

Disulfiram Therapy for Alcoholism

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Introduction

Alcohol dependence has been recognized to be a chronic relapsing illness and the desired goal of long-term abstinence often remains elusive. The chances of relapse are more in the first few months of abstinence. Hence detoxification alone may not be enough and the treatment needs to be continued for an extended period to achieve long-term abstinence.

This phase of treatment, termed the 'maintenance phase' is often difficult and challenging. Several psychosocial and pharmacological modalities have been used in the maintenance phase. One of the most important pharmacological modality is the use of deterrent therapy. Disulfiram is the most widely used medication for such therapy.

The following protocol gives the guidelines to be followed during introducing patients to disulfiram and subsequent follow up.

Rationale for use

Disulfiram is used as an aid in the management of alcohol dependent individuals who want to remain in a state of sobriety, but are unable to maintain an abstinent state. It acts as a deterrent and helps in delaying the decision to drink if motivation reduces temporarily. Disulfiram should be used in conjunction with supportive and psychotherapeutic interventions for the best results.

Substantial literature has been generated on the use of disulfiram in alcoholism, but the number of controlled clinical trials is limited. There is little evidence that disulfiram enhances abstinence, but there is evidence that disulfiram reduces drinking days especially in patients with supervised therapy. Studies have also suggested that the use of a 'disulfiram contract' is an effective approach to enhance adherence and maintain abstinence. Used alone, without proper motivation and supportive therapy, disulfiram is unlikely to have more than a brief effect on the drinking pattern. The therapy is more successful if disulfiram is used for an extended period of time. Among several measures, compliance is a strong predictor of outcome.

Pharmacology of Disulfiram

Mechanism of action

Disulfiram acts by binding irreversibly to the enzyme acetaldehyde dehydrogenase, (ALDH) leading to inactivation of the enzyme. When alcohol is consumed subsequent to disulfiram intake, there is an accumulation of acetaldehyde due to inhibition of the enzyme that metabolises it. Elevated levels of acetaldehyde are responsible for the unpleasant effects experienced. This is termed as the Disulfiram-Ethanol Reaction (DER).

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Pharmacokinetics

Absorption of disulfiram from the gastrointestinal tract is rapid but incomplete and approximately 20% is excreted in the faeces. Because of its high lipid solubility, disulfiram is widely distributed and accumulated in various fat depots. Disulfiram is rapidly metabolized to diethyldithiocarbamate (DDC), which is partly excreted as carbon disulfide in the expired air and is partly metabolized in the liver to Me-DDC. Me-DDC is metabolized further to the active metabolite Me-DTC (diethylthiocarbaminic acid methyl ester). The concentration of Me-DTC reaches its maximum after about four hours, but the maximum enzyme inhibiting effect (aldehyde dehydrogenase [ALDH]) is first reached after three daily doses. The plasma half-life for Me-DTC is about ten hours, but the enzyme inhibiting effect of ALDH lasts considerably longer. The effect can thus persist for 7 to 14 days after discontinuation. In patients receiving disulfiram maintenance treatment, the ingestion of alcohol brings about a typical disulfiram-alcohol reaction within the course of five to ten minutes. Metabolism is not appreciably affected by a mild to moderate decrease in hepatic function. The metabolites are chiefly excreted with the urine. A part is recovered in the expired air as carbon disulfide.

Toxicity

Drowsiness followed by coma, persistent nausea, vomiting, aggressive and psychotic behaviour, and ascending flaccid paralysis are manifestations of toxicity.

Drug Interactions

Disulfiram inhibits enzyme induction and thus may interfere with the metabolism of drugs taken concomitantly. An increase in the levels of oral anticoagulants, phenytoin, and oral hypoglycaemic may occur.

Indication

Disulfiram is recommended to persons suffering from alcohol dependence syndrome who are at risk of relapse.

Preparations of Disulfiram

200/250 mg oral tablet in package of 10 tablets.

Trade name: ESPERAL; DISULFIRAM; DIZONE.

Cost: Rs. 11 - 16 for 10 tablets depending on the brand.

Side effects

Common

Transient mild drowsiness, fatigue, impotence, headache, acneiform eruptions, allergic dermatitis and a metallic or garlic-like aftertaste may be experienced during the first 2 weeks of therapy. These complaints usually disappear later during therapy or with reduced dosage.

Uncommon

Optic neuritis, peripheral neuritis, polyneuritis, cholestatic and fulminant hepatitis, hepatotoxicity, occasional skin eruptions and psychotic reactions are uncommon side effects.

Contraindications for disulfiram therapy:

Absolute

- ⊙ Consent not given
- ⊙ Cerebral damage (e.g. dementia)
- ⊙ Psychosis resulting in inability to give consent for disulfiram
- ⊙ Hypersensitivity to disulfiram.

Relative

- ⊙ Severe myocardial disease or coronary occlusion
- ⊙ Diabetes mellitus
- ⊙ Advanced liver damage
- ⊙ Hypothyroidism
- ⊙ Epilepsy
- ⊙ Chronic and Acute nephritis
- ⊙ Peripheral neuropathy

Disulfiram should not be given if patient is staying alone or in a remote area.

Induction

Setting

Disulfiram can be started in the outpatient as well as inpatient setting.

When to start disulfiram therapy

Disulfiram should be started after detoxification from alcohol is completed and the patient is free of alcohol or alcohol containing beverages for at least 12 hours before the start of disulfiram

Baseline investigations

- ⊙ Haemogram
- ⊙ Liver function test: Attention should be paid to the liver enzymes (AST and ALT levels); Disulfiram should not be started if the AST and ALT levels are raised by more than 2-3 times above normal.

Pre disulfiram Counselling

The topic of disulfiram therapy may be discussed in the following way:

The patients' history of alcohol-related problems should be reviewed using information obtained in the intake assessment to make a diagnosis of alcohol dependence.

It should be recommended that patients consider disulfiram therapy and the rationale for doing so should be given. The patients' knowledge about disulfiram should be found out. If they have sufficient knowledge about disulfiram, that should be acknowledged and a brief review be offered. If they are unfamiliar with disulfiram, then a few minutes should be spent to explain about disulfiram:

“Disulfiram comes in tablet form. If you take it daily, it usually has no effect on you unless you drink alcohol. If you drink when you are taking disulfiram regularly, you will start to feel sick in about 5 minutes. You will flush, become nauseous and sweaty, you may have difficulty breathing and your heart rate will speed up. This reaction depends on how much you drink. You may also vomit and feel giddy and may faint because of the decrease in blood pressure. In rare cases, acute heart failure, unconsciousness, convulsions and death may occur. Disulfiram can help you refuse to drink because you know alcohol will make you sick. Because the effects of disulfiram can last up to 2 weeks after taking the last pill, if you were to feel like drinking one day suddenly, or for some specific reason, disulfiram can give you a reason not to drink. It also can buy you some time to change your mind again before you do decide to drink. Disulfiram therapy also gives you a way to seek help or advice before you decide to drink again. In disulfiram therapy, we can involve another person in your life to assist you in taking disulfiram at home. If you feel like drinking, you will want to stop taking your disulfiram, and you will have to discuss this with someone. You can talk about what you are feeling and perhaps find another way to deal with whatever reasons you have for wanting to drink.”

Consent for disulfiram

Before disulfiram is begun, informed consent is to be taken from the patient and the consent form should be signed by the patient along with a witness' signature. The consent form is provided in **Appendix 1**.

Beverages to be avoided with disulfiram therapy

It should be advised that certain beverages should be avoided with disulfiram. These include: alcohol in any form (i.e. beer, wine, Indian made foreign liquor and locally brewed liquor), vinegars, sauces, cough mixtures, vitamin tonics and elixirs that contain alcohol, and even mouthwashes which may contain alcohol.

Dosage and Administration:

Disulfiram should be started as a single tablet containing 250 mg, once a day. It may take at least 4 - 5 days to reach a steady state level. The timing of the dose should be fixed, such that the patient takes the tablet at a particular time of the day. Some patients may experience sedation with morning use; in such cases the dose may be shifted to night time.

Supervised disulfiram ethanol reaction (DER)

In certain cases, supervised DER may be carried out in those patients who are willing for it, and who are sceptical of the effect of disulfiram in causing a DER. This should be carried out in specialized De-addiction Centres only.

Supervision of disulfiram therapy

Disulfiram works best where a supervisor is involved in the administration of the medication. The supervisor may be a family member/ friend/ colleague with whom the patient is in daily contact. The supervisor should be chosen with the patients' consent. The supervisor should also be informed about the treatment and its implications. He/ she should ensure that the patient takes the medication and in front of him/ her.

Disulfiram identification card

In the end, a disulfiram identification card should be made available to the patient, stating that he/ she is taking disulfiram, and also contains in brief, the beverages to be avoided with alcohol, the signs and symptoms of disulfiram alcohol reaction, and its treatment.

Points to remember during initiation of disulfiram

- ⊙ Disulfiram therapy should be carried out after detoxification from alcohol
- ⊙ Disulfiram to be started at least 12 hours after last alcohol use
- ⊙ Disulfiram counselling should be carried out before start of therapy
- ⊙ Written consent should be obtained before start of therapy
- ⊙ A candidate may be chosen to supervise disulfiram therapy
- ⊙ Disulfiram should be started at dose of 250 mg

Follow up

The patient should be followed up in the outpatient clinic, if possible with a family member.

Frequency

The patient should follow up once in every 15 days for 2 to 3 visits initially; later the frequency may be restricted to once in a month or two.

Assessment during follow ups

During every follow up, the following assessment should be made:

- a. Regularity of Disulfiram intake: report should be collected from the patient as well as the accompanying person.
- b. Problems encountered in maintaining abstinent status.
- c. Consumption of alcohol, if any. If consumed whether it was in the absence/ presence of disulfiram intake. If it was in the presence of disulfiram, was a disulfiram alcohol reaction experienced? If no disulfiram alcohol reaction was experienced, then it is necessary to increase the dosage to 500 mg OD, after reconfirmation that the patient had been compliant on disulfiram 250 mg and carrying out a Disulfiram ethanol reaction.
- d. Side effects experienced. A systemic examination including examination for icterus, liver enlargement and examination of neurological system for signs of peripheral neuropathy should be carried out periodically.
- e. The motivation to continue abstinence from alcohol.

Investigations

Liver function tests, especially AST and ALT levels should be determined during follow up. This should be carried out initially once every 2 weeks for the first two months after the start of disulfiram, and later once in 3 months.

Counselling during follow ups

During every follow up the patient should be given a positive reinforcement in the form a verbal praise for continuing abstinence from alcohol and encouragement to continue disulfiram till the need for therapy. The patient should be counselled for the need to continue the medications, the possibility of DER if alcohol or beverages containing alcohol products are consumed, and the need for regular follow up.

Points to remember during follow up for disulfiram therapy

- ⊙ Follow up should be with a family member if possible.
- ⊙ Enquire for compliance, side effects, and any experience of disulfiram ethanol reaction.
- ⊙ Assess the patients' motivation for continued abstinence from alcohol.
- ⊙ Perform a systemic examination, including liver examination.
- ⊙ Perform liver function tests every 2 weeks for the first 2 months and later once every 3 months.
- ⊙ Counselling should be carried out during every follow up.

Duration of disulfiram therapy

Usually disulfiram therapy should be continued for a period of 6 to 9 months till the time the patient feels confident to abstain from alcohol without the need for treatment for the same, the risk for relapse has been reduced and patient is rehabilitated. However, in some patients, the therapy would have to continue for a longer period of time. Patients neither develop tolerance to disulfiram nor to the disulfiram ethanol reaction. During this time, he is expected to be able to master the coping strategies necessary to deal with difficult situations without resorting to alcohol.

Appendix 1

Consent for the administration of disulfiram

Disulfiram alcohol reaction : Disulfiram plus alcohol may produce reactions. Even a small amount of alcohol taken while on disulfiram may produce redness of the face, throbbing in the head and neck, headache, breathing difficulties, stomach distress, vomiting, sweating, thirst, chest pain, fast heartbeat, faintness, marked uneasiness, weakness, sensation of surroundings revolving around you, blurred vision, and confusion. Rarely in severe reactions, there may be a decrease in breathing, shock, acute heart failure, unconsciousness, convulsions, and death.

Side effects : Side effects of disulfiram taken alone may include drowsiness, numbness in extremities, metallic taste, and/ or allergic skin reaction. Liver damage is an uncommon reaction.

I have been informed that I must not drink alcoholic beverages while receiving disulfiram. I have been warned to avoid alcohol in disguised form i.e. sauces, vinegars, cough mixtures and mouthwashes. I understand that reactions, as described above, may occur with alcohol up to 14 days after ingesting disulfiram.

I have been counselled by the undersigned physician about disulfiram, the dosage, the need for administration of the disulfiram and the precautions and possible complications resulting from drinking alcoholic beverages, and the absorption or inhalation of alcohol in disguised form while taking disulfiram. I have had an opportunity to ask questions, and understand the benefits and risks of disulfiram.

I have been given the disulfiram card. This contains an identification data along with relevant information about disulfiram alcohol reaction with consequent treatment in advent of a disulfiram alcohol reaction.

I understand that disulfiram will be given to me on a monitored/unmonitored basis.

Signature of person to receive disulfiram

Date and Time

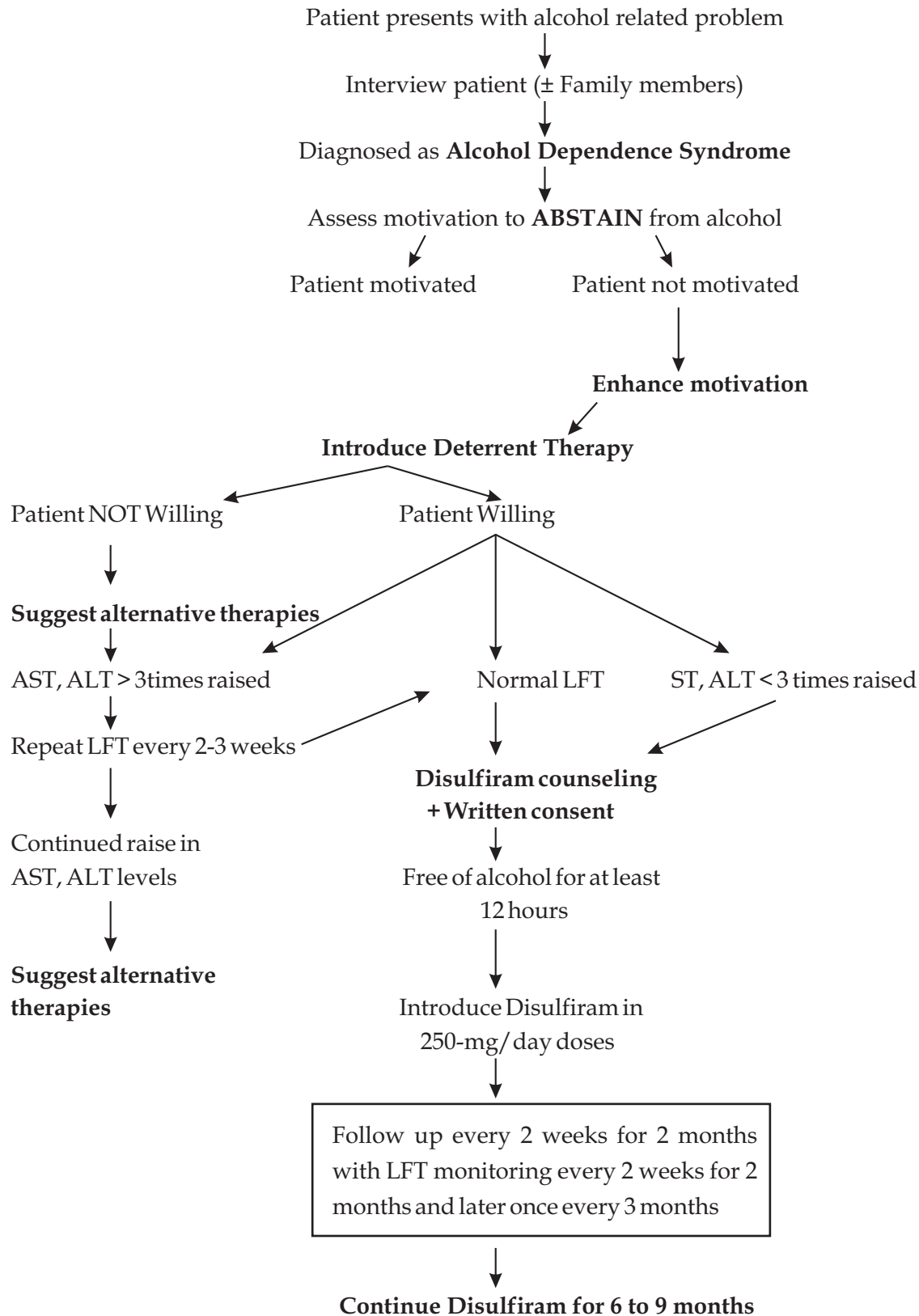
Signature of witness

Date and Time

Signature of the physician

Date and Time

Algorithm for Disulfiram Therapy



Frequently asked questions

Q1. Can disulfiram be given surreptitiously (without the consent of the patient)?

Ans. Disulfiram cannot be given without the consent of the patient. It is necessary to educate the patient regarding the side effects of Disulfiram as well as the nature of 'Disulfiram Ethanol Reaction' (DER) before initiation of Disulfiram.

Q2. Do deaths occur with Disulfiram?

Ans. Deaths with Disulfiram are very rare. The reported deaths in the literature are one in lakh users of disulfiram. Experience at our centre shows that disulfiram can be safely used in patients without fear of causing deaths.

Q3. Should one stop Disulfiram during other common illness such as fever, diarrhea because of the fear of interaction with other commonly prescribed medicines?

Ans. No. One can safely continue Disulfiram during common illness without fear of interaction with commonly prescribed medications.

Q4. The patient is having weakness after the start of Disulfiram and requests to stop Disulfiram. Should I stop it?

Ans. On most of the occasion, weakness is as a result of chronic effects of alcohol ingestion and NOT because of Disulfiram per se. One must check the patient's motivation if he is requesting to stop Disulfiram and conduct motivational enhancement therapy. Also LFT reports should be monitored.

Q5. Since the effect of disulfiram lasts for 10 - 14 days, should I ask the patient to ingest Disulfiram once every 10 days?

Ans. Though the effect of Disulfiram lasts for 10 - 14 days, Disulfiram should be taken every day to maintain constant and adequate blood levels.

Q6. The patient claims that he is addicted to whiskey only. He asks whether he can consume beer or wine. What should I do?

Ans. No alcohol containing beverages should be consumed when the patient is on disulfiram. For further details see the paragraph on Beverages to be avoided during Disulfiram therapy.

Q7. The patient has been taking Disulfiram since 9 months. Would he continue to remain free of alcohol lifelong as a result of this therapy?

Ans. Disulfiram prolongs the duration of abstinence in an alcohol dependent individual. There is always a risk of relapse at a future date. The risk of relapse reduces with increase in duration of abstinence.

Q8. What is the optimum dose of disulfiram in an individual patient?

Ans. Disulfiram should be started as a single tablet containing 250 mg, once a day. It may take at least 4 - 5 days to reach a steady state level. During follow up, if it is found that the patient is using alcohol while regularly compliant on disulfiram, then it is necessary to carry out a disulfiram ethanol reaction and increase the dosage to 500 mg OD if no reaction occurs.

Q9. Can disulfiram be administered to a patient who is in a state of alcohol intoxication or without their full knowledge?

Ans. Disulfiram should never be administered to a patient who is in a state of alcohol intoxication or without their full knowledge. Under both the circumstances, patient will develop disulfiram-ethanol reaction (DER) which can be life threatening.

Q10. What is disulfiram-ethanol reaction (DER)?

Ans. Disulfiram acts by binding irreversibly to the enzyme acetaldehyde dehydrogenase, (ALDH) leading to inactivation of the enzyme. When alcohol is consumed subsequent to disulfiram intake, there is an accumulation of acetaldehyde due to inhibition of the enzyme that metabolises it. Elevated levels of acetaldehyde are responsible for the unpleasant effects experienced. This is termed as the Disulfiram-Ethanol Reaction (DER). High levels of acetaldehyde produce nausea, substantial vomiting, hyperventilation, chest pain, flushing, throbbing headache, light-headedness, palpitation, blurred vision and other unpleasant symptoms. In rare cases arrhythmias, acute heart failure, convulsion and death may occur. The patient's reaction will be proportional to the dosage of both disulfiram and alcohol, and will continue to occur as long as alcohol is being metabolized.

Q11. How should disulfiram-ethanol reaction (DER) be treated?

Ans. The disulfiram-ethanol reaction is treated symptomatically. Patient will require monitoring of pulse and blood pressure. Vasopressors and antiarrhythmic agents may have to be given in case hypotension or cardiac arrhythmias occur.

Q12. How does disulfiram help in maintaining abstinence or preventing relapse?

Ans. The underlying principle for using disulfiram in treating alcoholism is that most alcoholics taking disulfiram will avoid drinking because they fear getting sick. Thus, disulfiram prevents impulsive drinking and allows the patient time to think about other ways to cope with acute cravings or stressful moments.

Q13. When to start disulfiram in a patient using alcohol?

Ans. Disulfiram should be started after detoxification from alcohol is completed and the patient is free of alcohol or alcohol containing beverages for at least 12 hours before the start of disulfiram.

Q14. At which time of the day, disulfiram should be used daily?

Ans. The timing of the dose should be fixed, such that the patient takes the tablet at a particular time of the day. Some patients may experience sedation with morning use; in such cases the dose may be shifted to night time. It is always advisable to take the tablets in the morning following the breakfast under the supervision of a significant family member. This helps in two ways; Firstly, it takes away from the patient the thought of using alcohol for the whole day and secondly it helps in building the trust between the patient and the significant family member.

Q15. What should be done if a patient develops psychosis while on disulfiram?

Ans. Psychotic reactions are uncommon with disulfiram. However, it is usually noted when a patient is on

disulfiram due to the following reasons: high dosage of disulfiram, combined toxicity (with metronidazole or isoniazid), or as a rare side-effect in some individual vulnerable for such reactions. Identification of the cause along with appropriate measures is required to be taken. To be on the safer side, it is always advisable to stop disulfiram first. If needed, anti-psychotic medications can be used for short-term basis as judged clinically.

Q 16. What is the optimum duration of therapy with disulfiram?

Ans. The optimal duration of disulfiram treatment is not known. The optimal duration of therapy varies with the individual patient and the agreed treatment goals. The patient will remain abstinent as long as he is compliant on disulfiram. It is advisable to give more emphasis on the agreed treatment goals of disulfiram treatment rather than setting an arbitrary duration of treatment.

Q 17. What should be the usual duration of treatment with disulfiram?

Ans. Usually disulfiram therapy should be continued for a period of 6 to 9 months till the time the patient feels confident to abstain from alcohol without medication, the risk for relapse has been reduced and patient is rehabilitated. However, in some patients, the therapy would have to continue for a longer period of time. Patients neither develop tolerance to disulfiram nor to the disulfiram ethanol reaction. During this time, the patient is expected to be able to master the coping strategies necessary to deal with difficult situations without resorting to alcohol.

Suggested reading

- ⊙ Fleming MF, Mihic S.J, Harris RA (2001). Ethanol. In Hardman JG, Limbird LE (Eds) *The Pharmacological Basis of Therapeutics*- tenth edition, Mc Graw Hill Publishing Company, New York, USA.
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