Manual for long-term pharmacotherapy

Anju Dhawan, Sonali Jhanjee

National Drug Dependence Treatment Centre
All India Institute of Medical Sciences, New Delhi

Developed Under

WHO (India)
and
Ministry of Health and Family Welfare
Government of India
Collaborative Programme, 2006-2007

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FOREWORD

The Ministry of Health and Family Welfare has identified training of General Duty Medical Officers as an important priority area as lack of trained manpower is a barrier in providing services for Drug De-Addiction Programme. As a coordinating centre, several training programmes sponsored by the MOH & WHO (I) have been conducted and coordinated by the National Drug Dependence Treatment Centre at AIIMS. The resource material developed as a part of the training activities sponsored by WHO (I) included a manual for physicians and a case book in the year 2004-05. It has also been our effort to update our resource material and develop new materials. In the year 2006-07, it was felt that a manual for long term pharmacological interventions in alcohol and opiate users is required. Long term pharmacological treatment is a key modality in the therapeutic armamentarium for treatment of substance use disorders.

We hope that the trainees will find this manual useful.

Dr. Rajat Ray

Chief, National Drug Dependence Centre

AIIMS, New Delhi

PREFACE

It is indeed a pleasure to compile this manual on pharmacotherapy for the World Health Organization (India) and Ministry of Health and Family Welfare (Government of India). This manual on long term pharmacotherapy is part of the resource material that has been developed for the training of General Duty Medical Officers. A manual on long term pharmacotherapy would be important as treatment for Substance Use disorders is a relatively specialized field. This manual is aimed at enabling the trainees to familiarize themselves with prescribing these drugs.

Treatment of Substance Use Disorders involves two phases-detoxification and long term management. The focus of this manual is on the long term management of alcohol and opiate dependence. For alcohol dependence both deterrent and anti-craving drugs are discussed. Both agonist and antagonist approaches to pharmacotherapy for opiate dependence have been incorporated.

It has been designed as a user friendly manual with algorithms and FAQ (frequently asked questions) at the end of every chapter. It is intended to be used in conjunction with training provided as part of the programme. In fact a draft copy of some of the chapters has been provided to the trainees during the training programmes to obtain their feedback.

We hope that the trainees find this manual useful and easy to understand. We look forward to any feedback and suggestions.

Dr. Anju Dhawan

Dr. Sonali Jhanjee

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We gratefully acknowledge the help we have received from several persons in the process of putting this manual together. First and foremost, we thank WHO (India) for sponsoring this manual and giving suggestions. We are also grateful to the Drug De-Addiction Programme, Ministry of Health and Family Welfare, Government of India for supporting us in the development of resource material on this important theme for the training programmes.

Acknowledgements are due to the Director and Dean, All India Institute of Medical Sciences for granting us permission to carry out this work.

We are especially grateful to Professor Rajat Ray, Chief, National Drug Dependence Treatment Centre, for conceiving the idea of developing this manual and providing his valuable input and guidance in finalizing the manual. We express gratitude to Prof. B. M. Tripathi for his suggestions in making the manual more user-friendly.

Most importantly, we are grateful to the contributors who put in substantial effort to make this manual technically sound and informative as well as easy to read. Thanks are also due to the trainees for their comments and suggestions.

Dr. Anju Dhawan

Dr. Sonali Jhanjee

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Disulfiram Therapy for Alcoholism

Rakesh Lal and Ravindra Rao***

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.

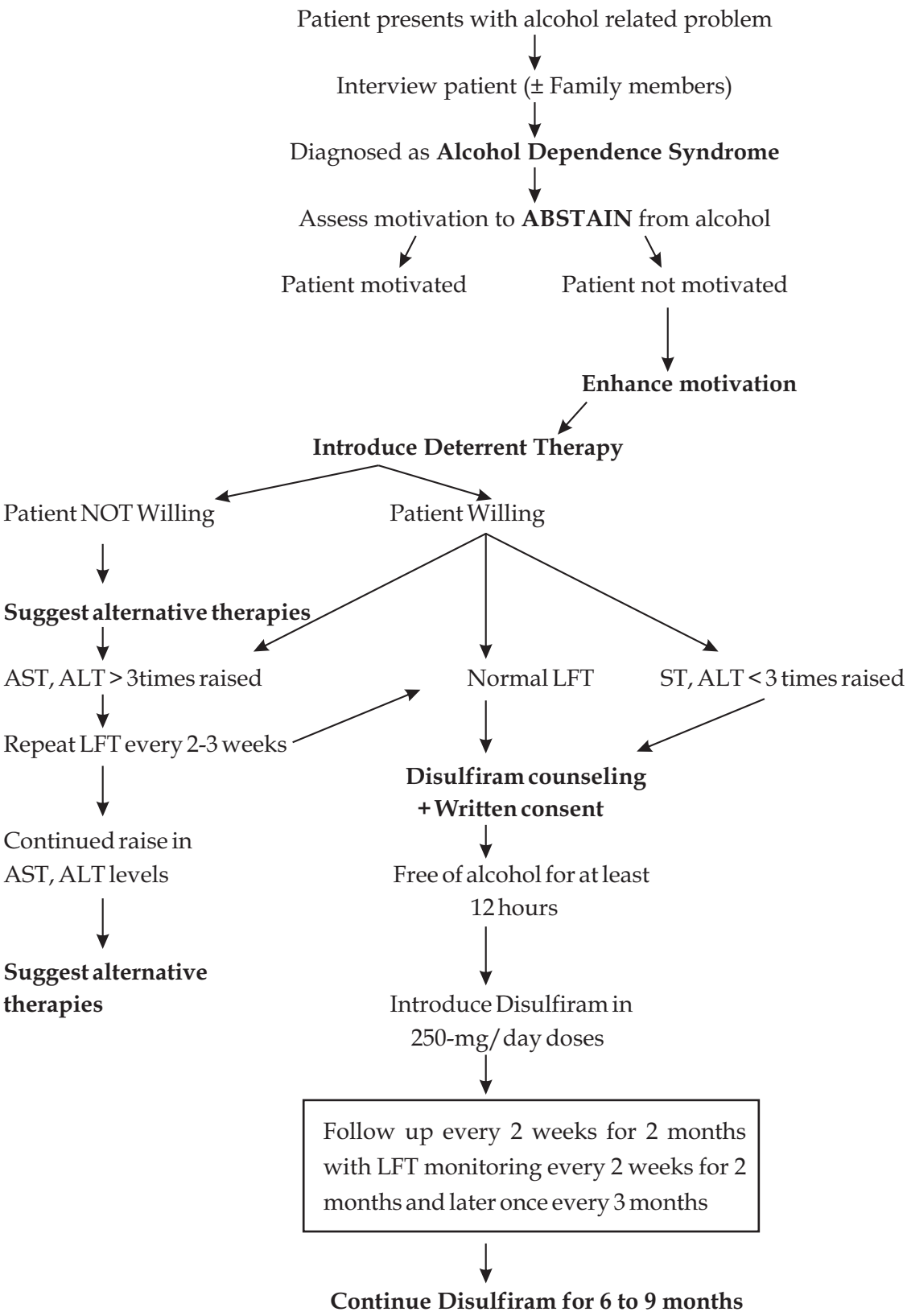
I have been counselled by the undersigned physician about disulfiram, the dosage, the need for administration of the disulfiram and the precautions and possible complications resulting from drinking alcoholic beverages, and the absorption or inhalation of alcohol in disguised form while taking disulfiram. 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

Q 1. 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.

Q 2. 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.

Q 3. 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.

Q 4. 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.

Q 5. 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.

Q 6. 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.

Q 7. 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.

Q 8. 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.

Q 9. 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.

Q 10. 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.

Q 11. 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 antiarrythymic agents may have to be given in case hypotension or cardiac arrhythmias occur.

Q 12. 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.

Q 13. 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.

Q 14. 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.

Q 15. 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.

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Anti-Craving Medications in the Treatment of Alcoholism

Atul Ambekar, Shivanand Kattimani***

Introduction

Alcohol use disorders constitute one of the most serious public health problems globally, not only because of their high prevalence and impact on the personal, family, occupational and social spheres, but also because of their economic and medical consequences. Alcohol dependece is a chronic disorder, with a relapsing and remitting course like other chronic diseases, such as diabetes and hypertension. The protocol for detoxification of alcohol-dependent patients (i.e. management of acute withdrawal symptoms of alcohol cessation) is well established, time-limited, and easy to understand. However, the major challenge in the treatment of alcoholism is the prevention of relapse to heavy drinking. Although behavioral approaches were universally available in drug abuse treatment programs by the late 1980s, currently, pharmacotherapy is considered central to interventional programs aiming for prevention of relapse. Many pharmacological agents can be used to prevent alcoholic relapse. Whereas deterrent drugs (such as Disulfiram) make the ingestion of alcohol unpleasant, there are others, which, appear to reduce alcohol intake by reducing the reinforcing effects of alcohol or by reducing the urge or craving to ingest alcohol. Use of Disulfiram has its own limitations and problems. In fact, some authors recommend that because of the problems with adverse effects and compliance, disulfiram should not be used in the primary care settings.

There is always a subgroup of patients who are not suitable candidates for disulfiram. Moreover, many patients also report 'craving' as an important factor posing risk for relapse. In the recent years, anticraving medications are taking prominence for treatment of alcoholism.

This chapter will focus upon pharmacotherapy for the long-term treatment of alcoholism other than deterrence-based approaches. Briefly, we will address issues related to craving in alcohol dependence. This will be followed with discussion about certain medications, which could be labeled as 'anti-craving' agents.

Rationale for Using Anti-Craving Medications: Craving in Alcoholism Concept and Measurement

The word 'craving' commonly means 'a strong desire or intense longing' and refers to intense desires for something. A 'craving' can be a strong, sudden, situation- specific, sometimes unexpected and culturally inappropriate, urge specifically to engage in the drug-taking behavior. Studies suggest that occasional drinkers report low alcohol craving, while heavy drinkers show a significantly higher craving especially in presence of increased levels of stress and when there is associated higher expectancies for reward and relief as a result of alcohol consumption.

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Direct relationship between craving and relapse, though not well established, appears to occur through intermediate factors.

Craving for alcohol is generally thought to arise either from the desire to experience alcohol's positive effects or from the desire to avoid the negative effects of withholding alcohol, such as withdrawal symptoms. Other models have suggested other important dimensions of craving, such as the desire and intention to consume alcohol, lack of control over alcohol use, and preoccupation with drinking-related thoughts and behavior. Irrespective of the model used for understanding 'craving', it is suggested that the term should be used only to convey a 'strong desire' to take drug.

Craving measures fall into two main categories with respect to their timeframe: (1) state measures, of current craving status, and (2) global measures, which ask the patient to describe his or her general experience of craving over the course of 1 day, 1 week, 1 month, or an even longer time period.

Incorporating craving measurements into routine clinical practice can produce several potential benefits. Its assessment can increase the patient's capacity to recognize and monitor his internal states that are related to drinking and this can be used in recommending appropriate treatment and in decisions regarding treatment intensity and duration. Studies have suggested that alcoholics who report higher levels of craving benefit the most from the anti-craving medication like naltrexone.

After this brief discussion on craving we now discuss the pharmacology and evidence-base for some of the important anti-craving agents.

Anti-Craving Medications for Alcoholism

I. ACAMPROSATE

Mechanism of Action

Acamprosate (calcium acetylhomotaurinate) is a simple derivative of the essential taurine amino acid and displays a structural resemblance to gamma-amino butyric acid (GABA). Acamprosate enhances the GABAergic neurotransmitter system, which is reduced in persons with chronic exposure to alcohol, and interferes with glutamate action in different pathways, such as the N-methyl-D-aspartate (NMDA) receptors. Acamprosate also acts on the calcium channels and reduces central nervous system hyperexcitability caused by cessation of alcohol intake. Acamprosate is thought to work by decreasing craving related to conditioned withdrawal.

Evidence-base

Studies conducted involving more than 4000 patients with alcohol dependence who had completed detoxification, provide consistent evidence of the efficacy of acamprosate in alcoholism rehabilitation; Most studies were randomized controlled trials comparing acamprosate with placebo or other anticraving agent such as Naltrexone. These outcomes have shown to be substantially homogeneous. Overall it was found that with acamprosate there is an increase in the cumulative abstinence period, decrease in the likelihood of return

to drinking, and better compliance compared to other approved anticraving agent, naltrexone. It has also been found that the effect is better with higher doses and that the effect is synergistic when acamprosate is combined with disulfiram. Cost-effectiveness of using acamprosate has also been studied and reported that use of acamprosate for 24 month period led to a net savings of 528 euros (equivalent to approximately US $880) per patient compared with no pharmacological treatment.

Pharmacokinetics (Absorption and Metabolism)

Only 10% of acamprosate is absorbed, of which 90% is excreted unchanged into urine. Since it is not metabolized in the liver, it can also be used in patients of alcohol dependence with mild to moderate liver dysfunction.

Indian Brands: T. Acamprol 333 mg Cost: Rs 6 per 333mg tablet

Dose and administration: Acamprosate is available as 333 mg tablets. The recommended daily dose for adults weighing over 60 kg is six tablets (1998 mg) orally in three divided doses (i.e. 2 t.d.s.), with meals. Adults weighing less than 60 kg should take four tablets (1332mg) per day. Usual practice is to start at half these doses and increase by one tablet a week.

Special tests prior to induction: Kidney function tests (KFT) and Liver function tests (LFT).

Adverse effects

Acamprosate is well tolerated with limited side effects. Most commonly encountered side effect is transient diarrhea (occurring in approximately 10 percent of patients). Occasionally, headaches, dizziness and pruritus have been described. Rash or isolated pruritus, paraesthesiae, decreased libido and confusion have all been reported at low frequencies.

Drug interactions

Tetracyclines may be inactivated by the calcium component in acamprosate during concurrent administration. There are no interactions with concomitant use of alcohol, diazepam, disulfiram, or imipramine. Thus, **patients with alcohol dependence can continue to use acamprosate during a relapse**.

Contraindications

Acamprosate is contraindicated in patients with known hypersensitivity to the drug, renal insufficiency or cirrhosis with severe hepatic decompensation, but patients with liver dysfunction of mild to moderate degrees may take it safely. The safety of acamprosate in pregnancy or lactation has not been established.

II. NALTREXONE

Mechanism of Action

Naltrexone, a potent opioid-receptor antagonist, blocks the effects of endogenous opioids, which increase after alcohol consumption. It is believed that naltrexone works through its blockage of μ-opioid receptors,

which reduces the reinforcing effects of alcohol leading to decreased feelings of intoxication and fewer cravings. It is approved for use in the treatment of alcohol dependence in conjunction with psychosocial interventions.

Evidence-base

In a systematic review of 11 double blind, placebo-controlled trials, researchers found that naltrexone reduces short-term relapse rates in patients with alcohol dependence when combined with psychosocial treatments. Although there is good evidence supporting short-term benefit with naltrexone, the evidence for longer-term use is less compelling. A meta-analysis concluded that in the seven studies of naltrexone versus placebo, involving 804 patients, carried for 3 months duration, naltrexone produced a modest benefit in reducing relapse rate and in improving abstinence rates. Authors reported that benefits were lost six months after completion of treatment and adverse effects were significantly more common in patients treated with naltrexone. In general, the number of patients treated in double-blind studies of the drug has been comparatively few, and longer-term outcome studies are lacking. To summarise, naltrexone appears to produce a modest effect on drinking behavior among alcoholics. It can be administered to those who are actively drinking, so that their consumption can be decreased.

Pharmacokinetics (Metabolism)

Naltrexone undergoes extensive first-pass metabolism in the liver to β-naltrexol. Although a much weaker antagonist than naltrexone, the half-life of β-naltrexol is longer, and plasma concentrations of the metabolite are always higher than those of the parent drug. The mean elimination half-life values for naltrexone and 6- β -naltrexol are four hours and 13 hours, respectively.

Indian Brands : T. Naltima 50 mg/T. Nodict 50 mg

Cost **:** Rs. 35-50 per 50 mg tablet

Dose and administration: Naltrexone is administered orally at 25 mg for 12 days, and then increased to the standard dose of 50 mg daily.

Special tests prior to induction : Liver function tests (LFT).

Adverse effects

Naltrexone has a dose-related hepatotoxicity, occurring at higher doses than those prescribed for alcohol dependence. Naltrexone generally is well tolerated; nausea is the most common adverse effect (reported by 10 percent of patients), followed by headache, anxiety, and sedation. Naltrexone is FDA pregnancy category C drug, meaning that no studies have been conducted to observe its adverse effects on pregnancy and on its outcome in animals and there are no adequate and well-controlled studies existing in pregnant women.

Drug interactions

Naltrexone blocks the action of opioid analgesics, which can be problematic in clinical practice for those

patients who are receiving opioids concurrently. Hence, Naltrexone should be avoided in patients receiving long-term opioid therapy for chronic pain or heroin dependence.

Contraindications

Contraindicated in patients with hepatitis or liver failure, and all patients should have hepatic transaminase levels checked monthly for the first three months and every three months thereafter.

Comparison between acamprosate and naltrexone : Both of these drugs have been compared in very few studies. A meta-analysis found that both drugs exerted significant, but modest, effects on drinking outcomes, with sizeable variability in results between studies (Kranzler *et al,* 2001). More recent rigorous studies of naltrexone have found less favorable outcomes than the earlier ones. Overall, evidence appears to be more in favour of acamprosate, because more number of studies have been conducted with it, with longer duration, and better acceptability in patient groups due to lesser adverse effects as compared to naltrexone.

One potential advantage of naltrexone (though not studied well) is its convenience of administration. Taking two tablets of acamprosate thrice a day may be cumbersome for some patients and may affect compliance as compared to the relatively simpler regimen of naltrexone one tablet per day. While there is limited evidence for a depot preparation of naltrexone, a depot preparation of acamprosate has not been attempted yet.

Table 1: Comparison between acamprosate and naltrexone

Attribute	Acamprosate	Naltrexone
Increases abstinence	Yes	May be
Decreases heavy drinking	May be	Yes
Longer-term efficacy (>1 yr)	Yes	No
Compliance	Good	Variable
Contingent on psychosocial intervention	Independent	Variable
Hepatic dysfunction	No	Yes
Use in opioid users including those on Methadone	Suitable	Unsuitable
Overall safety profile	Good	Good

Source: Mason (2003)

III. TOPIRAMATE:

Mechanism of Action

Topiramate is an anticonvulsant that inhibits dopamine release through antagonism of glutamate activity and facilitation of gamma-aminobutyric acid (GABA) transmitter in areas of the brain that may be associated with reward effects of alcohol. It inhibits mesocorticolimbic dopamine release, which is believed to be associated with craving for alcohol.

Evidence-base

It is an anticonvulsant indicated as adjunctive drug for treatment of refractory seizures. Topiramate at the dose of 25-300 mg/day is the best-studied anticonvulsant for treatment of alcohol dependence. In a 12-week double-blind study of actively drinking patients with alcohol dependence, topiramate was found to be more effective than placebo in initiating abstinence and in reducing self-reported drinks per day, drinks per drinking day, and heavy drinking days. In an open label small study of 12 weeks duration, alcohol dependent subjects received topiramate upto 300mg/day. Study subjects reported improvement in self-reported drinking outcomes and craving.

Pharmacokinetics

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours. The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose).

Indian Brands: T. Topex / T. Topirol / T. Topicon. Available in strengths of 25mg / 50mg / 100mg tablets
***Cost*:** Rs 3 per 25mg tablet, Rs 6 per 50 mg tablet, Rs 12 per 100mg tablet

Dose and administration: 25 to 300 mg per day (Increase 25 mg every week). Abrupt withdrawal should always be avoided.

Special tests prior to induction: Renal function tests.

Adverse effects: dizziness and somnolence, ataxia, impaired concentration, confusion, fatigue, paresthesias, speech difficulties, diplopia, and nausea. Depression and cognitive impairment have been reported.

Drug Interactions: Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia. In most cases, symptoms and signs abated with discontinuation of either drug.

Contraindication: Hypersensitivity to the drug. Avoid in those with history of renal stones. Abrupt withdrawal should always be avoided.

IV. SEROTONERGIC DRUGS:

IVa. Selective Serotonin Reuptake Inhibitors (SSRI) **:** Data on the effects of serotonergic medications on alcoholism are limited, and the results are less consistent. The serotonergic medications that have been most extensively evaluated are the selective serotonin reuptake inhibitors (SSRIs), particularly fluoxetine and citalopram. Even among studies conducted with SSRIs, findings have been variable. Some studies suggest that SSRIs are efficacious only in heavy drinkers or in certain subgroups of alcoholics. Both acute and chronic administration of SSRI, has been shown to reduce ethanol consumption. It was reported that fluoxetine up to 60 mg per day had no significant effect on alcohol consumption in persons who were alcohol dependent without major depression. In a study, it was shown that patients with major depression and alcohol dependence showed beneficial effect when treated with 20 to 40 mg per day of fluoxetine over 12 weeks than those receiving placebo, in terms of decreasing frequency and quantity of drinks, and reducing heavy drinking days. Other SSRI like fluvoxamine has shown similar results. At present use of SSRIs could only be recommended only for those alcoholics for whom SSRIs are otherwise indicated (e.g. as antidepressants) and dose required is higher than antidepressant dose.

IVb. Ondansetron **:** Ondansetron, a selective 5-HT3-receptor antagonist, has been shown in one study to have a beneficial effect on early onset alcohol dependence, presumably by modulating dopamine release in mesocorticolimbic dopamine pathways. In a randomized control study, ondansetron 4 mcg per kg twice per day was shown to significantly reduce self-reported drinking, increase percentage of days of abstinence and increase total number of days abstinent per study week in patients with early onset alcoholism. However there is insufficient evidence to justify its routine use at present.

V. COMBINATION OF DRUGS

V a. Combination of naltrexone with acamprosate **:** Naltrexone increases rate and extent of absorption of acamprosate. Diarrhoea and nausea are the most significant side effects. A review shows that the combination is better than acamprosate alone and better than combination of acamprosate with placebo. However, their individual and combined roles need better delineation. Overall, acamprosate appears to be more useful at achieving abstinence, while naltrexone seems more indicated for controlling alcohol consumption. Many alcohol dependent patients, particularly those that respond insufficiently on monotherapy could benefit from this combination regimen.

V b. Combination of acamprosate or naltrexone with disulfiram **:** Some researchers have reported increased benefit of disulfiram when used either with acamprosate or naltrexone.

V c. Composite combination of pharmacological and non-pharmacological intervention **:** One of the largest, multi-site clinical trial of pharmacologic and behavioral treatments for alcohol dependence (COMBINE trial), recruited recently abstinent alcohol dependent patients (n=1383) in outpatient setting to one of nine treatment groups. Eight treatment groups received Medical management (MM)[1]; four of these received

[1]Medical management provided by health professional to all patients consisted of nine, brief, structured sessions following standard protocol.

naltrexone (100 mg/ day), acamprosate (3 gm/day), both naltrexone and acamprosate, or placebo pills. The other four groups received in addition specialized alcohol counseling (up to 20 sessions of alcohol counseling by a behavioral specialist). The ninth group received only the specialized alcohol counseling, but no medications, and no more than four visits with a health professional for general medical advice. Contrary to the expectations, the researchers found no effect on drinking while on acamprosate and no additive benefit from combination of acamprosate and naltrexone. Highest chances of decreasing alcohol consumption were seen in patients who received medical management and naltrexone (but no alcohol counseling), at the end of four months. At the end of one year worst outcome was seen in patients who received medical management plus placebo and better outcomes in those who received medical management plus either naltrexone or specialized alcohol counseling. In other words, adding either naltrexone or specialized alcohol counseling to medical management enhanced the chances of decreasing heavy alcohol consumption, and reducing relapse.

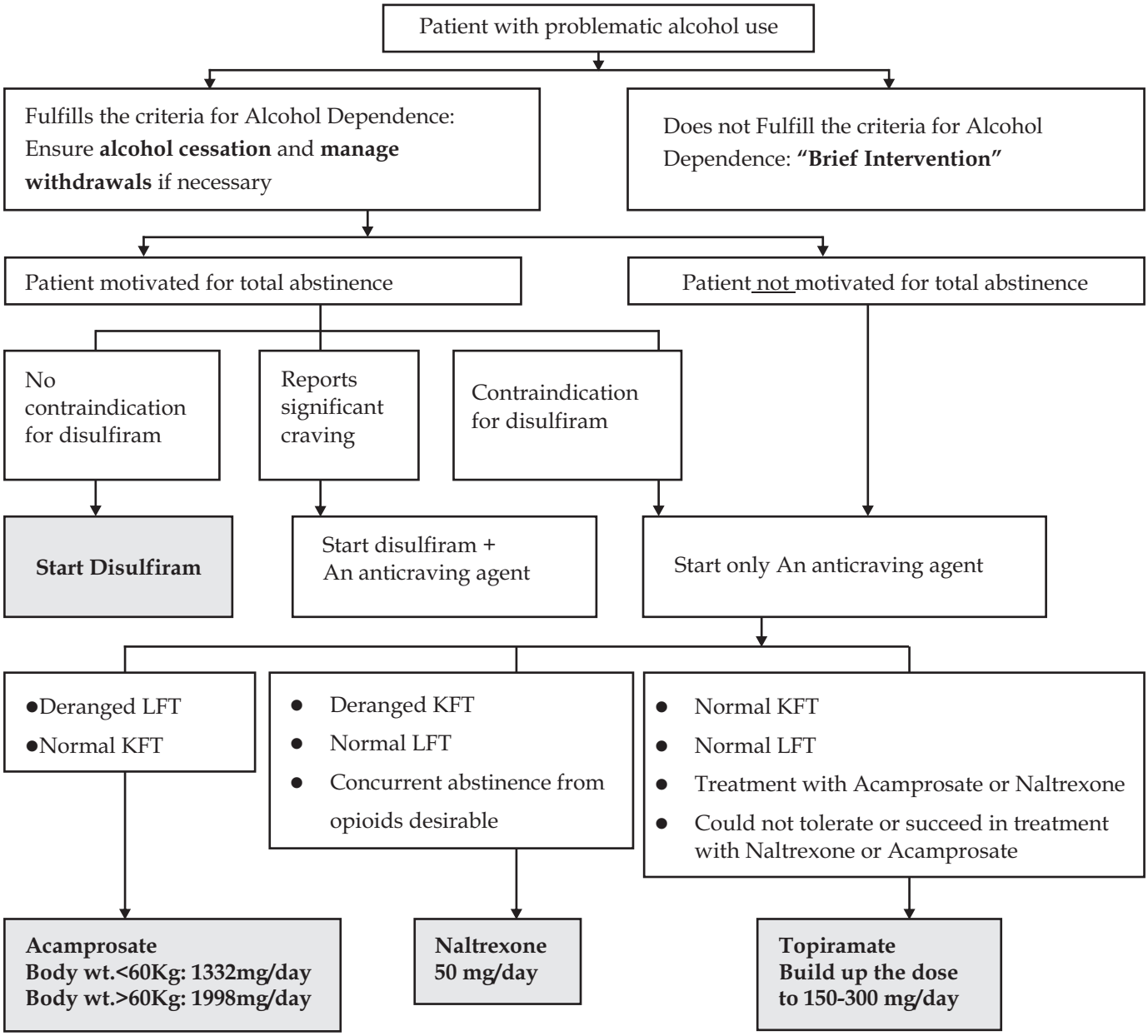
Conclusions

Thus, it can be seen that anti-craving agents could play a significant role in the long-term treatment of alcohol dependence. Many physicians are not aware that medications are effective in the treatment of addictive disorders and even if they are aware there is reluctance to use such medications. Despite many limitations, review of research confirms the safety and efficacy of acamprosate and naltrexone as treatments for alcohol dependence. There are insufficient data available to establish with any certainty the superiority of one drug over the other, at this moment. Acamprosate seems especially useful in a therapeutic approach targeted at achieving abstinence, whereas naltrexone seems more indicated for treatment goals oriented to controlled consumption. At present, acamprosate should probably be considered the first-line treatment for patients with moderate to severe alcohol dependence, because of the larger body of supporting evidence and the benefits extending after treatment. Naltrexone is indicated for alcohol-dependent patients in whom acamprosate has not proved effective or has not been well tolerated. There may be special indication for prescribing naltrexone to alcohol-dependent patients who are also dependent on opioids. The best choices for prevention of relapse are acamprosate and naltrexone with concurrent counseling through professional or self-help programs. Physicians may also consider the use of an SSRI in the presence of a comorbid mood or anxiety disorder. Topiramate and ondansetron show promise as treatments to increase abstinence.

Apart from these medications, non-pharmacological interventions like individual and group counselling and 12-step programmes are used in the rehabilitation of patients with alcohol dependence. Medications should be considered as adjuncts along with other nonphramacotherapeutic interventions like alcohol counseling, family psychoeducation, motivation enhancement therapy and family therapy and other methods that are helpful in changing lifestyles patterns in healthier direction.

Thus, the development and successful clinical use of 'relapse preventing medications' opens up a completely new perspective in the treatment of alcohol-dependent patients. The ultimate goal is to develop therapies that optimize the combination of pharmacotherapy and psychosocial treatment in reducing the morbidity and mortality related with alcohol consumption.

Pharmacological treatment of alcoholism suggested algorithm



Tips for follow-up:

- ⊙ Monitor LFT (Liver function tests) and KFT (Kidney function tests) at least once every three months even if normal. Increase frequency of tests if abnormal at any point in time
- ⊙ Look for side effects
- ⊙ Look for emergence of psychiatric symptoms and initiate appropriate treatment
- ⊙ Confirm reduction in alcohol consumed and frequency of consumption by family members
- ⊙ Enquire into reduction of craving
- ⊙ Non-pharmacological therapy is an integral part of the treatment (e.g., Motivational Enhancement Therapy, Relapse Prevention Sessions, Family Therapy and Occupational therapy)

Frequently asked questions

Q1. Can I prescribe these medications when patient wants to take medications but not ready to stop alcohol?

Ans. None of these medications require total abstinence from alcohol prior to starting these. If there is heavy dependence on alcohol, it is always better to treat withdrawal symptoms (detoxification) prior to starting these medications. Compliance is likely to be better if one stops drinking while on these medications. These medications do not cause adverse effects similar to that of disulfiram (a Disulfiram Ethanol Reaction) when alcohol is consumed while on these medications.

Q2. When do I say that the medication is not working?

Ans. Build-up the dose to the optimal levels, start non-pharmacological interventions and then wait at least for one month before declaring that the treatment is not effective. Assess in terms of decrease in craving, decrease in frequency of drinking, decrease in amount of drinking or decrease in episodes of heavy drinking compared to the baseline.

Q3. What is the frequency of visits and duration of treatment?

Ans. There are no fixed guidelines for this. In well motivated patients who have good social support and who show normal baseline investigations, a good follow-up schedule would be - monthly for the first six months then two monthly for the next six months. Encourage the patients to come with their family members. At the end of one year, decision to continue the treatment further may be taken in consultation with the patient.

Q4. Can family members give these medications to someone who does not want to come to clinic?

Ans. Though, these medications do not cause adverse effects when given clandestinely for someone who is unable to stop drinking, it is not an ethical practice. All patients must be seen to assess severity of problematic use of alcohol, comorbid other psychiatric or medical condition, and to assess the degree of motivation. Only then, in consultation and agreement with the patient, the suitable medication must be chosen. Poorly motivated patients need motivation enhancement therapy.

Q5. Patient is willing for total abstinence and is a candidate for disulfiram but he reports intense craving and he fears that he might give into his craving and start drinking leading to the Disulfiram Ethanol Reaction. What should I do?

Ans. In such cases, with informed consent, start disulfiram and also add an anticraving agent. Such a combination is likely to have a better outcome. The Disulfiram will help in cognitive arousal to be on guard, while the anti-craving agent will decrease the craving.

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Agonist maintenance therapy using buprenorphine

Anju Dhawan, Amardeep Kumar***

Introduction

Opioid dependence is a chronic relapsing disorder and single episode of treatment seldom leads to prolonged abstinence from drugs. Majority of heroin addicts relapse within the first year of treatment, most within the first three months. Over time, addiction assumes the characteristics of a drug career. Most persons who manage to achieve long-term abstinence have numerous treatment attempts in the past.

Detoxification is at best the first step in treatment to achieve a drug free state. It is easy to achieve, though, not the most significant accomplishment. The more difficult phase is to prevent relapse. As has been stated earlier, heroin addiction being, a chronic disorder requires long-term therapy usually measured in months if not, years. The focus of maintenance therapy is to restore life function, the person's capacity to earn, with improved self-esteem and personal dignity.

Opioid substitution or maintenance on an agonist drug is well accepted as an effective harm minimization treatment strategy. The basic principle of agonist maintenance treatment is to substitute illicit, medically unsafe, short acting and more reinforcing opioids with a medically safer, long acting agonist of known purity, potency and dosage. Methadone is the most extensively used drug for maintenance treatment in many countries. Studies have shown that as part of a broader programme of support and rehabilitation, methadone maintenance treatment reduces illicit opioid use, criminal activity, mortality and morbidity (including risk of HIV infection) and improves psychosocial functioning.

Buprenorphine, a partial opioid agonist, is another option for maintenance treatment of opioid dependence. It has been used widely in several countries. It is effective in reducing drug use, crime, health problems and risk of contracting HIV. When compared with methadone, methadone at high doses has higher rates of retention and better suppression of heroin use as compared to buprenorphine. Buprenorphine has the advantage over methadone of producing fewer withdrawal symptoms, safety in terms of respiratory depression and that it can be administered alternate day. It is currently the only option available in India as both methadone and LAAM are not available.

Rationale for use

Agonist maintenance eliminates drug hunger and produces cross-tolerance or blockade so that the person would not experience any narcotic or euphoric effects if they were to self-administer the illicit opioid.

The specific objectives of agonist maintenance treatment should be to reduce illegal and other harmful drug use, improve the patient's health and well-being, reduce the transmission of blood-borne infectious diseases, reduce deaths associated with opioid use, reduce crime committed by patients, facilitate an improvement in

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the patient's occupational and social functioning, improve the economic status of patients and their families and ultimately to achieve abstinence from drug use, including cessation of the opioid substitution treatment. All of these objectives will not necessarily be achieved with each patient and may not be achieved to the same degree.

Pharmacology

Mechanism of Action

Buprenorphine is a partial μ agonist and k antagonist, which has a relatively long duration of action. It is a semi-synthetic opium alkaloid derived from thebaine and is structurally related to its narcotic antagonist etorphine and diprenorphine. It is a long acting, highly lipophilic opioid and 25-50 times more potent than morphine (in analgesic action). It produces analgesia and other central nervous system effects that are qualitatively similar to those of morphine. Buprenorphine binds to more than one opioid receptor. It has higher affinity and low intrinsic activity at opioid receptor. Buprenorphine can substitute for morphine or heroin and suppresses symptoms of agonist withdrawal. However, at very high levels of addiction, it may precipitate withdrawals.

At low doses buprenorphine in humans produces morphine like subjective, physiological and behavioural effects. These include analgesia, sedation, pupillary constriction and euphoria. When the dose of buprenorphine is increased, the intensity of its actions does not seem to exceed that achieved with 30-60 mg morphine. When given sublingually, morphine like subjective effects (euphoria) reached a ceiling at about 8-16 mg. The pharmacokinetic data revealed dose-related increase in plasma concentration of buprenorphine, indicating that the apparent ceiling on the effects of buprenorphine was not attributable to limited sublingual absorption. For all measures, there was a ceiling dose, beyond which no greater effect was observed. Respiration was maximally suppressed after administration of 16 mg buprenorphine. The ceiling effect on the euphoria and respiratory depression respectively limit abuse liability and increase the safety in clinical practice. The potential for lethal overdose is remote even at 10 times of the therapeutic dose. Moreover, due to its partial agonistic action, it can precipitate withdrawal in morphine dependent individuals. Following repeated administration, buprenorphine attenuates or blocks the subjective effects of parenterally administered morphine or heroin.

It binds tightly to and slowly dissociates from the receptors and its slow rate of dissociation contributes to buprenorphine's long duration of action. For this reason its effect can be prevented by prior or simultaneous administration of narcotic antagonists rather than later.

Pharmacokinetics

Buprenorphine is less effective by oral route and its bioavailability by this route is 15 percent but when administered sublingually, its bioavailability increases to 51 percent. There is no limit in sublingual absorption and plasma concentration is linearly related to dose. Peak blood levels are achieved after 5 min when administered through i/v route. It is metabolised in liver by glucoronide conjugation and

N-dealkylation and has an active metabolite norbuprenorphine. Elimination half-life of intravenous buprenorphine is 3.21 hours and for sublingual buprenorphine is 27.2 hours. Following three times daily chronic sublingual dosing of 0.4 mg, steady state levels of buprenorphine are achieved at about 4 days.

Effectiveness

A recent study of meta-analysis on buprenorphine maintenance versus placebo or methadone maintenance has been published by Cochrane Database. This report is based on an extensive search of data up to 2001 from various sources including medline. This study reported that thirteen studies met the inclusion criteria, all were randomised controlled trials and all but one was double blind. The methodological quality of these studies was good. Retention in treatment and drug use were the two important outcome measures.

Retention in Treatment

Buprenorphine maintenance treatment compared favourably with placebo in retaining patients in treatment although it appeared significantly less effective than methadone in retaining patients in treatment.

Illicit drug use

Buprenorphine was more effective than placebo in suppressing heroin use. However, only high dose and very high dose buprenorphine suppressed heroin use significantly above placebo. The study concluded that buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but is not more effective than methadone at adequate doses. The Indian studies too have documented the efficacy of buprenorphine in reducing drug use and improving psychosocial functioning.

Buprenorphine substitution programme: Experience from India

The use of buprenorphine maintenance for the treatment of opioid addicts is still very limited in the country. A project on community-based treatment for heroin addiction using buprenorphine was carried out by the De-addiction Centre, All India Institute of Medical Sciences as early in 1993. This study included buprenorphine maintenance as a part of community based treatment in a quasi-experimental pre-post design. The project included 108 male subjects with heroin dependence. The dosage of buprenorphine used in this project was low and treatment was provided for a period of 6-11 months. Three sessions on psychosocial intervention were also carried out. At follow up about 70 percent had improved indicating no use or very little use of heroin in spite of the low doses used.

Another study that was carried out in Nagaland used buprenorphine maintenance on opioid dependent subjects. Fifty-four male opioid dependent patients were given buprenorphine in low doses and were followed up to six-months. The Addiction Severity Index (ASI) scores reduced significantly in the 'drug' and 'family' domain of ASI at six months of follow up indicating reduction in problems in these domains.

Data from SHARAN (a Delhi based NGO) in the year 1995-1997, showed that out of 447 injecting drug users on buprenorphine, 148 (33%) had stopped injecting while 158 (35%) had reduced the frequency of injecting and sharing of equipment.

Two more recent studies-one by United Nations Office on Drugs and Crime and another by UK Department for International Development have been carried out in 2006. The preliminary results show reduction in drug use including injecting drug use, high risk injecting behaviour as well as improved quality of life.

More recent studies have used dosages in the range of 4-8 mg/day.

In India, the experience with sublingual buprenorphine indicates that the treatment is beneficial to drug users and is feasible to implement with training of doctors and paramedical staff. Further, the treatment has the potential to retain clients in treatment as well as link them with other services.

Indications

The selection criteria for inclusion of patients in maintenance treatment may vary. However, a confirmed diagnosis of opioid dependence is a pre-requisite; thus patients need to be evaluated for dependence on opioids. These include comprehensive history and physical examination to clearly document drug use and dependence. The history can be corroborated by family members. The veins may show clear signs of recent injecting as well as scarring from the past. Pupils may reveal recent drug use or withdrawal. A urine test can also detect recent use of the drug. Besides a confirmed diagnosis of opioid dependence, other criteria such as duration of opioid dependence and number of failed abstinence attempts have been included in the selection criteria for opioid substitution treatment based on recommendations of a national meeting of experts.

The following are useful guidelines:

Suitability

- Above 21 years of age
- Regular opioid use for at least 5 years
- Proof of at least 2 unsuccessful attempts to achieve abstinence following treatment from recognised treatment centres
- Certification by a Medical Officer
- Willingness to give body fluids to check illicit drug consumption on demand

Side Effects

The information of adverse effects of buprenorphine is available from the study on post marketing surveillance of higher strength buprenorphine from India conducted by NDDTC, AIIMS. The subjects had received 2.8 mg (median) of buprenorphine per day for 138 days (median). Altogether 10 centres participated and contributed 5551 observations. Evaluation included subjective symptoms, assessment of objective parameters, and laboratory investigations on a sub-sample. Ten commonly reported symptoms were

generalized weakness (49%), sense of high (44%), muscle ache (39%), yawning (38%), relief from pain (37%), constipation (33%), lacrimation (26%), craving (27%), anxiety (19%) and sleeplessness (19%). About 5 percent had hypertension. Pupil size, pulse and respiration were normal. Out of 55 subjects, 6 showed elevated liver enzymes. All the symptoms are known effects of use of buprenorphine and concomitant use of additional prescription medicines like anxiolytics and antidepressants or symptoms of opioid withdrawal. No dangerous event or mortality was reported in this sample.

Toxicity

Overdose deaths have been reported with intravenous use or very high doses of combination of Buprenorphine and benzodiazepines or alcohol. The interaction mechanism is unclear, but it appears not to be related to the drug's absorption, distribution, metabolism, or elimination from the body. The interaction potential of sublingual buprenorphine and oral benzodiazepines is unclear.

Drug Interactions

Buprenorphine should be used with caution along with anaesthetic agents, phenothiazines and cimetidine.

Contraindications

Drug reactions

A person with an established history of side effects (hypersensitivity) to buprenorphine should not be put on buprenorphine maintenance.

Incapable of providing informed consent

Buprenorphine maintenance should not be considered if a person couldn't provide informed consent to treatment due to a psychiatric condition such as acute psychosis, major depressive illness or cognitive impairment. Buprenorphine should only be prescribed after the person's condition has been adequately treated.

Primary dependence on non Opioid drugs

Buprenorphine maintenance is not appropriate for people who are primarily dependent on non-opioid drugs such as alcohol, benzodiazepines, amphetamines, or combinations of these.

Concomitant use of other drugs

Concurrent use of high dose of hypnotic, sedative or alcohol leads to aggravation of respiratory depression.

Severe medical illness

It should be used cautiously in patients suffering from bronchial asthma. Severe respiratory impairment, hepatic impairment, pheochromocytoma, inflammatory bowel disease, hypothyroidism and severe prostatic hypertrophy are contraindications to buprenorphine treatment.

Pregnancy

Buprenorphine, at this time, should not be used in pregnant women and breast-feeding women due to lack of adequate data on it's safety. All women who intend to undertake buprenorphine treatment should be advised of the issues in relation to safety of buprenorphine in pregnancy. Contraception advice should be given to women not wishing to become pregnant.

Neonatal abstinence syndrome-

Babies born to women taking buprenorphine are at risk of developing a neonatal abstinence syndrome. Hospitals that care for neonates should be able to care of abstinence syndrome.

Young or very young subjects

The data on use of Buprenorphine maintenance in adolescent drug users is limited. Due to the short duration of drug use in this age group, a drug free approach should be attempted.

Caution should be exercised in treating people with buprenorphine who have high-risk polydrug use, concomitant medical conditions, concomitant psychiatric conditions or chronic pain.

Contraindications

- Pregnancy
- Known hypersensitivity
- Primary dependence on non-opioid drugs
- Young patients
- Certain medical illnesses

Dependence and abuse potential

It is an abusable compound and physical dependence produced by buprenorphine has been confirmed. Mild withdrawal syndrome develops following abrupt withdrawal that is delayed in onset by 2 days to 2 weeks and lasts for 1-2 weeks.

Buprenorphine is a safe compound, well tolerated by patients and has a ceiling effect on it's effects thus preventing respiratory depression when taken alone. Buprenorphine's unique effects and pharmacology make it an important treatment option.

Preparation of Buprenorphine

Buprenorphine is available in strengths of 0.2mg, 0.4mg and 2mg of sublingual tablets. The higher strength tablet (2mg) can be obtained only at specialised de-addiction clinics. However, lower strength tablets (0.2mg and 0.4mg) can be obtained at chemist shop with a triplicate prescription.

Trade name and cost :

Some of the market trade names with the price of medication are as follows-

Addnok , Bupin and Norphin.

The price of 0.4mg tablets is Rs 3.50 approximately and that of 2mg tablet is Rs 15 approximately.

Induction

Patients who are assessed as suitable for buprenorphine treatment should be supplied with verbal and written information about all aspects of the maintenance treatment-what to expect and what not to expect, and their rights and responsibilities. The dose should be titrated according to the clinical effect in the individual patient.

Procedure for buprenorphine (s.l) administration-First and foremost is the establishment of diagnosis of opioid dependence clinically and confirmation by urine screening for recent opioid consumption. After that 2mg to 4mg of s/l buprenorphine is given to the patient. Another 2 mg may be given on day 1 if withdrawal symptoms persist after 2 hours. Dose increments can be done every day by 2 mg/day. In most patients daily dose of 4 to 8 mg of buprenorphine is sufficient.

Dosage and Administration

In the analgesic dose range, 10 mg of intramuscular morphine is equivalent to 0.4-0.6 mg buprenorphine sublingually. For treatment of opioid dependence, approximately 4 mg of sublingual buprenorphine is equivalent to a daily dose of 40 mg of oral methadone.

Buprenorphine is orally ineffective due to its extensive metabolism and sublingual administration is effective as it bypasses the intestinal and hepatic metabolism. Buprenorphine sublingual tablets should be kept under the tongue until dissolved, which usually takes 5 to 10 minutes. Daily dosing is recommended during the initial period of stabilisation. Evidence suggests that subsequently a significant proportion of patients on buprenorphine can be adequately maintained by receiving a dose every alternate day and some even every third day. A trial of alternate day dosing has been tried at NDDTC, AIIMS for patients who have been stable on buprenorphine for at least two weeks. A steady dose requirement and no evidence of intoxication or dangerous use of other drugs represent stability. Less frequent dosing (alternate day/twice a week) has several benefits that include reduced time spent in travel to the dispensing point, more time to undertake activities that promote improved social functioning and fewer congregations of patients around dosing points. **Take away medication is best avoided to prevent diversion.**

Length of maintenance treatment/Completion and Termination

Patients should remain in treatment for the minimum time it takes to achieve their agreed treatment goals. The length of time required for treatment will vary amongst individuals. Regular reviews will assist in determining need for continued treatment. There is no optimal duration of buprenorphine treatment and removing people from treatment too early may result in very poor outcomes, including high rates of relapse into illicit opioid use and a consequent increased risk of overdose. Setting an arbitrary duration of treatment and withdrawing treatment at that endpoint is not recommended. The treatment approach should include working towards goals, that when achieved, prepare a patient to live well without buprenorphine. In most situations stabilization on buprenorphine for at least one year would be required before withdrawal from it although most patients need about two years of treatment. An important objective of buprenorphine treatment is the successful withdrawal from buprenorphine combined with continued good functioning, including good health and social functioning. Planning for successful withdrawal from buprenorphine should commence from the initiation of treatment. The decision to withdraw voluntarily from buprenorphine should be a joint decision of the patient and the prescribing doctor, with information contributed by the social worker or nursing staff, who may be evaluating the psychosocial functioning of the patient. When all agree about the timing and method of withdrawal from buprenorphine, patients tend to be more successful in their buprenorphine reduction. It remains, however, the patient's right to withdraw from medication at any time. Forcing a patient off buprenorphine when they do not feel capable of coping without the treatment may result in return to opioid use and related problems. Unless there is a specific reason for involuntary termination from treatment, this approach is not recommended. The elements of treatment that assist patients to complete withdrawal successfully are:

Dose

A flexible approach to dose reduction, individualizing reduction regimens is best. A slower rate of reduction is required if relapse is likely, or the patient is not coping. In some cases, reductions in buprenorphine dose may need to be suspended or an increase in dose considered.

Increased psychosocial support during withdrawal

More frequent supportive, skills oriented and relapse prevention counselling, more frequent monitoring and review, access to residential programme if necessary (residential withdrawal or rehabilitation programme) and involvement of significant others (including family) in providing support should be explored.

Aftercare services

Counselling, continuing case management and structured group programme are all likely to assist outcome after completion of withdrawal from buprenorphine. The staff should remain involved in the care of patients who have voluntarily withdrawn from maintenance treatment for at least a few months after completion of withdrawal. In case of relapse, the patient should have easy access back into treatment. Treatment should be offered quickly and without recrimination.

Involuntary termination of treatment

At the beginning of treatment, patients should be informed about the conditions in which the treatment may be temporarily suspended or terminated. These may include violence or threat of violence against staff or other patients, property damage or theft from the service centre, drug dealing on or near the service premises, diversion of medication and unacceptable disruption in the locality. If the patient is to be involuntarily withdrawn from buprenorphine treatment, reduction in dosage should be gradual. Rapid dose reduction or abrupt cessation of treatment is warranted only in cases of violence, assault or threatened assault. In general, involuntary withdrawal from buprenorphine should not take less than 14 days. The patient should be advised regarding other treatment options, including detoxification. He should also be warned of the increased risk of overdose after completion of withdrawal. A plan for subsequent readmission into treatment for each patient involuntarily withdrawn from the programme should be made and documented in the patient's case record.

Transfer to Naltrexone

Naltrexone has the potential to assist people to remain abstinent from opioids after withdrawal from buprenorphine. The clinical experience from NDDTC, AIIMS has shown that some patients who were stabilised on buprenorphine maintenance could be shifted to naltrexone after tapering maintenance treatment.

Maintenance Buprenorphine

- ⊙Treatment duration-At least six months
- ⊙Flexible dose
- ⊙Other modalities of intervention

Summary and Conclusions

Opioid dependence is a relapsing disorder. Agonist maintenance treatment is associated with reduced drug use, improved psychosocial functioning, reduced risk of transmission of blood borne infections such as HIV and reduced mortality. Buprenorphine as an agonist maintenance agent is an important treatment option to treat opioid dependence. It is a safe compound, well tolerated by patients with significantly lower risk of respiratory depression as compared with other opioids such as methadone. Data from clinical trials generally indicate that buprenorphine has comparable efficacy to moderate doses of methadone. The feasibility and effectiveness of buprenorphine maintenance in Indian setting has been documented. Dosages prescribed in Indian patients have been in the range of 4 mg to 8mg per day. These have been found effective and need to be used for an adequate duration.

Treatment algorithm for buprenorphine maintainence for opioid dependent patients

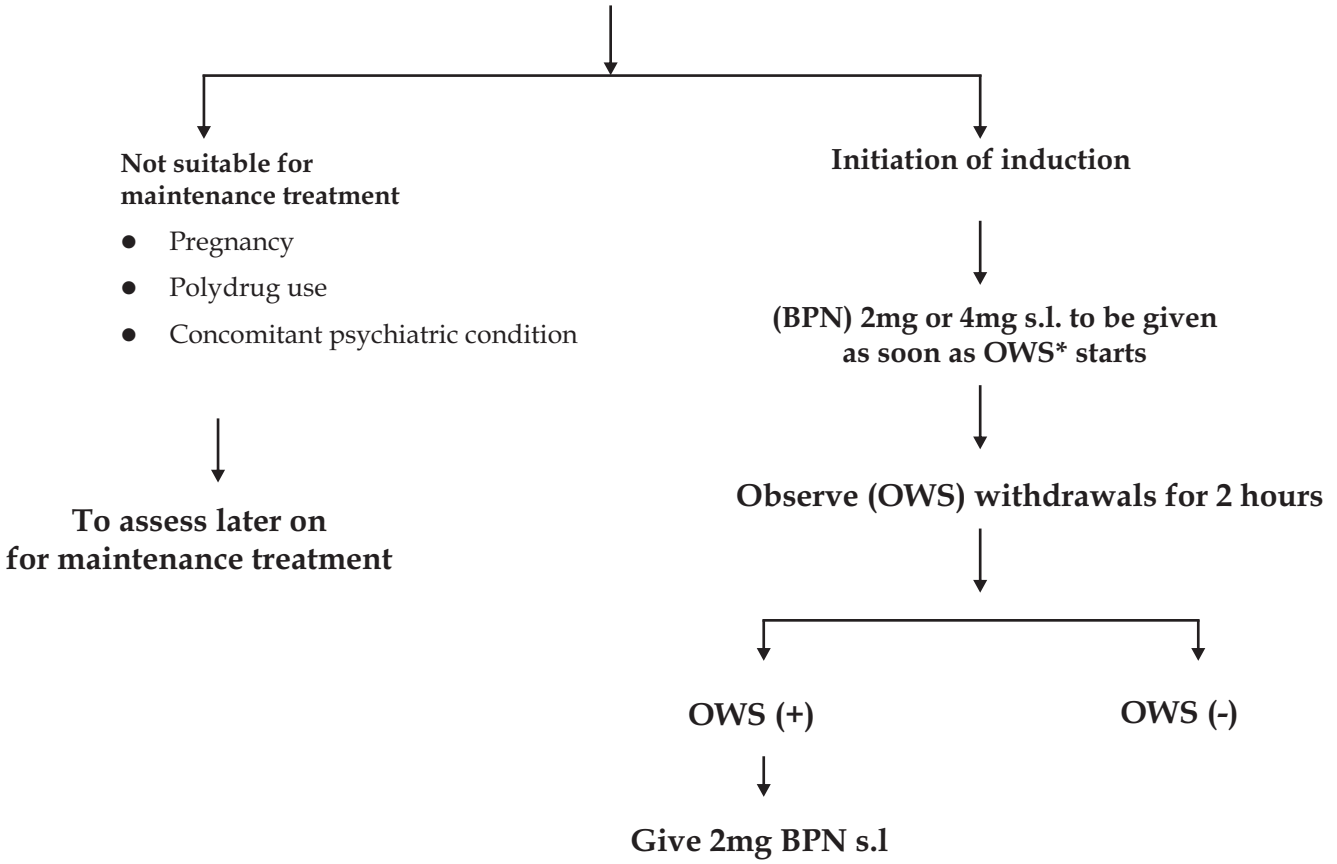
I. DETERMINATION OF DAILY DOSE REQUIREMENT

Patient Selection

Above 21 years of age

Regular opioid use for at least 5 years

At least 2 unsuccessful abstinent attempts from recognized treatment centres



Buprenorphine 2 mg can be added next day if required (total 8mg/day). Subsequent increase in doses should preferably be more slow and every 2-3 days at the rate of increment of 2mg/day only. Maximum dose that has been used in our clinical setting is 24 mg/day but such dose requirements are rare and usual daily dose is in range of 4-8 mg/day and some patients may require upto 12 mg/day.

**Opioid withdrawal syndrome*

Frequently asked questions

Q1. Is buprenorphine easily available for maintenance treatment?

Ans. Buprenorphine is available in strengths of 0.2mg, 0.4mg and 2mg of sublingual tablets. The higher strength tablet (2mg) can be obtained only at specialised de-addiction clinics. However, lower strength tablets (0.2mg and 0.4mg) can be obtained at chemist shop with a triplicate prescription. Thus, it would be appropriate to say that maintenance treatment can be carried out only at de-addiction centres.

Q2. Who are the suitable candidates for buprenorphine maintenance?

Ans. The suitability criteria for inclusion of patients in maintenance treatment may vary. However, a confirmed diagnosis of opioid dependence is a pre-requisite; thus patients need to be evaluated for dependence on opioids. These include comprehensive history and physical examination to clearly document drug use and dependence. The history can be corroborated by family members. The veins may show clear signs of recent injecting as well as scarring from the past. Pupils may reveal recent drug use or withdrawal. A urine test can also detect recent use of the drug, if this facility is available at the centre. Besides a confirmed diagnosis of opioid dependence, other criteria such as at least 5 years of regular opioid use and two unsuccessful abstinent attempts from recognized treatment centres have also been included in the selection criteria for opioid substitution treatment in certain places which helps in further justifying the need for buprenorphine maintenance.

Q3. Can buprenorphine maintenance be advised during pregnancy?

Ans. Buprenorphine is, at this time, contraindicated for pregnant women and breast-feeding women. There is insufficient evidence to state that it is safe in these circumstances. All women who intend to undertake buprenorphine treatment should be advised of the issues in relation to safety of buprenorphine in pregnancy. Contraception advice should be given to women not wishing to become pregnant.

Q4. What should be done if a patient misses a dose of buprenorphine?

Ans. In such cases, patient should be given the usual daily dose of buprenorphine. There is no point in adding the missed dose with the next dose. However, the reason for missing the dose needs to be enquired properly with the counselling of the patient if required.

Q5. What should be done if a patient did not come for treatment for 3-4 days?

Ans. These situations are not infrequent in the buprenorphine maintenance programmes. However, in such circumstances, it is important to enquire the reason for absentism, ask for emergence of opioid withdrawal symptoms and their management along with the clinical examination of the patient for features of recent opioid use or withdrawal symptoms. If the facility of urine screening for psychoactive substances is available, this should be done. After assessing the patient, maintenance treatment should be continued and issues related to compliance should be addressed.

Q 6. What will happen if the patient stops using buprenorphine abruptly?

Ans. Mild withdrawal syndrome develops following abrupt buprenorphine withdrawal that is delayed in onset by 2days to 2 weeks and lasts for 1-2 weeks.

Q7. How to determine that the patient is not using any illicit opioids along with buprenorphine maintenance?

Ans. It is important to understand that when the patient uses illicit opoids, he develops complications in all the spheres of life. Thus, information needs to be obtained from the family members regarding use of illicit opioids and psychosocial as well as occupational recovery of the patient. Apart from this, the patient needs to be examined for the evidence of recent opioid use such as recent injection mark, pupillary constriction along with other evidence of overdose/intoxication. If facilities for urinary screening of psychoactive substances are available, this should be done regularly for the presence of illicit opioids.

Q8. What should be done if the patient is found using illicit opioids while on buprenorphine maintenance treatment?

Ans. If the patient is found using illicit opioids while on buprenorphine maintenance treatment, he should not be incriminated. Rather, assessment of the cause for the same is required. Afterwards, the cause needs to be addressed by the joint decision of the doctor, social worker and clinical psychologist along with the patient and family member so that treatment goals can be achieved. The dose of buprenorphine may often have to be increased in such a case as it indicates inadequate blockade of acute effects of the illicit drug that is consumed.

Q9. What should be done if the patient is using alcohol concurrently while on buprenorphine maintenance?

Ans. This is not an infrequent situation in patients with polydrug dependence. In such situations, the patient needs to be told about the risk of respiratory depression with the concomitant use of alcohol. This oppourtunity should also be used to motivate the patient to seek treatment for alcohol use as well if he is a problem drinker.

Q10. What measures are required to prevent diversion of buprenorphine from the treatment centre?

Ans. It is important to supervise the dispensing of buprenorphine to prevent diversion from the treatment centre (directly observed therapy). Buprenorphine sublingual tablets should be kept under the tongue until dissolved, which usually takes 5 to 10 minutes.

Q11. What should be the adequate duration of maintenance treatment with buprenorphine?

Ans. Patients should remain in treatment for the minimum time it takes to achieve their agreed treatment goals which is usually about 1-2 years. The length of time required for treatment will vary amongst individuals. Regular reviews will assist in determining the need for continued treatment. There is no

fixed optimal duration of buprenorphine treatment and removing people from treatment too early may result in very poor outcomes, including high rates of relapse into illicit opioid use and a consequent increased risk of overdose. Setting an arbitrary duration of treatment and withdrawing treatment at that endpoint is not recommended. The treatment approach should include working towards goals, that when achieved, prepare a patient to live well without buprenorphine. In most situations stabilization on buprenorphine for about two years would be required before withdrawal from it. An important objective of buprenorphine treatment is the successful withdrawal from buprenorphine combined with continued good functioning, including good health and social functioning.

Q12. How should successful withdrawal of a patient from buprenorphine maintenance treatment be carried out?

Ans. Planning for successful withdrawal from buprenorphine should commence from the initiation of treatment. The decision to withdraw voluntarily from buprenorphine should be a joint decision of the patient and the prescribing doctor, with information contributed by the social worker or nursing staff, who may be evaluating the psychosocial functioning of the patient. When all agree about the timing and method of withdrawal from buprenorphine, patients tend to be more successful in their buprenorphine reduction. It remains however, the patient's right to withdraw from medication at any time. Forcing a patient off buprenorphine when they do not feel capable of coping without the treatment may result in return to opioid use and related problems. The elements of treatment that assist patients to complete withdrawal successfully are flexible approach to dose reduction, increased psychosocial support during withdrawal and provision of aftercare services.

Q13. When does the buprenorphine maintenance treatment need to be terminated involuntarily?

Ans. At the beginning of treatment, patients should be informed about the conditions in which the treatment may be temporarily suspended or terminated. These may include violence or threat of violence against staff or other patients, property damage or theft from the service centre, drug dealing on or near the service premises, diversion of medication and unacceptable disruption in the locality. If the patient is to be involuntarily withdrawn from buprenorphine treatment, reduction in dosage should be gradual. Rapid dose reduction or abrupt cessation of treatment is warranted only in cases of violence, assault or threatened assault. In general, involuntary withdrawal from buprenorphine should not take less than 14 days. The patient should be advised regarding other treatment options, including detoxification. He should also be warned of the increased risk of overdose after completion of withdrawal. A plan for subsequent readmission into treatment for each patient involuntarily withdrawn from the programme should be made and documented in the patient's case record.

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Long-Term Use of Naltrexone For Opiate Dependence

Sonali Jhanjee and Indra Mohan***

Introduction

Opioid dependence causes several familial, occupational, social and medical complications among dependent individuals and their families. One of the treatment options available to treat such individuals is the use of maintenance medication (substitution with an orally active opioid drug,like methadone and buprenorphine), which has proven to be the most effective treatment for opioid dependence.However, opiate antagonists like naltrexone offer a treatment approach that is distinctly different from that of agonist maintainence. These opiate antagonists have been used for some time as antidotes after opiate overdosage, but their application in the treatment of opioid dependence is more recent.

Opiate antagonists are substances that bind to the opiate receptors but do not produce morphine like effects. The first clinically useful antagonist was nalorphine, which reduced morphine effects, but also produced some agonist effects. Because of it's potential for increasing rather than decreasing respiratory depression, nalorphine has been replaced by naloxone as an antidote for opioid overdosage. Naloxone and naltrexone are relatively pure antagonists in that they produce little or no agonist activity at usual doses. Naloxone however has limited utility as a maintainence agent because it is poorly absorbed and has a duration of only a few hours following oral administration. Among the opiate antagonists, naltrexone, which became available for general use in 1985, has emerged as the most extensively studied agent to prevent relapse in opiate dependent patients. Naltrexone is an orally active and long acting potent pure narcotic antagonist.

Structure

Naltrexone was developed by substituting an N-methyl group on the opiate agonist oxymorphone with a methylcyclopropyl moiety.

Pharmacokinetics

Naltrexone is rapidly and completely absorbed following oral administration and reaches peak plasma concentration within an hour. It has high first pass metabolism and oral bioavailability is 60%, with 20% of the drug being bound to plasma proteins.

Naltrexone undergoes first-pass metabolism in the liver via glucuornic acid conjugation with transformation to the active metabolite 6-beta naltrexol. The half-life of this drug is about 4 hours and that of its active metabolite is 10-12 hours.

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Pharmacodynamics

Naltrexone is a non-specific opiate antagonist that binds to all three opiate receptors sites ( ) as a function of dose administered.

The pharmacological duration of naltrexone is longer than might be predicted by the plasma kinetics. The plasma half-life of naltrexone is 4 hours, but the duration of opioid receptor blockade is much higher and a 50 mg dose of naltrexone blocks 25 mg of heroin for 24 hours, 100 mg for 48 hours and 150 mg for 72 hours. This pharmacodynamic property of naltrexone makes it easy to be administered in simple and convenient regimens.

Indications

1. Maintenance treatment for detoxified patients with Opiate dependence.
2. Prevent relapse in patients with Alcohol dependence
3. Opiate detoxification protocols: It has established usefulness when combined with clonidine as part of outpatient detoxification protocols.

Preparations of Naltrexone

50 mg oral tablet in package of 10 tablets

Trade name **:** Naltima *(Intas pharma),* Noddict *(Sun Pharma)*

Cost **:** Rs 40-45/ tablet depending on the brand.

Long-term use of naltrexone for opiate dependence(as a maintenance agent)

Rationale for use

As an opiate antagonist, naltrexone selectively competes with both exogenously administered opiates for central nervous system (CNS) and non-CNS opiate receptors and blocks their activity. If an individual stabilized on opiate antagonist consumes an opiate agonist like heroin, he will not experience the euphoric effects as the opiate receptors are already blocked and hence not available for the opiate agonist to act. In this manner, over time, the *drug seeking behaviour* becomes extinct. This blockade eventually reduces *craving* and *de-conditioning of cue related craving* as patients are exposed to people, places and things formerly associated with opiate use while being protected from opiate effects. In addition due to the constant occupation of opiate receptors by antagonists, *physical dependence* is not re-established. Since the medication is without any addictive property, diversion is not an issue. Tolerance does not appear to develop to the antagonism of opioid effects even after more than one year of naltrexone ingestion. Cravings for opiates, opiate seeking and using behaviour, if viewed as conditioned responses, should then extinguish as a consequence of not being reinforced.

Thus, a long acting drug like naltrexone is ideal for use in preventing relapse to opioid use.

Evidence base

Patients involved in meaningful relationships, employed full time, or attending school and living with family members are most likely to benefit from naltrexone treatment. Follow up of naltrexone treated patients indicates that 30-40% are opioid free for 6 months after terminating treatment.

However, naltrexone treatment has a very high early dropout rate. Only 10-20% take naltrexone for 6 months or longer, although certain specific motivated populations like **addicted professionals** and **former prisoners** on probation have significantly higher rates of accepting naltrexone and remaining in treatment. This may be due to the fact that naltrexone has no reinforcing properties of its own and is perceived as a subjectively neutral drug that prevents addicts from getting high. Kirchmayer and colleagues in 2002 systematically reviewed controlled clinical trials that there was insufficient evidence to justify naltrexone use in the maintainence of addicts, except to decrease the possibility of reincarceration of prisoners treated with combined behaviour therapy and naltrexone. However a metanalysis of fifteen studies involving 1071 patients in 2006 found significant heterogeneity in the efficacy of naltrexone.The authors attributed this to the potential moderating effect of treatment retention This study concluded that retention was the key variable for understanding the mechanisms of the effect of naltrexone in opioid dependence and that the drug may be effective if the retention rate is increased above a certain level.

Patient Selection

Naltrexone therapy is suitable and recommended for patients with the following characteristics:

- Younger persons at early stages of opiate dependence.
- Persons currently abstinent but concerned about possible relapse and willing to be on a medication that does not produce a high.
- Employed individuals and professionals (healthcare workers, lawyers, pilots, business people) facing loss of employment or licensure due to opiate abuse.
- Former opiate dependent persons who have been drug-free e.g., in a rehabilitation centre, therapeutic community, or prison and wishing to remain abstinent.
- Opiate-dependent persons who prefer to try alternative pharmacotherapy, other than methadone or buprenorphine.
- Individuals who have been drug-free but recently relapsed on opiates.

Patients, as well as their support persons, need education on how naltrexone works and the critical importance of compliance with the dosing regimen. *It is advisable to supervise the ingestion of naltrexone either from the treatment centre (by the nurse/pharmacist) or tell a family members like wife, parent to administer the medication.*

Dosage and Administration

Naltrexone is available in 50 mg tablets and the recommended daily dose is 50 mg per day. *Initiating naltrexone maintenance requires that the patient be opiate free.* An opiate antagonist like naltrexone can precipitate an acute withdrawal syndrome in patients who are dependent on or are regular users of opioids. So patients should be detoxified and should be abstinent from short acting opiates (e.g. heroin) for about 3 days and from longer acting opiates (e.g. methadone) for about 7 days or more as judged by self report, urine toxicology screening test and Naloxone Challenge test.

Naloxone testing for residual dependence (Naloxone Challenge test)

It has been advocated that an intravenous or subcutaneous challenge of 0.4-0.8 mg of Inj. Naloxone (if available in the centre) be given prior to the administration of naltrexone to test for residual opioids so that withdrawal signs and symptoms are not precipitated. A positive test indicative of residual opioids would consist of typical signs and symptoms of opiate withdrawal.These include yawning, abdominal cramps, irritability, anxiety, chills etc. These signs and symptoms often last only 30-60 minutes and in such a situation naltrexone should be withheld for at least 24 hours.

Intravenous:

Inject 0.2 mg naloxone.

Observe for 30 seconds for signs or symptoms of withdrawal.

If no evidence of withdrawal, inject 0.6 mg of naloxone.

Observe for an additional 20 minutes.

Subcutaneous:

Administer 0.8 mg naloxone.

Observe for 20 minutes for signs or symptoms of withdrawal.

Note: The naloxone challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids.

Naltrexone Induction

When the required period of abstinence from opioids is complete as judged by clinical examination and self report, urine toxicology screening test (if available), negative naloxone challenge test(if available), naltrexone can be initiated carefully in the dose of 25mg and if no withdrawals occur after 1 hour then another dose of 25 mg is given.The recommended dosage subsequently is 50mg/day.

After the first 1-2 weeks, it is usually possible to graduate the patient (50, 75, 100 mg on subsequent days) to three doses per week (100mg on Mondays and Wednesdays and 150mg on Fridays). It may also be give in the dosing regimen of 100mg every other day or 150 mg every third day. As compliance is often poor, these flexible

dosage regimens makes it possible to supervise the ingestion of naltrexone from the treatment centre (directly observed treatment.)

Progress in treatment is determined by psychosocial parameters (e.g finding a job, job performance) and absence of drug abuse as confirmed by urine tests.

Retention/Compliance

Naltrexone maintenance is effective as long as the drug is taken regularly. Despite it's relatively pure antagonist activity and minimal side effects, naltrexone has not been widely accepted by addict and has a very high early dropout rate. This may in part be due to the fact that naltrexone does not have any agonist properties and thus does not induce euphoria. In large multimodal programmes in USA, only 5-10% of opiate dependent patients show an interest in naltrexone at any given point in time and many patients drop out early. Only 10-20% takes naltrexone for 6 months or longer, although its acceptance among (opiate users) certain target groups such as health professionals, employed individuals and former prisoners on parole is high. Retention and compliance have been best in motivated individuals with strong support systems. Conversely, individuals with poor socio-economic supports or few incentives for rehabilitation tend to fare poorly.

However, even short term (30 days or more) treatment with naltrexone has been associated with improved outcome at 6-month follow up. Appropriate patient selection and explanation of need for adequate duration of therapy can reduce the drop out rate. Naltrexone works best in the presence of a structured rehabilitation programme.

Guidelines for providing naltrexone maintenance treatment

- Good occupational functioning
- Good social support
- Higher motivation
- Short duration of drug use (3years or less)
- Been on agonist maintenance for several months and has achieved good occupational and social functioning
- Opts for antagonist maintenance when given a choice
- Clearly prepared for abstinence

One or more of the above criteria may be satisfied.

These guidelines should be used along with clinical judgment.

Therapy Duration

No standard duration of therapy is recommended although it is generally used for 6-12 months. It has to be used for a minimum period of 3 months.The guiding principles for discontinuation of therapy are an extended period of opiate abstinence and achievement of stable and significant psychosocial recovery.

Naltrexone as part of a comprehensive treatment programme

Naltrexone works best within a comprehensive treatment programme that deals with all aspects of a patient's problems. Adjunctive psychiatric evaluations, counseling, relapse prevention sessions, coping skills, significant family member involvement and participation in psycho-education group sessions are vitally important and these must be tailored to individual patient needs. Counselling involving families and/or significant others has been repeatedly recommended as beneficial because these persons serve as support and/or coercive agents fostering treatment retention and compliance.

Side effects and contraindications

It has few side effects. Most patients report no symptoms at all and the profile of reported adverse effects includes gastrointestinal distress (nausea, vomiting, diarrhoea, and abdominal pain), anxiety, restlessness, dysphoria, mild hypertension, headache and insomnia. It has been suggested that some effects might be attributed to a mild, temporary abstinence syndrome influenced by naltrexone's complete opiate blockade. These adverse effects are most prominent in the first several days of use and improve rapidly for patients remaining in treatment. Adverse effects can be minimized by ensuring an adequate interval between cessation of opiate use and initiation of naltrexone therapy and by a graduated initial dosage schedule starting with 12.5 or 25 mg daily for the first few days.

The potential for hepatotoxicity at high doses has been raised as a more serious concern. However convincing reports of elevated liver function test results have been limited to patients receiving 250mg to 300mg daily, five to six times higher than the recommended maintenance dosage for opiate dependence. As a precaution, patients should receive a full battery of liver function tests prior to receiving naltrexone, and it is *contraindicated* in patients with liver failure or acute hepatitis. Caution should be exercised in using naltrexone with patients whose levels of liver enzymes are 2-3 times above normal values.

As a guideline, liver function tests should be repeated monthly for the first 3 months and every 3 to 6 months thereafter, if there is no evidence of rising enzyme levels. If persistent elevation in liver enzyme occurs, naltrexone should be discontinued.

Because naltrexone is excreted through the kidneys, caution should be used in patients with severe renal impairment.

It is contraindicated also in persons who are taking opiate agonists

Patients taking naltrexone will lose their tolerance to opioids just as will drug free patients. This means, by definition, that they will be more sensitive and thus vulnerable to overdose if they resume heroin use at

previous levels. Patients should be advised that taking large quantities of exogenous opiates in an attempt to overcome blockade provided by naltrexone can be dangerous. Life threatening opiate intoxication may result including respiratory arrest or circulatory collapse.

In patients requiring elective surgery, cessation of naltrexone 72 hours prior to surgery is recommended.

Safety in pregnant women and in children and adolescents

It is advisable to avoid use in this population as safety and efficacy of naltrexone in this population has yet to be adequately established.

Drug interactions

Because naltrexone is an opiate antagonist, it blocks the pain relieving effects of opiate analgesics. In patients maintained on naltrexone, non-opiate pain medications or approaches should be tried when possible.

The safety and efficacy of combined use of disulfiram and naltrexone are unknown and given that both medications are potentially hepatotoxic, their concomitant use is not routinely recommended.

Increased lethargy and somnolence have been reported with the combined use of naltrexone and thioridazine. If a neuroleptic were required in combination with naltrexone, a nonsedating neuroleptic is preferable. Although formal drug interaction studies have been not been conducted with antidepressant medication the incidence of adverse events repoted by patients receiving naltrexone in addition to antidepressants was similar to that of patients receiving naltrexone in a large safety study.

Depot naltrexone

As medication compliance with the oral preparation has been low, the safety and effectiveness of a depot formulation of naltrexone is currently under study.

Characteristics of Naltrexone treatment

- Once daily or less frequent oral administration.
- Blocks the euphoric effects of opiates.
- No psychotropic or reinforcing effects.
- Non-addicting with no withdrawal symptoms on cessation.
- No tolerance to opiate antagonism.
- Absence of serious adverse effects or toxicity even on long-term use.
- Essentially no abuse liability.
- No potential for diversion.
- Relatively easy availability.

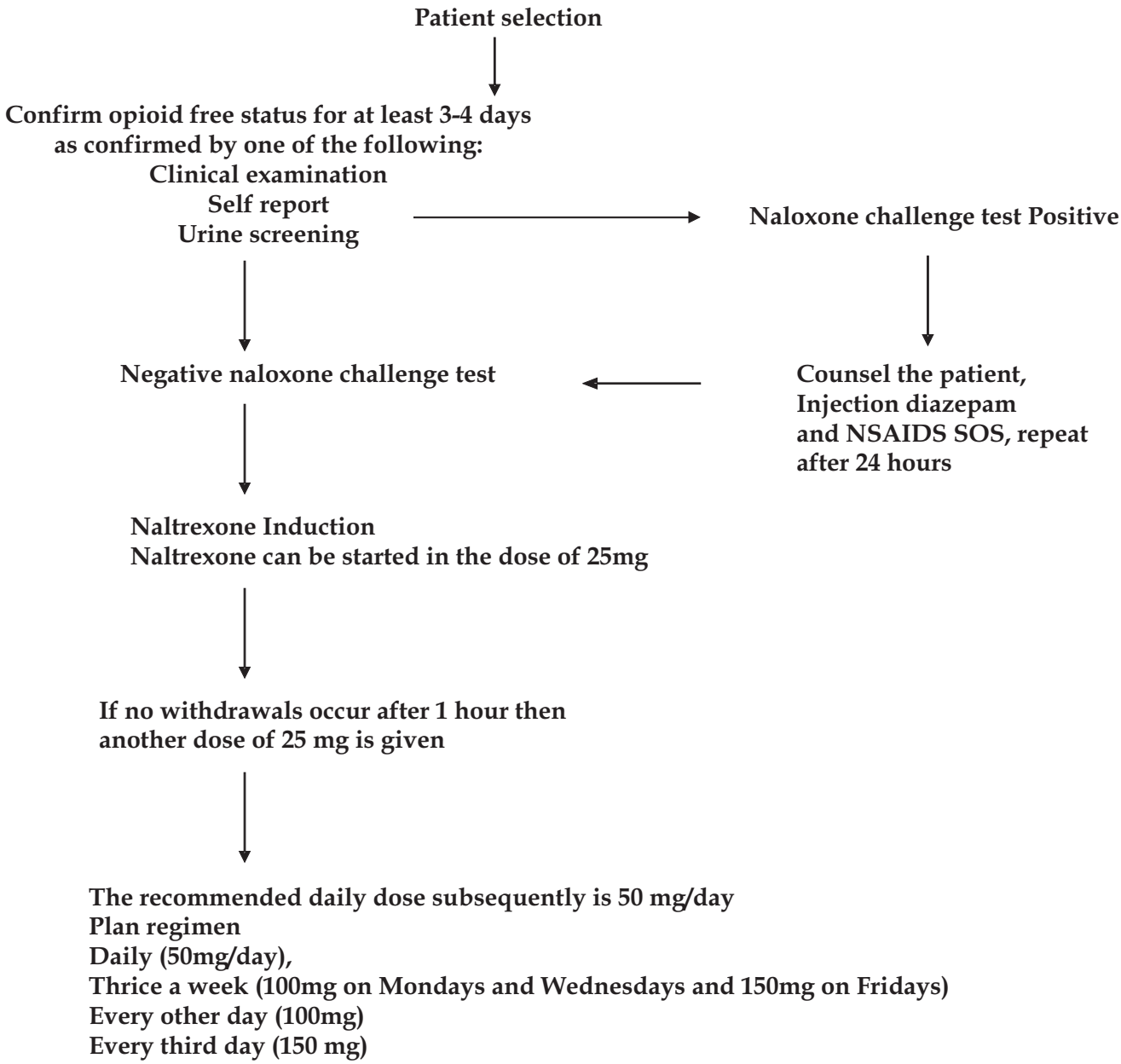
Steps for clinical action

- Instill sufficient motivation among patients to begin treatment;
- Successfully withdrawing patients from illicit opiates or agonists, and keeping them opiate-free until it is safe to start naltrexone;
- Maximizing retention in treatment and compliance while taking naltrexone;
- Involving family and/or significant others in the therapeutic process.

The practitioners should consider the following evidence-based conclusions:

1. Naltrexone is effective in a variety of treatment settings where motivation to stay in treatment, avoiding opiate use and taking medications is supported by appropriate psychosocial support.
2. Therapy providing coping skills to identify triggers and avoid relapse if opiate and/or other drug use occurs may be more beneficial than a strict abstinence orientation.
3. Patients and their support persons need education on how naltrexone works and how to use it.
4. Individualized flexible dosing schedules are possible and may be helpful.

Treatment Algorithm for Naltrexone Maintenance for Opioid Dependent Patients



In cases of Buprenorphine/Pentazocine dependence upto 5mg of Naloxone is required for precipitating Opioid withdrawal symptoms

Frequently asked questions

Q1. What should be done if the information regarding opioid use given by the patient and the family member differs in the patients being considered for naltrexone treatment?

Ans. The usual requirement of naltrexone induction is the presence of opioid-free status in the patient for at least for 3-4days (for patients using longer acting opioids up to 7 days of opioid free period are required). If there is any discrepancy in the accounts given by the patient and the family member about opiate-free period, the patient needs to be explained regarding the possibility of precipitated opioid withdrawal syndrome with shorter opioid-free period. In case of further doubts, naltrexone induction may be postponed and initiated after the required period of abstinence.

Q2. What is naloxone challenge test (NCT)?

Ans. Naloxone is an opioid antagonist with plasma half-life of 1 hour in adults. It is inactive orally because of high first pass metabolism in liver. Injected i.v, it acts in 2-3 min. Presence of residual opioid in the body precipitates opioid withdrawal syndrome if intravenous or subcutaneous injection of 0.4-0.8 mg of naloxone is given. These signs and symptoms often last only 30-60 minutes and in such a situation naltrexone should be withheld for at least 24 hours. When the naloxone challenge test is negative, naltrexone can be started immediately.

Q3. What should be done if naloxone is not available at the centre?

Ans. If there is no doubt about opioid-free period, naltrexone can be started without doing naloxone challenge test (NCT). If there is any doubt about opioid-free period, naltrexone induction can be withheld for another 1-2 days.

Q 4. Can naltrexone induction be undertaken on the out-patient basis?

Ans. Naltrexone induction can be undertaken at the out-patient or the in-patient basis. For patients being considered for naltrexone induction on the out-patient basis, the most important task lies in ensuring the adequate opioid-free period. As a precautionary measure, naloxone challenge test can be done. If naloxone is not available at the centre, minimum required opioid-free period can be increased to avoid precipitated opioid withdrawal syndrome.

Q5. How long does naltrexone take to work?

Ans. Naltrexone's effect on blocking opioid receptors occurs shortly after taking the first dose. However, it is advisable to allow the drug to reach a steady state levels(i.e. 3-4 days) for complete blockade of exogenous opioid effects.

Q6. At what time of the day, should naltrexone be taken?

Ans. The timing of day has nothing to do with effect/side-effect of naltrexone. However, it should be taken on a fixed time everyday.

Q7. What does it feel like to be on naltrexone?

Ans. Aside from side-effects, which are usually short-lived and mild, patients usually report that they are largely unaware of being on medications. Naltrexone usually has no psychological effects and patients don't feel either "high" or "down" while they are on naltrexone.

Q8. What should be done if a dose of naltrexone is missed?

Ans. After the achievement of steady blood level of naltrexone (i.e. within a week), if a patient misses a single dose, adding up the missed dose is not required. Rather the patient is required to take the usual dose regularly

Q9. For how long does the effect of naltrexone persists after stopping it?

Ans. The effect of naltrexone persists for 24-72 hours depending on the dose of naltrexone used.

Q10. Will the patient get sick if he stops naltrexone suddenly?

Ans. Naltrexone does not cause physical dependence and it can be stopped at any time without withdrawal symptoms.

Q11. What will happen if the patient uses opioids while on naltrexone?

Ans. After stabilization with naltrexone is achieved, use of opioids by the patient will not be able to produce any effect due to blockade of opioid receptors by naltrexone. However, if the patient uses very high doses of opioids to overcome the blockade of receptors produced by naltrexone, life threatening opioid intoxication may result, including respiratory arrest and circulatory collapse.

Q12. What should be done if the patient is regularly using opioids while on naltrexone?

Ans. In such situation, first thing to do would be to check the compliance on naltrexone. The family members should be advised to supervise the intake of naltrexone. After ensuring the compliance, if the situation remains the same, it would be useful to check with the patient if he perceives the effects of opioid. If the patient perceives the effects of opioid, this mean that effective blockade of opioid receptor has not been achieved. In such circumstances, increasing the daily dose of naltrexone to 75-100 mg/day should be considered. Alternatively, patient's motivation to stop using the opioid should be assessed as well.

Q13. What should be done if the patient starts using alcohol or relapses to alcohol use following cessation of opioid use with naltrexone?

Ans. One of the clinical uses of Naltrexone is to reduce craving for alcohol as well. However the above situation may still arise and here it is useful to discuss with the patient the harm due to alcohol use and to motivate him to get additional treatment for alcohol use as well.

Q14. What should be done if the liver function tests (LFT) get deranged while the patient is on naltrexone?

Ans. Convincing reports of elevated liver function test due to naltrexone have been limited to patients receiving 250mg to 300mg daily, five to six times higher than the recommended maintenance dosage for opiate dependence. As a precaution, however patients should receive a full battery of liver function tests prior to receiving naltrexone, and it is *contraindicated* in patients with liver failure or acute hepatitis. If enzyme level rises 2-3 times above normal value, naltrexone should be discontinued till the LFT returns to normal. However, the other potential causes of LFT derangement such as viral hepatitis and alcoholic hepatitis should also be explored and treated accordingly.

Q15. What should be done if the patient needs medication for pain or surgery while on naltrexone?

Ans. In such cases, the patient should carry a card explaining that he is on naltrexone and that should also instruct the physician on pain management. Many pain medications that are not opioids are available for use. If the patient is going for elective surgery, naltrexone should be discontinued at least 72 hours beforehand.

Q16. Are there some people who should not take naltrexone?

Ans. Naltrexone should not be used with pregnant women, individuals with severe liver or kidney damage or with patients who cannot achieve abstinence for at least 3-5 days prior to initiating medications. Also, people who are dependent on opioid drugs, like heroin or morphine must stop their drug use at least 3-7 days prior to starting naltrexone.

Q17. How long should the patient continue naltrexone?

Ans. There is no general rule about exact duration of treatment with naltrexone although most studies recommend a period of 6 months-1 year. The guiding factors are significant period of abstinence from illicit drugs along with stable and significant psychosocial recovery like doing a job, fulfilling family and financial commitments etc.

Suggested reading

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