkB degradation, and sensitize cells to gemcitabine. Lastly, DSF/Cu reverses doxorubicin resistance by increasing c-Jun NH2-terminal kinase (JNK) expression and phosphorylation. Abbreviation: P-gp, P-glycoprotein.[107]

DSF combined with Cu in reversing drug resistance in cancers

DSF has been shown to inhibit several drug resistance-related targets in cancers and, thus, especially when used in combination with Cu, is considered as a novel strategy for overcoming drug resistance (**Fig. 4**).

Copper: a crucial player in cancer

Cu controls a number of endogenous biological processes. Many studies are being conducted on Cu chelators, including D-pen, tetrathiomolybdate (TM), clioquinol, and trientine, both in vitro and in vivo as well.[68–69] It has been demonstrated that D-pen is a reliable Cu chelator and can remove Cu in vivo. Goonerante et al. reported that the performance of D-peninre moving surfeit Cu is as effective as TM in both low and high-dose Cu diets.[69] Early research reported that the combination of D-pen and Cu could lead to cell death in endothelial cells and lymphocytes, possibly as a result of ROS production.[70] a clinical trial in glioblastoma showed significant ceruloplasmin depletion.[71] Moreover, TM also shows antiproliferative activity in vivo. In a mouse model of pancreatic islet cell carcinoma, the antiproliferative effect of TM was considered to reduce ATP production by mediating cytochrome c oxidase.[72] Decreasing Cu levels with TM also influencesMEK1/2 kinase activity and BRAF-driven tumorigenesis.[73] Therefore, it is not surprising that reducing intracellular Cu can alter tumor biology.

Hypertension

Disulfiram dose(125-500mg) taken per day can result in hypertension has been documented in very few earlier reports to cause reversible or dose-dependent stage-I and stage-II hypertension within 2-3 weeks of administration,[104-105] while a systematic review observed no change in blood pressure (BP) with 6 weeks of DSF (250 mg/day) therapy.[106] Surprisingly, most of the related articles were during the period between 1950s and 1980s.

CASE REPORT

A 39-year-old married adult male, from urban and middle socio-economic background, presented with a history of daily alcohol consumption (92-123 g of ethanol/day) and chewing of tobacco (15-20 packets) for 10 years with the dependence pattern since 4 years. He was diagnosed with alcohol dependence syndrome, and tobacco dependence. On admission, vital parameters showed marginal alcohol withdrawal sympathetic activity with pulse rate of 96 beats/min and BP of 140/90 mm of Hg. After alcohol detoxification, his BP had stabilized to 120/84 mm of Hg on day-8 of admission.

Haematological and biochemical tests, including serum glucose (105 mg/dl), blood urea (25 mg/dl), complete blood count, and 1.0 mg/dl of creatinine was within acceptable ranges. With the exception of increased liver enzymes (serum glutamic oxaloacetic transaminase 120 units/L, serum glutamic pyruvic transaminase 56 units/L,

and gamma-glutamyl transferase 96 units/L), liver function tests were normal.

His abdominal ultrasonography revealed a slightly enlarged liver with grade 2 fatty infiltration. The patient and spouse were informed about the nature of the condition and the several treatment options, including DSF, in light of the frequent relapses. A dose of 500 mg per day was started once written informed consent for DSF therapy was obtained.

Patients were discharged with DSF (500 mg/ day), and multi-vitamin supplementation. At discharge, his vital parameters were stable with pulse of 86 beats/min, and BP of130/80 mm of Hg.

Blood sugar dysregulation

- Hypoglycemia: disulfiram inhibits dopamineβ-hydroxylase, leading to altered norepinephrine levels, which may reduce gluconeogenesis and contribute to low blood sugar.
- Hyperglycemia: it may also impair insulin secretion and lead to increased blood glucose levels in some cases.
- Disulfiram has been linked to pancreatitis, which can worsen insulin resistance and affect glucose metabolism

Disulfiram- ethanol reaction (DER) and diabetes

If alcohol is consumed, the acetaldehyde buildup can trigger severe hypoglycemia, along with nausea, Vomiting and cardiovascular complications.

Diabetic patients are at higher risk for hypertension and heart disease, and disulfiram can worsen cardiac stress, arrhythmias, and blood pressure fluctuateons.

Effect on Type-2 Diabetes

- Disulfiram has been shown to reduce inflammation, which plays a major role in insulin resistance and type 2 diabetes.
- In some animal studies, disulfiram improved glucose tolerance and insulin sensitivity by suppressing inflammatory pathways (e.g., NLRP3 inflammasome).
- When taken with certain diabetes medications (like insulin or sulfonylureas), there could be an increased risk of hypoglycemia due to additive effects on glucose lowering
- Disulfiram has been shown to inhibit the NLRP3 inflammasome, a protein complex involved in inflammation. This could theoretically improve insulin sensitivity and reduce diabetic complications.
- Some animal studies indicate that disulfiram may enhance insulin sensitivity, helping cells respond better to insulin and improving blood glucose control

REFERENCES

1. Suh, J.J., Pettinati, H.M., Kampman, K.M. and O'Brien, C.P., 2006. The status of disulfiram: a half of a century later. *Journal of clinical psychopharmacology*, *26*(3): 290-302.
2. Chick, J., Gough, K., Falkowski, W., Kershaw, P., Hore, B., Mehta, B., Ritson, B., Ropner, R. and Torley, D., 1992. Disulfiram treatment of alcoholism. *The British Journal of Psychiatry*, *161*(1): 84-89.
3. Hughes, J.C. and Cook, C.C., 1997. The efficacy of disulfiram: a review of outcome studies. *Addiction*, *92*(4): 381-395.
4. Barth, K.S. and Malcolm, R.J., 2010. Disulfiram: an old therapeutic with new applications. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, *9*(1): 5-12.
5. Johansson, B., 1992. A review of the pharmacokinetics and pharmacodynamics of disulfiram and its metabolites. *Acta Psychiatrica Scandinavica*, *86*(S369): 15-26.
6. Petersen, E.N., 1992. The pharmacology and toxicology of disulfiram and its metabolites. *Acta Psychiatrica Scandinavica*, *86*(S369): 7-13.
7. Glud E: The treatment of alcoholic patients in Denmark with Antabuse. Q J Stud Alcohol, 1949; 10: 185-197.
8. Jacobsen E, Martinsen-Larsen O: Treatment of alcoholism with tetraethylthiuram disulfide, lAMA, 1949; 139: 9.
9. Gelbman F, Epstein NB: Initial clinical experience with Antabuse. Can Med Assoc J., 1949; 60: 549-552.
10. Barrera SE, Osinski WA, Davidoff E: The use of Antabuse in chronic alcoholics. Am J Psychiatry, 1950; 107: 8-13.
11. Dale PW, Ebaugh FG: Antabuse therapy in chronic alcoholism. Am J Med Sci, 1950; 107: 774-780.
12. Bowman KM, Simon A, Hine CH, et al: A clinical evaluation of tetraethylthiuramidsulfide in the treatment of problem drinkers. Am J Psychiatry, 1951; 107: 832- 838.
13. Winship GM: Antabuse treatment. In: Wallenstein RS, ed. Hospital treatment of alcoholism. New York: Basic Books, 1957; 23-51
14. Christensen JK, Ronsted P, Vaag UH: Side effects after disulfiram. Acta Psychiatr Scand, 1984; 69: 265-273.
15. Ciraulo DA, Barnhill J, Boxenbaum H: Pharmacokinetic interaction of calcium carbamide and antidepressants. Am J Psychiatry, 1985; 142: 1373-1374.
16. Williams EE: The effect of alcohol on workers with carbon disulfide. JAMA., 1937; 109: 1472-1473.
17. Ferguson JKW: A new drug for the treatment of alcoholism. Can Med Assoc J., 1956; 74: 793-799.
18. Taylor JA: Metronidazole: a new agent for combined somatic and psychic therapy of

alcoholism. Bull Los Angeles Neurol Soc, 1964; 29: 158.
19. Hoff EC: The use of disulfiram. Conn Med, 1955; 19: 793-799.
20. Malcolm, R.; Olive, M.F.; Lechner, W. The safety of disulfiram for the treatment of alcohol and cocaine dependence in randomized clinical trials: guidance for clinical practice. Expert Opin. Drug Saf., 2008; 7: 459-472.
21. Faiman, M.D. Biochemical Pharmacology of Disulfiram. In: Biochemistry and Pharmacology of Ethanol; Majehowicz E., Nobel E.P., Eds.; Plenum Press: New York, 1979; 325-348.
22. Peachy JE, Annis H: New strategies for using the alcohol-sensitizing drugs. In: Naranjo CA, Sellars EM, eds. Research advances in new psychopharmacological treatments for alcoholism. New York: Elsevier Science Publishers, 1985; 199- 216.
23. Linton PH, I/lain JD: Metronidazole in the treatment of alcoholism. Q J Stud Alcohol, 1966; 28: 544-547.
24. Goldstein, M.; Anagoste, B.; Lauber, E.; McKeregham, M.R. Inhibition of dopamine beta-hydroxylase by disulfiram. Life Sci., 1964; 3: 763-767.
25. Mussachio, J.; Kopin, I.J.; Snyder, S. Effects of disulfiram on tissue norepinephrine content and subcellular distributions of dopamine, tyramine and their beta-hydroxylated metabolites. Life Sci., 1964; 3: 769-775.
26. Sauter AM, Boss D, Von Wartburg JP: Reevaluation of the disulfiram alcohol reaction in man. J Stud Alcohol, 1977; 38: 1680-1695.
27. Peachy JE, Zlim DH, Robinson GM, Jacob M, Cappell H: A placebo controlled double blind comparative clinical study of the disulfiram and calcium carbamide acetaldehyde mediated ethanol reactions in social drinkers. Alcoholism (NY), 1983; 7: 180-187.
28. Vesall ES, Passanatini GT, Lee CH: Impairment of drug metabolism by disulfiram in man. Clin Pharmacol Ther, 1971; 12: 785-792.
29. Vilicer L, Nelson K: Development of reversible hypertension during disulfiram therapy. Arch Intern Med, 1984; 144: 1294-1297.
30. Borg OB, Holmstedt B, Kvand H, Skroder R: Concentration of serotonin in CSF from alcoholics before and during disulfiram therapy. Acta PharmacolToxicol (Copenh), 1980; 47: 305-307.
31. Lake CR, Major LF, Zeigler MG, Kopin I J: Increased sympathetic nervous system activity in alcoholic patients treated with disulfiram. Am J Psychiatry, 1977; 134: 1411-1414.
32. Goodwin DW: Metronidazole in the treatment of alcoholism: a negative report. Am J Psychiatry, 1967; 123: 1276-1278.
33. Armor D J, Polich J, Stambul HB: Specific therapies: In: Armor D J, Polich J, Stambul HB, eds. Alcoholism and treatment. New York: Wiley, 1978; 146-147
34. Obitz FW: Control orientation and disulfiram. J Stud Alcohol, 1978; 39: 1297- 1298.
35. Rush BR, Malla A: A comparison of disulfiram acceptors and refusers on selected demographic characteristics. Drug Alcoho Jacobsen E, Martinsen-Larsen O: Treatment of alcoholism with tetraethylthiuram disulfide, lAMA, 1949; 139: 918-92.
36. Fuller RK, Neiderhiser DH: Evaluation and application of a urinary diethylamine method to measure compliance with disulfiram therapy. J Stud Alcohol, 1981; 42: 202-207
37. Fuller RK, Branchley L, Brightwell DR, et ak Disulfiram in the treatment of alcoholism: a Veterans Administration Cooperative Study. lAMA, 1986; 256: 1449- 1455.
38. . Fuller RK, Roth HP: Disulfiram for the treatment of alcoholism: an evaluation of 128 men. Ann Intern Med, 1979; 90: 901-904.
39. Fawcett J, Clark CA, Aagesen CA: A double blind placebo control trial of lithium carbonate for alcoholism. Arch Gen Psychiatry, 1986; 4: 248-258.
40. Kellan AMP, Wesolkowski JM: Disulfiram implantation for alcoholism. Lancet, 1968; 1: 925-926.
41. Malcolm MT, Madden JS: The use of disulfiram implantation in alcoholism. Br J Psychiatry, 1973; 123: 41-45
42. Whyte CR, O'Brian PMJ: Disulfiram implant: a controlled trial. Br J Psychiatry, 1974; 124: 42-44.
43. Obholzer AM: A follow-up study of nineteen alcoholic patients treated by means of tetraethylthiuram disulfide implants. Br J Addict, 1974; 69: 19-23.
44. Lewis M J, Bland RC, Baile WB: Disulfiram implantation for alcoholism. Can Psychiatry Assoc J., 1975; 20: 283-286.
45. Wilson A, Davidson W J, Blanchard R, White J: Disulfiram implantation: a placebo controlled trial with two year follow-up. J Stud Alcohol, 1978; 39: 809- 819.
46. Wilson A, Davidson W J, Blanchard R, White J: Disulfiram implantation: a trial using placebo implants and two types of controls. J Stud Alcohol, 1980; 41: 429- 436
47. Antabuse package insert. East Hanover, NJ: Odyssey Pharmaceuticals, Inc., 2001
48. Dadock, B.J.; Kaplan, H.I.; Sadock, B.J.; Eds. Kaplan & Sadock's Synopsis of Psychiatry, 8th ed. Lippincott, Williams and Wilkins: Philadelphia, 2004; 1018-1019.
49. Poulsen, H.E.; Loft, S.; Andersen, J.R.; Andersen, M. Disulfiram therapy –adverse drug reactions and interactions. Acta Psychiatr. Scand., 1992; 86 (s369): 59-66.
50. Jacobsen, E. Deaths of alcoholic patients treated with disulfiram (tetraethylthiuram disulfide) in Denmark. Denmark J. Stud. Alcohol, 1952; 13: 16-26.

51. Brewer, C.; Meyers, R.J.; Johnson, J. Does disulfiram help to prevent relapse in alcohol abuse? CNS Drugs, 2000; 14: 329-341.
52. Lewison, E.F. (1976) Spontaneous regression of breast cancer. Natl. Cancer Inst. Monogr, 44: 23–26.
53. Carnero, A. et al. (2016) The cancer stem-cell signaling network and resistance to therapy. Cancer Treat. Rev, 49: 25–36.
54. Chen, D. et al. (2006) Disulfiram, a clinically used anti-alcoholism drug and copper binding agent, induces apoptotic cell death in breast cancer cultures and xenografts via inhibition of the proteasome activity. Cancer Res, 66: 10425–10433
55. Kleiger, G. and Mayor, T. (2014) Perilous journey: a tour of the ubiquitin proteasome system. Trends Cell Biol, 24: 352–359.
56. Liu, X. et al. (2016) Targeting ALDH1A1 by disulfiram/copper complex inhibits non small cell lung cancer recurrence driven by ALDH-positive cancer stem cells. Oncotarget, 7: 58516–58530.
57. Morrison, B.W. et al. (2010) Disulfiram induces copper-dependent stimulation of reactive oxygen species and activation of the extrinsic apoptotic pathway in melanoma. Melanoma Res, 20: 11–20.
58. Li, Y. et al. (2020) Disulfiram/copper induces antitumor activity against both nasopharyngeal cancer cells and cancer-associated fibroblasts through ROS/MAPK and ferroptosis pathways. Cancers, 12.
59. Yang, Z. et al. (2019) Disulfiram modulates ROS accumulation and overcomes synergistically cisplatin resistance in breast cancer cell lines. Biomed. Pharmacother, 113: 108727.
60. Skrott, Z. et al. (2017) Alcohol-abuse drug disulfiram targets cancer via p97 segregase adaptor NPL4. Nature, 552: 194–199.
61. Choi, S.A. et al. (2015) Disulfiram modulates stemness and metabolism of brain tumor initiating cells in atypical teratoid/rhabdoid tumors. Neuro. Oncol., 17: 810–821.
62. Ying, H. et al. (2015) Disulfiram attenuates osteoclast differentiation in vitro: a potential antiresorptive agent. PLoS ONE, 10: e0125696.
63. Chiba, T. et al. (2014) Disulfiram eradicates tumor-initiating hepatocellular carcinoma cells in ROS-p38 MAPK pathway-dependent and -independent manners. PLoS ONE, 9: e84807.
64. Cen, D. et al. (2002) Disulfiram induces apoptosis in human melanoma cells: a redox-related process. Mol. Cancer Ther, 1: 197–204.
65. Yip, N.C. et al. (2011) Disulfiram modulated ROS-MAPK and NFkappaB pathways and targetedbreastcancercellswithcancerstemcell-likeproperties.Br.J.Cancer, 104: 1564–1574.
66. Cheriyan, V.T. et al. (2014) Disulfiram suppresses growth of the malignant pleural mesothelioma cells in part by inducing apoptosis. PLoS ONE, 9: e93711
67. Pan, Q. et al. (2002) Copper deficiency induced by tetrathiomolybdate suppresses tumor growth and angiogenesis. Cancer Res, 62: 4854–4859.
68. Gooneratne, S.R. and Christensen, D.A. (1997) Effect of chelating agents on the excretion of copper, zinc and iron in the bile and urine of sheep. Vet. J., 153: 171–178
69. Matsubara, T. et al. (1989) Inhibition of human endothelial cell proliferation in vitro and neovascularization in vivo by D-penicillamine. J. Clin. Invest, 83: 158–167
70. Brem, S. et al. (2005) Phase 2 trial of copper depletion and penicillamine as antiangiogenesis therapy of glioblastoma. Neuro. Oncol, 7: 246–253
71. Ishida, S. et al. (2013) Bioavailable copper modulates oxidative phosphorylation and growth of tumors. Proc. Natl. Acad. Sci. U.S.A., 110: 19507–19512
72. Suh, J.J.; Pettinati, H.M.; Kampman, K.M.; O'Brien, C.P. The Status of Disulfiram: A Half of a Century Later. J. Clin. Psychopharma col, 2006; 26: 290–302. [CrossRef] [PubMed].
73. Stokes, M.; Abdijadid, S. Disulfiram. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2020.
74. Johansson, B. A Review of the Pharmacokinetics and Pharmacodynamics of Disulfiram and Its Metabolites. Acta Psychiatr. Scand, 1992; 86: 15–26. [CrossRef] [PubMed]
75. PubChemDisulfiram. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/3117 (accessed on 30 November 2020)
76. StrOmme JH. Distribution and chemical forms of diethyldithio- carbamate and tetraethyl disulphide (disulfiram) in mice in rela- tion to radioprotection. Biochem. Pharmacol, 1966; 15: 287- 297.
77. Stromme JH. Interaction of disulfiram and diethyldithio- carbamate with serum proteins studied by means of a gel-filtra- tion technique. Biochem. Pharmacol, 1965; 14: 381-391.
78. Agarwal RP, Mcpherson RA, Philips M. Rapid degradation of disulfiram by serum albumin. Res. Commun. Chem. Pathol. Pharmacol, 1983; 42: 293-310.
79. Johansson B. Plasma protein binding of disulfiram and its metabolite diethylthiocarbamic acid methyl ester. J. Pharm. Pharmacol, 1990; 42: 806-807.
80. Koppaka, V.; Thompson, D.C.; Chen, Y.; Ellermann, M.; Nicolaou, K.C.; Juvonen, R.O.; Petersen, D.; Deitrich, R.A.; Hurley, T.D.; Vasiliou, V. Aldehyde Dehydrogenase Inhibitors: A Comprehensive Review of the Pharmacology, Mechanism of Action, Substrate Specificity, and Clinical Application. Pharmacol. Rev, 2012; 64: 520–539. [CrossRef]
81. Hulanicki, A. Complexation Reactions of Dithiocarbamates. Talanta, 1967; 14: 1371–1392. [CrossRef] [PubMed]
82. Johansson, B.; Stankiewicz, Z. Inhibition of Erythrocyte Aldehyde Dehydrogenase Activity and Elimination Kinetics of Di ethyldithiocarbamic Acid Methyl Ester and Its Monothio Analogue after Administration of Single and Repeated Doses of

Disulfiram to Man. Eur. J. Clin. Pharmacol, 1989; 37: 133–138. [CrossRef] [PubMed]
83. Gessner, P.K.; Gessner, T. Disulfiram and Its Metabolite, Diethyldithiocarbamate; Springer: Dordrecht, The Netherlands, 1992; ISBN 978-94-010-5028-9.
84. Faiman, M.D.; Jensen, J.C.; Lacoursiere, R.B. Elimination Kinetics of Disulfiram in Alcoholics after Single and Repeated Doses. Clin. Pharmacol. Ther, 1984; 36: 520–526. [CrossRef] [PubMed]
85. Gessner, T.; Jakubowski, M. Diethyldithiocarbamic Acid Methyl Ester. A Metabolite of Disulfiram. Biochem. Pharmacol, 1972; 21: 219–230. [CrossRef]
86. Hu,P.; Jin, L.; Baillie, T.A. Studies on the Metabolic Activation of Disulfiram in Rat. Evidence for Electrophilic S-Oxygenated Metabolites as Inhibitors of Aldehyde Dehydrogenase and Precursors of Urinary N-Acetylcysteine Conjugates. J. Pharmacol. Exp. Ther, 1997; 281: 611–617.
87. Hald J, Jacobsen E, Larsen V. The sensitizing effect of tetraethylthiuramdisulphide (Antabuse) to ethyl alcohol. Acta Pharmacol, 1948; 4: 285-296.
88. Eldjarn L. Metabolism of tetraethylthiuramdisulphide (Anta- buse, Aversan) in man, investigated by means of radioactive sulfur. Scand. J. Clin. Lab, 1950; 2: 202-208.
89. lber FL, Dutta S, Shamszad M, Krause S. Excretion of radio- activity following the administration of 35 sulfur-labeled disulfiram in man. Alcoholism Clin. Exp. Res, 1977; 1: 354- 359.
90. Pedersen SB. Analysis and preliminary pharmacokinetics of disulfiram. Arch. Pharm. Chemi. Sci. Ed, 1980; 8:65-82.
91. Johansson B. Rapid and sensitive on-line precolumn purification and high-performance liquid chromatographic assay for disulfiram and its metabolites. J. Chromatogr, 1986; 378: 419- 429.
92. Kaslander, J. Formation of an S-glucuronide from tetraethyl- thiuram disulfide (Antabuse) in man. Biochem. Biophys. Acta, 1963; 71: 730-732.
93. Stromme JH.Metabolism of disulfiram and diethyldithiocarbamate in rats with demonstration of an in vivo ethanol-included, Inhibition of glucuronic acid and conjunction of the thiol. Biochem. Pharmacol, 1965; 14: 393-410.
94. Merlevede E, Casier H.Arch. Int. Pharmacodyn. Ther, 1961; 132: 427-435.
95. Faiman MD, Haya K, EwingJA. Am J. Phsychiatry 1978; 135: 623-624.
96. Deitrich, R.A.; Erwin, V.G. Mechanism of the inhibition of aldehyde dehydrogenase in vivo by disulfiram and diethyldithiocarbamate. Mol. Pharmacol., 1971; 7: 301-307.
97. Malcolm, R.; Olive, M.F.; Lechner, W. The safety of disulfiram for the treatment of alcohol and cocaine dependence in randomized clinical trials: guidance for clinical practice. Expert Opin. Drug Saf., 2008; 7: 459- 472.
98. Meltzer, H.Y.; Ed. Psychopharmacology: The Third Generation of Progress, Raven Press: New York, 1987; 1610-1611.
99. Faiman, M.D. Biochemical Pharmacology of Disulfiram. In: Biochemistry and Pharmacology of Ethanol; Majehowicz E., Nobel E.P., Eds.; Plenum Press: New York, 1979; pp. 325-348.
100. Goldstein, M.; Anagoste, B.; Lauber, E.; McKeregham, M.R. Inhibition of dopamine beta-hydroxylase by disulfiram. Life Sci., 1964; 3: 763-767.
101. Mussachio, J.; Kopin, I.J.; Snyder, S. Effects of disulfiram on tissue norepinephrine content and subcellular distributions of dopamine, tyramine and their beta-hydroxylated metabolites. Life Sci., 1964; 3: 769-775.
102. Volicer L, Nelson KL. Development of reversible hypertension during disulfiram therapy. Arch Intern Med, 1984; 144: 1294-6
103. Rogers WK, Benowitz NL, Wilson KM, Abbott JA. Effect of disulfiram on adrenergic function. Clin Pharmacol Ther, 1979; 25: 469-77.
104. Peachey JE, Brien JF, Roach CA, Loomis CW. A comparative review of the pharmacological and toxicological properties of disulfiram and calcium carbimide. J Clin Psychopharmacol, 1981; 1: 21-6.
105. Li, H., Wang, J., Wu, C., Wang, L., Chen, Z.S. and Cui, W., 2020. The combination of disulfiram and copper for cancer treatment. *Drug discovery today*, *25*(6): 1099-1108.