

SYSTEMATIC REVIEW

Adverse Drug Reactions to Disulfiram Treatment with or without Alcohol Challenge in the Indian Setting: Systematic Review

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ABSTRACT

Background: Disulfiram has been used for treating alcohol dependence in the Indian population for the last three decades. The safety concerns associated with adverse effects raise a high index of suspicion for disulfiram therapy in Indian population. Surprisingly few reviews exist on adverse reaction to disulfiram treatment and most of such articles published during the 1990s. Moreover, such systematic investigation relevant to the Indian population is missing in the literature. The present review aims to narrate and discuss disulfiram induced adverse reactions in the Indian setting.

Materials and methods: We analyzed clinical trials, observational studies and case reports of adverse drug reactions to disulfiram therapy reported in the Indian setting. Relevant studies published within 2017 in the electronic databases: Medline, IndMED, Ermed, and Embase were included. The Naranjo adverse drug reaction probability scale (NADRPS) was used for assessing adverse drug reactions to disulfiram treatment.

Results: The present review identified four open-label trials, four observational studies and 24 case reports describing thirty-two cases of disulfiram-induced adverse reactions in the Indian setting. Psychiatric adverse events and de novo convulsions were the common adverse reactions to disulfiram treatment without alcohol challenge in this setting. The NADRPS score was found to be from 5–9 and the magnitude of the adverse effects associated with disulfiram-ethanol reaction was largely associated with surreptitious use.

Conclusion: The review is a pioneer attempt for an evidence base summary of common adverse reactions and temporal association of dose-dependent adverse effects to disulfiram treatment in the Indian setting. The results of the review open an area of discussion regarding ethnic variations and the adverse effects of disulfiram in clients treated for alcohol dependence in this setting.

Keywords: Adverse drug reaction, Disulfiram, India.

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BACKGROUND

The burden and problems due to alcohol dependence are well documented at the global level.¹ Disulfiram is the oldest and the first medication approved by FDA for treating alcohol dependence.² It is a well-known empirically tested deterrent agent that produces a disulfiram-ethanol reaction (DER) for those who concomitantly use alcohol and disulfiram due to the accumulation of acetaldehyde. DER may develop within 5–15 minutes of alcohol intake and include flushing, sweating, nausea, vomiting, palpitations, dyspnoea, tremors, confusion, restlessness, drowsiness, and hypotension.³ The general side effects of disulfiram in the absence of alcohol consumption are a headache, general weakness, and dizziness which may subside within weeks of the onset of therapy.⁴ Disulfiram has been used for treating alcohol dependence in the Indian population for the last three decades.⁵⁻¹² Although found to be efficacious, disulfiram is no longer considered as first-line treatment for alcohol dependence due to difficulties with compliance and toxicity¹³⁻¹⁵ Treatment adherence to disulfiram is notably affected in India due to its common surreptitious use by mixing in food items with the agreement of caregivers or sold as traditional medicines by faith healers.^{16,17} The safety concerns associated with the adverse effects of disulfiram therapy raises a high index of suspicion of its use in Indian population.¹⁸ The exploration of the pre and post disulfiram treatment status may help to fill the lacuna regarding the temporal association of adverse reactions to disulfiram treatment. Surprisingly few reviews exist on adverse reaction to disulfiram treatment which was published during the 1990s.¹⁹ Moreover, such systematic investigation relevant to the Indian population is missing in the literature.

OBJECTIVES

The objectives of the present study are to narrate and discuss the systematic evidence regarding adverse reactions to disulfiram treatment with or without alcohol challenge in the Indian setting.

MATERIALS AND METHODS

We analyzed clinical trials, observational studies and case reports related to adverse drug reactions to disulfiram therapy reported in the Indian setting. Adverse drug reactions to disulfiram treatment are more reported as case reports as compared to other hierarchy of evidence. Therefore, the CAse REport (CARE) guidelines—a consensus-based clinical case report guideline was used for standardization of case reports.^{20,21} Disulfiram-induced adverse drug reactions were rated based on NADRPS scores. NADRPS is a simple and widely used scale that categorizes the severity of adverse drug reactions as follows: definite if the overall score is 9 or greater, probably for a score of 5 to 8, possible for 1 to 4, and doubtful if the score is 0.²²

Search Strategy

Relevant studies conducted in the Indian setting and published up to 2017 in the electronic databases: Medline, IndMED, Ermed, and Embase were included. The search strategy used the following keywords: “disulfiram” “alcohol dependence” “adverse drug reaction” “case report” “safety” and “Indian setting”.

- *Selection criteria:* We included studies and case reports published in the English language based on the following criteria: (a) disulfiram as a primary medication for producing adverse effects with or without alcohol challenge (b) adverse effects associated with disulfiram reported in the Indian setting. Disulfiram reactions associated with other substances such as cocaine were excluded in this review. A pre-designed data extraction scheme was used for screening and retrieval of data and all the references with insufficient details were requested in full text. Studies were initially selected based on information from title and abstract and the potentially relevant references were reviewed for possible inclusion and duplicates were excluded. An extensive evaluation of the relevant articles was carried out and assessed for final inclusion.

Data Extraction

Data extraction scheme included the following aspects: author, disulfiram dosage regimen, disulfiram pre and post-treatment status, major findings and NADRPS score. Both the authors independently searched and selected the potentially relevant studies. Data extraction was jointly carried out and further reviewed as per desired guidelines.

RESULTS

Study Selection

The search strategy identified 567 relevant references which we electronically screened and 161 were retrieved for detailed evaluation. Of these, 61 were controlled and cross-sectional studies conducted at the global level. Finally, 38 unique studies including case reports met the inclusion criteria for the review. Figure 1 provides the sequence of the inclusion process of references in the systematic review.

Description of Studies

Open-label Trials

Four open-label trials conducted among 358 alcohol-dependent men found that disulfiram was superior in preventing alcohol relapse as compared to naltrexone, acamprosate and topiramate treatment. Disulfiram was administered in a daily dose of 250 mg for a period of 26–52 weeks, and the commonly observed adverse effects were nausea, drowsiness, abdominal pain, and diarrhea. All the reported adverse effects were minimal in severity and disappeared within the 1–2 week of the initiation of disulfiram treatment (De Sousa; 2004, 2005, 2008, 2009).²³⁻²⁶

Observational Studies

The review identified one observational study that evaluated the treatment response to carefully administered disulfiram to a selected population of 75 subjects with alcohol challenge. Disulfiram was administered in a loading dose of 1500 mg–2500 mg per day in divided

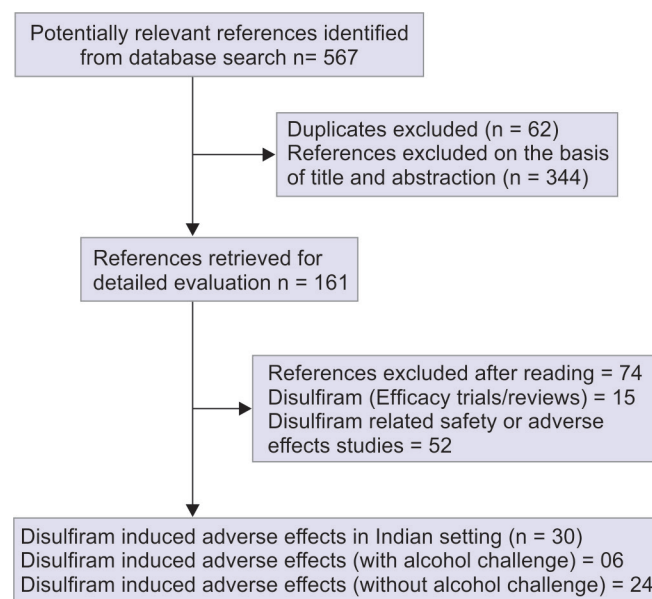


Fig. 1: Flow chart of the inclusion process of references in the systematic review

doses with a challenging maximum dose of 90 mL alcohol. The study reported psychotic episodes and skin reactions (n = 3) as the side effect of disulfiram treatment which was disappeared within 2 to 3 days of discontinued medication (Bagadia et al.).²⁷

Three studies explored the adverse effects of disulfiram treatment (125–500 mg per day) among 261 subjects within a period of one to 2 months. In that two of the studies noted psychiatric reactions as major adverse effect to disulfiram treatment. However further analysis found that these symptoms were present before taking the drug and was aggravated with disulfiram treatment (Srinivasan et al., Murthy).^{28,29} The fourth study found few adverse drug reaction to disulfiram treatment such as gastrointestinal symptoms, skin reactions, anxiety and depression to a daily dosage regimen of 125 mg (Palitty et al.).³⁰

Case Studies

The present review identified thirty-two cases of disulfiram-induced adverse reactions with and without alcohol challenge in the Indian setting.³¹⁻⁵⁴ Most of the case reports were adequate with the quality of information as per 13 items checklist in the CARE guidelines. The failure to add the word “case report” in the title (Item-I) was the only major missing component as per CARE guidelines in the included case studies (n = 18). Descriptions of the included case reports are summarized as per characteristics of cases such as author, disulfiram dosage regimen, disulfiram pre- and post-treatment status, major findings and NADRPS score (Tables 1 and 2).

Disulfiram-Induced Adverse Drug Reactions without Alcohol Challenge

There are 26 cases describing disulfiram-induced adverse drug reactions without alcohol challenge, and the mean age of the participant is 36 years (SD = 7). Most of the clients were taking 250–500 mg disulfiram tablets, and adverse effects were reported within one week to 3 months of the initiation of therapy. Most of the clients were dependent users of alcohol for 4 to 10 years and nine of them were co-morbid dependent users of alcohol and tobacco. Disulfiram was found to be the probable causal factor for adverse effects as the NADRPS Score was found to be from 5–9. All the adverse effects were reduced or completely resolved by stopping or reducing the dose of disulfiram. Adverse reactions to disulfiram treatment as observed in the case reports are described below.

Psychiatric Adverse Events

The onset of the symptoms of psychosis was reported within 3 to 4 weeks of disulfiram use in four cases with

oral intake of up to 500 mg disulfiram. The delusion of persecution and auditory hallucination were the major symptoms of psychosis and recovery was reported within one to two weeks of stoppage of disulfiram.

Four case reports were available on disulfiram induced catatonia in which the age of the clients was ranged from 28–54 years. Symptoms of catatonia such as mutism, rigidity, posturing were reported within 36–72 hours of administration of 500 and 2500 mg of disulfiram in two of the cases. None of the cases reported any organic etiology for developing catatonia but two cases were having the previous history of disulfiram-induced catatonia. Most of the catatonic symptoms resolved within 3–7 days of discontinuation of disulfiram with or without specific management such as injection lorazepam.

Two case reports of clients with alcohol dependence syndrome reported delirium like reactions such as fluctuating sensorium, self-muttering behavior, altered sleep-wake cycle following 48 hours to 8 weeks of disulfiram use. The symptoms of withdrawal delirium were reported following the surreptitious administration of 600 to 900 mg disulfiram in one of the case. Delirium like reaction associated with disulfiram in both the cases resolved within 72 hours of stoppage of disulfiram.

De novo Convulsions

The present review identified ten cases regarding de novo convulsions associated with disulfiram use and the majority of the cases were young male clients with age ranging from 29–36 years (N = 7). More than half of the clients were co-morbid dependent users of alcohol and tobacco (N = 5), and half of the clients reported alcohol withdrawal seizures (N = 4). Most of the cases reported generalized tonic-clonic seizures within 1–4 week of the initiation of 250–500 mg disulfiram (N = 8). However, one case reported the onset of recurrent myoclonic seizures of limbs followed by generalized tonic-clonic seizures within one week of initiation of 125 mg disulfiram. Effective seizure control was reported by reducing the dose of disulfiram up to 125 mg (N = 4) and stopping of disulfiram (N = 6). Majority of the cases maintained alcohol abstinence with or without disulfiram use at 4 to 34 weeks follow-up (N = 6).

Reversible Hypertension

Four cases reported disulfiram induced hypertension in which majority of the case were young male adults with age ranging from 29–39 years. In this, three cases reported de novo convulsions along with hypertension (systolic blood pressure of 170–200 and diastolic blood pressure of 100–110) within four weeks of initiation of 125–500 mg of disulfiram therapy. All the four cases have established the diagnosis of alcohol and tobacco dependence syndrome.

Table 1: Disulfiram associated adverse drug reactions without alcohol challenge

Author	Study design /Setting	Age	Dosage regimen	Pre-disulfiram therapy Status	Post-disulfiram therapy Status	Management of DSF induced reaction	Findings/ Outcome	NADRPS Score
Mohapatra et al. (2017)	Case report/ Odisha	32	250mg/bd for 1 month	Daily alcohol intake of 250-750 ml (40% alcohol by volume) for 5 years. Family history of Schizophrenia and co-morbid alcohol dependence (Father)	Psychosis - Delusion of persecution Auditory hallucination & Sleep disturbances	DSF stopped Added Tab. Lorazepam 4 mg/day and stopped after 2 weeks.	Complete recovery of presented symptoms after 2 weeks of stopping disulfiram	6
Thamiz SJ et al. (2016)	Case report/ Puduchery	48	250 mg/od for 2 month	Alcohol dependence syndrome for 1 year	Psychosis – Delusion of persecution	DSF stopped Added Tab. Chlorpromazine 400 mg/day and Tab Clonazepam 2 mg/day and stopped after 2 weeks.	Patient maintained well within 2 weeks of stoppage of disulfiram.	6
Alamela et al (2016)	Case report/ Karnataka	34	250mg/bd for 3 month	Alcohol dependence syndrome for 15 years No prior significant medical history such as seizures, HTN, DM etc.	Dystonia (sudden onset of experiencing deviation of neck to the leg side and posturing and uprolling of eyeballs - oculogyric crisis)	DSF stopped Added injection promethazine 25 mg IM.	Symptoms resolved within 5 days of specific treatment and discontinuation of disulfiram.	6
Kumar et al. (2016)	Case report/ Karnataka	28	250mg/od for 6 months & 2500 mg during admission	Positive family history of Schizophrenia (Elder brother), Alcohol dependence syndrome for 5 years, Co-morbid Paranoid Schizophrenia for 3 years	Malignant Catatonia (On 36 hrs of DSF overdose) & Neuroleptic Malignant Syndrome (On 4th day after DSF overdose)	Gastric lavage & Activated Charcoal Inj. Lorazepam (IV) & Tab Lorazepam 2mg Hs later At ICU - Tab. Bromocriptine 2.5mg Cap. Danitrolene 25mg TID and stopped on 13th day	Catatonic symptoms and NMS improved on 13th day of admission by stopping DSF and adding specific and supportive measures.	6
Goswamiet al. (2015)	Case report/ Assam	54	250mg/od for 10 days	Previous history of DSF induced catatonia Normal LFT, RFT, Serum electrolytes, CT brain, USG abdomen	Catatonia (mutism, Rigidity, and staring)	DSF stopped Added Inj. Lorazepam TID Tab. Baclofen 60 mg Tab. Amisulpiride 100 mg OD	Recovery of presented symptoms after four days of stopping DSF.	9
Vrishabhendraiah, et al (2015)	Case report/ Karnataka	35	250 mg/bd for first 5 days and 250 mg/od for next 10 days	No prior significant medical history such as seizures, HTN, DM etc. No prior organic etiology and normal laboratory parameters related to seizures. Alcohol dependence syndrome	Generalized tonic clonic seizures	Stopped DSF	No seizure episode till 1 month after discontinuing DSF.	5
Mohapatra et al. (2015)	Case report/ Odisha	35	250 mg/bd for 2 months	Alcohol dependence syndrome for 10 years Tobacco dependence syndrome for 6 years	Peripheral neuropathy (Numbness and tingling sensation of feet since 1 month)	Stopped DSF	Patient improved well at 8th week of discontinuation of disulfiram therapy.	6

(Cont...)

(Cont...)

Author	Study design /Setting	Age	Dosage regimen	Pre-disulfiram therapy Status	Post-disulfiram therapy Status	Management of DSF induced reaction	Findings/ Outcome	NADRPS Score
Kukreti et al. (2015)	Case report / New Delhi	27	600-900 mg DSF daily basis in last one week (Surreptitious use)	Alcohol dependence syndrome for 7 years No prior significant medical history such as seizures, HTN, DM etc.	Withdrawal delirium (Auditory hallucinations, muttering, violent aggressive behaviour, altered sleep wake cycle and fluctuating sensorium and constipation following 48 hours of last intake of disulfiram)	Intravenous (IV) fluids, syrup lactulose (60 ml OD for 2 days) Inj. haloperidol 2.5 mg inj. promethazine 12.5 mg intramuscularly	Delirium improved within 72 hours of treatment and patient was abstinent to alcohol at 6 month follow-up.	6
Layek AK (2014)	Case report / West Bengal	38	500mg/day for 5 months	Alcohol dependence syndrome	Peripheral neuropathy (Tingling and numbness in lower extremity)	Stopped disulfiram and added gabapentin	Patient's symptoms resolved over 3 months	6
Kulkarni et al. (2013)	Case report / Karnataka	29 (N=1) 31-36 (N=3) 31-36 (N=5) 42 (N=1) 60 (N=1)	125mg/day (N=1) 250mg/day (N=5) 500mg/day (N= 2)	Alcohol and tobacco dependence syndrome in 63% of subjects No prior significant medical history such as seizures, HTN, DM etc.	Generalized tonic -clonic seizure in 63% of subjects within 1 week (N=3), 2 week (N=2), 3 week (N=2) and 4 week (N=1) of initiation of DSF. DSF-induced HTN (N=3) Fatty liver (N=7 among subjects with 250-500mg dose) Elevated liver enzymes (N=5)	DSF dose reduced or stopped. Added Valproate 1gm (N=5) Topiramate (N=1) Carbamazepine (N=1)	Effective seizure control by dose reduction (N= 4) or stopping DSF (N= 3) Alcohol abstinence at 4-34 weeks follow up.	6
Sreejayan et al. (2013)	Case report / Karnataka	30	250 mg/od for 1 month	Alcohol dependence syndrome (12 years)	Myoclonic seizures (Sudden jerky movements of the body with increasing frequency.) Enuresis on 7th day disulfiram therapy	DSF stopped.	Patient maintained well without any presented symptoms at 2month follow up.	6
esia et al. (2013)	Case report / North Eastern region	40	250 mg/bd for 2 weeks and 250 mg/od for 1 week	Alcohol dependence syndrome and BPAD with mania		DSF stopped.	No episode of enuresis after discontinuation of disulfiram therapy till 2 weeks	6

(Cont...)

Author	Study design /Setting	Age	Dosage regimen	Pre-disulfiram therapy Status	Post-disulfiram therapy Status	Management of DSF induced reaction	Findings/ Outcome	NADRPS Score
Kulkarniet al. (2013)	Case report / Karnataka	39	500 mg/day for 8 weeks	Alcohol and tobacco dependence syndrome for 4 years No prior significant medical history such as HTN,DM etc. Family history of alcoholism (Father)	Reversible Hypertension(Occipital head ache & giddiness) First 2 week- BP-146/100 First 4th week- BP-170/110	DSF gradually reduced to 250 mg/day and 125 mg/day on 4-5th week onwards. Added Telmisartan 40 mg and hydrochlorothiazide 12.5 mg/day DSF & other medications completely stopped on week 10	Patient has maintained baseline BP levels and abstinence to alcohol and tobacco at 6 month follow-up.	6
Nayak et al. (2011)	Case report / Karnataka	47	250 mg bd/5 days and 250 mg/od (6th day).	Hypertension, alcohol dependence syndrome Normal serum electrolytes, RFT,LFT Past history DSF induced catatonia	Catatonia- Rigidity, posturing, Gazing, puffiness of face and itching, hypertension	DSF stopped Anti-hypertensive Anti- histamines	Catatonic symptoms resolved three days after discontinuation of DSF.	6
Saddichha et al. (2011)	Case report / Odisha	32	250 mg od/3 weeks and 500 mg/od (3rd day).	Alcohol dependence syndrome	Dose dependent catatonia (staring, mutism, stupor, posturing, grimacing, and withdrawal and autonomic instability)	DSF stopped Lorazepam 6mg/day	Catatonic symptoms resolved within 7 days after discontinuation of DSF. Patient discharged with 125 mg/day	6

Table 2: Adverse drug reactions associated with DER

Author	Study design /Setting	Age	Dosage regimen	Pre-disulfiram therapy Status	Post-disulfiram therapy Status	Management of DSF induced reaction	Findings/ Outcome	NADRPS Score
Ravishankar (2016)	Case report/ Karnataka	39	Not reported (Surreptitious use)	Type-II DM & Hypertension Alcohol dependence syndrome	Haemoptysis in early morning hours, pain in peripheral joints, uneasiness, dysphagia during alcohol intake since one and half month	Antidiabetics, antihypertensives, Tab Librium 10 mg tid Multivitamin supplementation	Haemoptysis and joint pain subsided following discontinuation of disulfiram therapy.	6
Jadhav et al. (2016)	Case report/ Maharashtra	47	Not reported	Alcohol dependence syndrome and Disulfiram use since 1 month, Anti-psychotic use since 8 month No prior or after exposure to any chemicals or irritants	Acute Generalized Exanthematous Pustulosis during 15 days of DSF therapy.	DSF stopped Topical and systemic steroids	Rash subsided with topical and systemic steroids.	9
Ghosh et al. (2015)	Case report/ Assam	28	250 mg/od for 3 weeks	Alcohol dependence syndrome, No prior significant medical history such as HTN, DM etc.	Catonia (mutism, waxy flexibility, and posturing) after 5 days of drinking 60 ml IMFL	Inj. Lorazepam	Recovery of presented symptoms after seven days of stopping DSF.	6
Babu et al. (2014)	Case report/ Karnataka	35	250mg/od for 3 months	Alcohol dependence syndrome No prior significant medical history such as HTN, DM etc.	Ischemic stroke episode (Left sided hemiplegia) within 10-15 minutes of drinking 150 ml of whisky.	Patient was treated with mannitol, glycerol, antiplatelet drugs, statins, folic acid and vitamin B complex supplements	Patient recovered from hemiplegia at 1 month follow-up (power 4/5 in affected limb)	6
Manjunatha et al. (2011)	Case report/ Karnataka	32	250mg/od for 20 days and 250 mg /od for 25 days (Surreptitious use)	Alcohol dependence syndrome (9 years) Tobacco dependence syndrome (7 years)	Subacute vocal cord paralysis, facial palsy and paraesthesias of lower limbs	Patient was treated with lorazepam, thiamine supplementation and gabapentin	Patient recovered from the presenting symptoms but had relapse on alcohol.	6
Sherif et al (2006)	Case report/ Karnataka	37	250 mg/day for 8 months 500mg/day for 1 day (Surreptitious use)	Alcohol abuse No prior significant medical history Normal blood investigations except slight elevation in liver enzymes	Enuresis and Psychosis:- Self muttering, irrelevant speech, auditory hallucination, thought insertion, thought withdrawal within 2 days of alcohol intake	Stopped disulfiram and benzodiazepam added	No psychiatric illness upto 8th week follow-up.	6

Follow-up of the cases revealed that the client has achieved baseline BP levels and abstinence to alcohol and tobacco at 6-month follow-up by adding antihypertensive and reducing doses of disulfiram.

Peripheral Neuropathy

The present review identified two cases of peripheral neuropathy within 2–5 months of initiation of 500 mg disulfiram therapy. The symptoms of peripheral neuropathy were giddiness, bilateral joint pain, numbness and tingling sensation in feet which resolved completely within two weeks of reduced disulfiram regimen (250 mg/day). However optic neuropathy reported in one of the cases on the 10th week of disulfiram therapy which persisted even after 6 months of discontinuation of disulfiram therapy.

Miscellaneous Symptoms

A case of dystonia was developed in a client with 500 mg disulfiram treatment for 3 months. Symptoms of dystonia resolved with specific management and stoppage of disulfiram. Enuresis was reported to a client in the first week of disulfiram therapy which resolved within two weeks of discontinuation of medication. A client with a previous history of contact dermatitis developed the same episode on the fourth day of 750 mg disulfiram which completely resolved with specific management and without discontinuation of disulfiram therapy.

Adverse Drug Reactions Associated with DER

The present review identified six case reports of adverse drug reactions associated with the disulfiram-ethanol reaction in which disulfiram was surreptitiously administered in three cases. Haemoptysis, vocal cord paralysis and psychosis were the three reported symptoms associated with the disulfiram-ethanol reaction in which disulfiram was administered without knowledge of the client by the caregivers. All these symptoms were resolved with specific management and discontinuation of disulfiram. Catatonia and ischemic stroke episode were reported in two clients who were taking 250 mg disulfiram for 3 weeks to 3 months respectively. Catatonia was developed after 5 days of disulfiram-ethanol reaction which resolved within a week of stopping disulfiram therapy. However ischemic stroke episode developed within 15 minutes of alcohol intake in which recovery was reported after 1 month of stoppage of disulfiram.

DISCUSSION

The present review is a systematic attempt to generate substantial data regarding disulfiram induced adverse reactions in clients treated for alcohol dependence in the Indian setting. The results of the review specifically

support the following findings; (a) psychiatric adverse events and de novo convulsions were the common adverse reactions to disulfiram treatment without alcohol challenge in this setting, (b) the magnitude of the adverse effects associated with disulfiram-ethanol reaction was largely associated with surreptitious use in this setting, (c) there is a temporal association between adverse effects and dosage of disulfiram as symptoms aggravated or abated upon increase or stoppage of disulfiram.

The review identified that psychiatric adverse effects were noted among clients who treated for alcohol dependence with 500 mg disulfiram in this setting. Furthermore, the psychiatric symptoms were aggravated after the initiation of disulfiram therapy for clients with the previous history of psychiatric illness. Researchers noted the reporting of psychiatric adverse effects to disulfiram treatment in Indian population.⁵⁵ However, the results of the review provide an evidence base for the same. Pharmacogenetic studies suggest ethnic variations regarding the effects of disulfiram in Asian population.⁵⁶⁻⁵⁸ This opens an area of discussion on the possible expansion of knowledge regarding ethnically mediated genetic differences in isozyme levels of dopamine β -hydroxylase or brain acetaldehyde dehydrogenase in this setting.⁵⁹

Three cases in the present review were having comorbid and family history of psychiatric illness and developed symptoms of psychosis, catatonia, and delirium after the initiation of disulfiram therapy. This further suggests the cautious use of disulfiram in clients with a history of psychiatric illness.⁶⁰ The acute and chronic onset of delirium like reactions were observed in two case reports of the present review in which higher and lower doses of disulfiram therapy were attributed to the onset of the illness. Most of the previous studies suggest that delirium is associated with the disulfiram-ethanol reaction.^{61,62} However, both the case reports in the present review reported onset of delirium like reaction without alcohol challenge.

The review found a temporal association of adverse effects and dosage of disulfiram as symptoms aggravated or abated upon increase or stoppage of disulfiram. Catatonia, withdrawal delirium and dermatitis were the commonly reported cases with high doses of disulfiram in this setting. The above-mentioned symptoms were developed within a week of initiation of 750–2500 mg disulfiram. The findings of one case report in the present review revealed the presence of malignant catatonia with a heavy dose of disulfiram. This is in corroboration with recent findings.⁶³ Psychotic episodes, peripheral neuropathy, and dystonia was reported within one to three months of initiation of 500 mg disulfiram. The findings of the review also suggest that convulsions were clearly associated with the increasing dose of disulfiram as there

were no other causes for the induction of seizures in any of the cases.

The present review identified cases of vocal cord paralysis and hemoptysis as disulfiram-ethanol reaction followed by surreptitious administration of disulfiram. Further, it was found that disulfiram was secretly administered without client's knowledge by quacks and family members. This may be due to the overemphasis on outweighing the benefits over potential risks associated with the surreptitious use of disulfiram.⁶⁴ A recent study found an increasing trend of the prescribing disulfiram without informed consent by physicians and faith healers in Indian settings.⁶⁵ Therefore, there is an urgent need to sensitize the healthcare professionals and the public to safeguard the ethical rights of clients in order to prevent the potentially life-threatening complications associated with the surreptitious use of disulfiram.

This review has the following limitations. The results of the review are mainly based on case reports which limit the generalization of the findings. CARE guidelines were used for assessing the methodological quality of case reports. Some assumptions have been made in NADRPS scoring due to inadequate data in available reports. The present review is a pioneer attempt for an evidence base summary of common adverse reactions and temporal association of dose-dependent adverse effects to disulfiram treatment in the Indian setting.

CONCLUSION

Psychiatric adverse events and de novo convulsions were the common adverse reactions to disulfiram treatment without alcohol challenge in this setting. Most of the adverse drug reactions were reversible with specific management and stoppage of disulfiram. The results of the review open an area of discussion regarding ethnic variations and the adverse effects of disulfiram in clients treated for alcohol dependence in this setting.

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