

Pharmacotherapy in Substance Use Disorder

4

Raman Deep and Anju Dhawan

Summary: The physical and psychological sequelae experienced consequent to stopping/reducing the amount of substance used after a period of prolonged usage is known as withdrawal symptoms. Medicines are needed to control these. Long term medicines are also needed to reduce harmful usage of psychoactive substances and minimize chances of relapse.

Introduction

Whenever a patient tries to stop or even cut down the substance use, the first problem he faces is varying degree of physical and psychological discomfort. The degree of discomfort experienced depends on the type, amount and duration of substance use. The time to onset of discomfort may vary depending on the half life of that substance. This is the 'phase of withdrawals' and generally lasts for initial few days to weeks.

The second problem faced is the risk of relapse. A person may restart his substance use over next few months due to various factors. In addition, patient may require pharmacotherapy for associated medical and psychiatric conditions, if any.

The role of pharmacotherapy is to help the patient

deal with both the short term and long term problems associated with withdrawal symptoms and help patient maintain abstinence for long periods. While the need of medication in phase of withdrawals is clear to most people, the requirement of long term medication is often questioned by patients, family members and even the medical and nursing fraternity.

Is long term medication really required?

Addictive disorders are relapsing in nature. Patients abstain and restart substance use. They "go and come back" repeatedly, referred to as the "revolving door phenomenon".

Even though withdrawals do not persist beyond few days, there is persistence of strong urge to take substance (known as craving).

Neurobiological changes as a result of long term substance use takes a long time to normalise. Patient may need some form of treatment till his socio-occupational functioning is regained. Long term medication allows patient to focus on social and occupational aspects rather than substance-seeking.

Hence, the patient is not "cured" after the withdrawal phase is over. Rather he commonly requires long term pharmacotherapy so that his chances of returning to substance are minimized. In clinical practice, few patients with very short substance use history and good motivation may not be given long-term pharmacotherapy and are maintained "Drug-Free". The research supporting use of such method is minimal.

Regarding this subgroup, most patients are given pharmacotherapy till their treatment goals are met which may take few months to more than a year. The kind of medicines used and their dosing will be discussed in greater detail later in the chapter.

Broad principles of treatment

Treatment goals

The ultimate treatment goal is total abstinence. However, it may not be achievable in all cases. The next goal is to minimize the health-related, social and economic harm caused by substance (harm minimization). It can be done by using safer forms of substance; safer route; safer paraphernalia; reduction of the medicine doses or substance-using days along with imparting education.

The rationale is that despite the continuing substance use, the risk to which patient is exposed is significantly lessened. Harm minimization acknowledges that there is a broad

spectrum of damage and the risks are hierarchical (less severe to most severe). Thus the most damaging consequences should be given priority in management.

Remember: Goals of treatment differ from patient to patient. It is very important to set the goals after discussion with patient rather than impose upon.

Treatment Goals

- Abstinence
- Harm minimization
- Improved Physical and Psychological health
- Improved socio-occupational functioning
- Reduced Involvement in Illegal activities
- Reduced Burden on Family
- Improved quality of life

Treatment setting

The treatment can be delivered on out patient basis (OPD) as effectively as inpatient setting.

Selection criteria for OPD treatment:

1. Patients with mild to moderate dependence
2. Medically stable patient
3. Good social support
4. Friends ready for frequent follow-up in OPD
5. Willing to give body fluids for examination to confirm abstinence
6. Patients with poor motivation
7. With anticipated disciplinary problems

In contrast, following patients are preferred for In-patient setting:

1. Those who are unable to abstain on OPD basis
2. Those having severe withdrawals (current or past history)
3. Those with medical complications
4. Co-morbid psychiatric/medical illness
5. Out-station patients
6. Poor social support
7. Patient in crisis

Remember: Both settings can be equally effective provided misadventures appropriately.

Phases of treatment

- I. Phase of Withdrawals
- II. Maintenance phase

I. Phase of Withdrawals

Traditionally it was referred to as 'detoxification phase' but the term was a misnomer and it is replaced by 'phase of withdrawals' nowadays. This is the initial phase of treatment of substance dependence and includes

- Treatment of withdrawal symptoms
- Assessment and treatment of medical and psychosocial complications
- Building up of mutual trust and therapeutic relationship with patient

Methods used

The treatment of withdrawals is done as follows:

1. Gradual reduction of the substance
2. Abrupt cessation of the substance of abuse and administration of specific medications.

The medications used are:

1. Substances which have similar pharmacological effects as the original substance of use, can be given in the equivalent doses e.g. benzodiazepine for alcohol withdrawal; buprenorphine for heroin withdrawal. The patient experiences minimal withdrawals as a result.
2. Substances which have pharmacological properties specifically to suppress symptoms of withdrawal, e.g. clonidine suppress hyper adrenergic symptoms of opiate withdrawal.
3. Provide general symptomatic relief, e.g. sedatives, anti-emetics, antidiarrheals and analgesics.
4. By and large, abrupt total cessation of the primary substance of dependence and prescription of a medicine with similar properties is the widely accepted method. The medicine is then gradually tapered over few days to weeks.
5. Treating doctor needs to review the dosage schedule according to the withdrawal symptoms and periodic assessment is required throughout the withdrawal phase.

- 6 Prolonged usage is, however, not recommended as these medicines themselves have abuse liability. Use of IV fluids and parenteral substances to control withdrawal is not recommended, until there are specific indications, e.g. presence of severe dehydration or some medical complications.

Duration of withdrawal phase

It depends on several factors:

- Type of substance use (e.g. more in heroin than cannabis users)
- Degree and duration of dependent use
- Treatment setting (faster in inpatients)
- Subjective ability to tolerate withdrawal.

Opioid detoxification requires approximately 2 weeks though duration may be longer in OPD setting. Alcohol and benzodiazepines detoxification is generally over in 1-2 weeks. Certain substances like cannabis produce minor and short lasting withdrawals and may not require medication.

Treatment of withdrawal symptoms

A. Alcohol withdrawal:

A group of sedative/hypnotic drugs (Benzodiazepines) are the medicines of choice in management of alcohol withdrawal. Usually divided daily doses of 20-40 mg of diazepam or 40-80 mg of chlordiazepoxide are required. The dose may be higher depending on severity of withdrawal. The dose of benzodiazepines is gradually tapered off over next 7-10 days. Oral administration of thiamine is necessary in all the patients for prevention of alcohol related

neurological complications, viz. Wernicke's encephalopathy.

In patients with mild to moderate dependence, loading dose of benzodiazepine may be given. Hence, patient is given 20 mg diazepam every 2 hourly till sedation first day of withdrawal. As the half-life of diazepam is long, the patient is comfortable and requires no further doses from next day onwards. This shortens the withdrawal phase.

During this phase, the patient must be monitored closely for withdrawal symptoms e.g tremors, anxiety, insomnia etc. The blood pressure and pulse rate should be recorded daily if the patient is admitted. The orientation of patient should be checked because some times during alcohol withdrawal patient may slip into a potentially life-threatening complication e.g. Seizures or Delirium tremens. Early symptoms of latter are severe alcohol withdrawal (generalized tremors) coupled with disorientation to time, place and person. It is a medical emergency and treatment of choice is intravenous diazepam, which needs to be given in doses of 10-20 mg every 30-60 minutes till patient is sedated or signs and symptoms of withdrawal subside.

B. Opioid withdrawal

The starting dose of medication needs to be decided according to amount of opioid consumed by a patient converted into equivalent doses of compound used for detoxification. Subsequent doses needs to be adjusted according to the severity of withdrawal symptoms which peak during 2nd-3rd day and generally lasts for 2 weeks. Usually the doses required are 1.2-4.0 mg sublingual buprenorphine or 6-10 capsules of dextropropoxyphene (65mg) initially and tapered off gradually after third day. Usually, medicines

are required for two weeks, though it may be somewhat longer in OPD setting. Certain withdrawal symptoms like insomnia, restlessness and mild body aches persist even after two weeks, and can be managed symptomatically by sedatives and non-narcotic analgesics as well as non-pharmacological treatments.

Methods for accelerating the treatment of withdrawal phase are also available but have not been shown to provide any additional benefit. Opioid withdrawal in contrast to alcohol withdrawal poses no risk of being life threatening. However, it is immensely discouraging for the patient. Patient should be monitored for common withdrawals like sneezing, running eyes and nose, diarrhea, body aches and sleep disturbances. Blood pressure, pulse rate and sleep duration should be recorded. Careful medical examination in addition to screening for hepatitis B, C and HIV is required in injection substance users specially if there is b/w sharing needles/syringes.

C. Sedative-hypnotic withdrawal

Sedative hypnotic withdrawal is managed by gradual tapering of the substance of dependence. In cases of mild to moderate dependence, an outpatient treatment regime with gradual reduction in doses can be carried out in well motivated patients. In patients with severe dependence, particularly with dependence on short acting benzodiazepines, inpatient detoxification is preferred. In inpatient setting, the substances can be tapered off at a rate of 10% daily. In patients dependent on short acting benzodiazepine (e.g alprazolam), risk of withdrawal seizures and delirium should be kept in mind and to prevent these potentially life threatening conditions, treatment is started with equivalent doses of long acting benzodiazepines (e.g diazepam), which then should be tapered off as usual. Usually, it takes 2-3 weeks for treatment of withdrawal phase.

D. Multiple substance withdrawal

In patients, where dependence to more than one substance has been clearly identified, the specific medication for each category of the substance of dependence should be given. Frequently, patient requires inpatient treatment and the period of detoxification is longer than in patients with single substance dependence.

Agents used to treat withdrawal phase

Opioid withdrawal: Buprenorphine, Despropoxyphene, Clonidine

Alcohol withdrawal: Long acting benzodiazepines (Chlordiazepoxide/ Diazepam)

Benzodiazepine withdrawal: Shift to long acting benzodiazepines

Nicotine withdrawal: Nicotine gums and Nicotine Transdermal patch

General management during withdrawal: Analgesics/Sedatives/And antiemetics and Anti diarrhoeals.

II. Maintenance phase

The need for long term medication has already been discussed at the beginning of the chapter. One important limitation is that till date specific medications to treat cannabis, cocaine or amphetamine abuse are not available. Treatment of these substances relies on non-pharmacological modalities along with some general medications for sleep/pain.



ADH: Alcohol Dehydrogenase
ALDH: Acetaldehyde Dehydrogenase

A. For Alcohol use disorders

Deterrent agents (Disulfiram)

Disulfiram is the most commonly used deterrent in clinical practice. Disulfiram irreversibly inhibits the activity of a particular enzyme in the body (called as aldehyde dehydrogenase -ALDH). Alcohol normally is broken down to acetaldehyde in the body and the above mentioned enzyme further breaks acetaldehyde. In absence of this enzyme activity, there is accumulation of toxic levels of acetaldehyde in liver and systemic blood circulation, which causes a lot of unpleasant symptoms if a person takes alcohol. This has been termed as disulfiram ethanol reaction (DER). Usually patient experiences nausea, vomiting, headache, redness, flushing, fall in BP, and even coma may occur. (This is potentially fatal).

Side effects: Patient may experience drowsiness, gastric irritation and uncommonly, hepatotoxicity, peripheral neuropathy, skin reactions and psychosis. Side effects are not very common and patients can be monitored for early detection in case side effects occur. All patients need to be monitored with regular 3 monthly liver function tests and once a year ophthalmology check-up for rare ophthalmologic side effects (optic atrophy). Symptoms suggestive of numbness and tingling in extremities should be asked in follow up visits. Generally, Disulfiram is avoided in patients who tend to be impulsive, suffering from psychiatric illness in which patient is incapable to give consent or in pregnant women. Disulfiram therapy should be initiated only after the patient and the family member has been informed about the rationale for its use as well as the necessary precautions. An informed consent of patient is a necessary prerequisite and it should include:

1. Education about the signs and symptoms

of DER, and the actions required to be taken if they notice these signs or symptoms.

2. It should be explained that DER can occur with alcohol intake even in small doses.
3. Precautions to avoid all alcohol containing substances e.g certain cough syrups, after shave lotions, perfumes and vinegar
4. It has to be emphasized that there is a possible risk of DER up to 14 days after last dose of disulfiram.

It is a good practice that the patients be provided small cards containing the signs and symptoms of DER and necessary first aid methods in case of occurrence of DER.

Treatment of DER: This should be treated as an emergency.

The fall in blood pressure should be controlled on a priority basis and patient should be monitored for irregular heart rate. If DER is mild, reassurance and oral fluids suffice. In patients with moderate or severe DER, intravenous fluids and, in some patients, dopamine infusion is necessary to control the severe hypotension. Rest is mainly supportive treatment and close monitoring of the patient.

Remember: Family members frequently ask for prescription of Disulfiram without knowledge of patient. Under no circumstances should it be started without obtaining patient's consent. Disulfiram is not given facetiously or as means of punishing patient for taking alcohol. It is suitable for those patients who are motivated for leaving alcohol and acknowledges that the motivation level may at times fluctuate. Disulfiram will therefore act as a deterrent in the high risk situations. DER, if experienced, will outdo the positive reinforcement effects of alcohol. Disulfiram is available as 250 mg tablets and the usual dose is 1-2 tablets/day.

Anti-Craving Agents:

Acamprosate is thought to reduce the 'craving' that is experienced by alcohol dependent patients. Acamprosate has a chemical structure similar to that of amino acid neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate, and evidence suggests that it acts by stabilising the imbalance of neurotransmitters which is seen in alcohol dependency. Acamprosate is available in 333 mg strength tablets and is given as 2 tablets three times a day. It is important to note that unlike Disulfiram, Acamprosate does not lead to any reaction with alcohol. Acamprosate is well tolerated. Adverse events were mostly seen early in treatment and were usually mild and transient in nature in the form of nausea, diarrhoea, abdominal pain and uncommonly irregular heart rate. Acamprosate should not be taken by people with kidney problems or allergies to the substance.

Naltrexone used primarily in opioid dependence has been found to reduce craving for alcohol through its effect on opioid receptors. It is thought to reduce reinforcing effects of alcohol. The dose is 50 mg per day.

Fluoxetine, used primarily in depression, has also shown benefit and can be preferred in patients with concomitant depression.

Alcohol: Long term pharmacotherapy

- A. Deterrent: Disulfiram, Calcium Carbimide, Miconidazole,
- B. Anti Craving: Acamprosate, Naltrexone, Fluoxetine

Acamprosate 333 mg; Naltrexone 50 mg;
Fluoxetine 20/40mg

B. For Opioid use disorders

OPIOD: Long term pharmacotherapy

- Opioid Agonist Substitution
Methadone (Not available in India)
Buprenorphine, Morphine
- Antagonist therapy
Naltrexone

Agonist substitution and maintenance:

Agonist is an agent which acts at same opioid receptors and thereby producing similar psychoactive effects. Dole and Nywander in 1964 introduced the concept of substitution as long term treatment for opioid dependence. Some suggest that it might be appropriate to target at rehabilitation rather than total abstinence in these patients. It was recommended that narcotic medication, if used in these patients to satisfy their craving, will help in controlling illicit substance use and related behavior thereby making them accessible to rehabilitation. Methadone is the most commonly used agonist substitution agent for opioid dependent patients in the USA and Europe. In India, historically, substitution and maintenance program had been practiced through opium registry, wherein registered opium addicts were given a certain amount of tincture opium till registration of new cases was discontinued in 1959.

Buprenorphine (2-8 mg/day) and Morphine (60-360mg/day) has been used in our set-up successfully as maintenance agents.

Maintenance generally lasts between 6 months to two or more years.

Many people do not feel comfortable with the idea of maintenance therapy and may raise reservations about the moral and ethical issues involved in such a treatment strategy. However, it is important to understand that all the patients may not be able to achieve total abstinence and due to long standing substance use, may require some form of agonist substance as a substitute. Harm minimisation is the underlying principle as exemplified below:

Philosophy of Agonist Substitution:

- **Heroin:** Illicit, medically unsafe, short acting drug of unknown purity/potency, multiple administrations, IV. use, associated criminal activities.
- **Agonist drug:** Medically safe, long acting drug, known purity/ potency, once daily, combined with psychosocial rehabilitation

The merits of and arguments in support of substitution maintenance treatment are:

- Reduction in illicit substance consumption.
- Avoidance of medical complications due to impurities in street preparations
- Avoidance of the complications of parenteral administration and overdose.
- Better nutritional and health status.
- Decrease in criminal behavior.
- Improvement in social behavior and psychological well being.
- Improvement in inter-personal and family relationships
- Increased productivity
- Better Quality of life
- Decreased family burden
- Cost effective

Remember: While taking agonist maintenance, patient should be asked for any withdrawals or craving as well as experience of significant euphoria/ drowsiness/ intoxication.

The dose of agonist is carefully titrated and kept sufficient enough to control craving and withdrawals and yet not enough to produce euphoria/intoxication.

Regular Urine Screening is a must in order to ensure compliance and rule out the continuing use of illicit substances.

Buprenorphine:

Buprenorphine is a partial agonist of some brain receptors as opioids and produces similar but sub-maximal effects. The prolonged action of buprenorphine makes it effective when dispersed in once daily dosage or even every 2-3 days. Buprenorphine is available in sublingual preparation (2/4 mg). The tablet must be placed under the tongue and allowed to dissolve. Chewing and swallowing the tablet will make it less effective. It dissolves within 2-8 minutes after placing it under the tongue. The effects begin within 30-60 minutes of taking the dose and peak within 2-4 hours, lasting between 4 hours to 3 days, depending on the dosage. Side effects of buprenorphine are sedation, drowsiness and constipation. Tolerance to these effects can be expected to develop during continued buprenorphine therapy. No apparent health risk has been reported and it is relatively safe. Liver damage and pregnancy must be ruled out before starting.

Nurses must supervise the proper intake of medication and it must be seen that the tablet is completely dissolved before the patient leaves. There is a risk of illegal diversion and intravenous

administration by substance using population. Injecting the tablet is dangerous, and can lead to severe vein damage, blood clots and other health complications. Hence, plain buprenorphine is given supervised by a trained nurse and not allowed to be taken home.

A new formulation containing combination of Buprenorphine and Naltrexone has recently been approved and made available in India. It has added advantage that it is inactive in case taken intravenously and hence can be given as "take home".

Antagonist therapy (Naltrexone)

Opioid antagonists are substances that bind to opioid receptors in the brain but do not produce opioid like effects. If an individual stabilized on opioid antagonist consumes an opiate agonist e.g. heroin, he will not experience the euphoric effects as the opioid receptors are already blocked and hence not available. In this manner, substance seeking behavior fades away as no euphoria is experienced despite substance intake. This phenomenon helps the patient in achieving a drug free life style.

Introduction of Naltrexone in the early 1980s, which is effective orally, with long duration of action and minimal side effects, has revolutionized this approach.

Naltrexone, available as 50 mg tablets, is well absorbed orally from the GI tract.

There are three common schedules for administration:

- Daily (50 mg/day),
- Twice a week (150 mg on Mondays and 200 mg on Thursdays)
- Thrice a week (100 mg on Mondays and Wednesdays, and 150 mg on Fridays)

Naltrexone therapy should be started, only after detoxification phase has been completed. This is necessary as there is a risk of precipitation of severe withdrawal features if the patient has consumed an opioid in the past 2-3 days. Confirmation of abstinence for past 3 days is absolutely important while starting first dose of Naltrexone. However once started and patient stabilized on Naltrexone, the continued use of heroin would not have any effect at all in usual doses.

The common side effects of naltrexone are mild opioid withdrawal like symptoms (nausea, abdominal pain, dyspepsia), skin rash and derangement in liver function test.

The only important contraindication of naltrexone therapy is the presence of hepatic failure. Baseline liver function tests are mandatory before starting naltrexone therapy as is their regular monitoring. The duration of naltrexone therapy has been recommended to be at least 6-12 months. Naltrexone therapy is beneficial in patients with a high level of motivation.

Naltrexone blocks the effects of *amortius* and heroin. However, large doses of heroin or opioids taken over Naltrexone can lead to overdose. Respiratory depression, coma and even death may occur.

Selection criteria for Agonist:

- Long duration of substance use (>3-5 years)
- Minimal abstinence period or unsuccessful attempts (2 or more)
- No regular occupation
- Poor social support
- Willing to come regularly and give urine for screening for substance use

Selection criteria for Antagonist:

- Young adults
- Short duration of opioid use
- Past history of significant abstinence
- High motivation
- Professionals like doctors, dentists etc.
- No co-morbid psychopathology
- Good social support

Patient should be involved actively in the treatment plan and the available options should be discussed with him.

C. For Benzodiazepine Dependence- no medication is yet available for long term maintenance

D. For Nicotine Dependence

Use of Nicotine Chews (available in 2/4mg) makes the treatment easier. It is advised to chew it very slowly to facilitate slow release of nicotine and can be used every 2-3 hourly initially and tapered off in next few weeks. Nicotine transdermal patches are available in India and can be used. It is possible to tide over this period with intensive psychological intervention in addition to nicotine chews.

Bupropion is the first non-nicotine agent to be approved for treatment of nicotine dependence. It is an antidepressant also found to be effective for abstinence from nicotine. Precise mechanism of action is not known. It reduces the craving, controls the withdrawal symptoms and blocks the reinforcing properties of nicotine. It is available in 150 mg and started at 150 mg for first week and increased to 300 mg in next week. Dosing is between 300-600mg/day. It has to be started 2 weeks prior to quit date as it usually takes time to onset of action. Side effects include

dry mouth, insomnia, anxiety, tremors and a small risk for seizures. Bupropion should be used cautiously in patients receiving substances that reduce the threshold for seizures. The treatment has to be continued for few months (possibly more than 6 months).

Naltrexone is shown to reduce craving for nicotine. Recently another substance by name of Varenicline has been reported to be treatment for use in nicotine dependence

Issues related to termination of treatment:

As already discussed above, various treatment goals must be met before stopping medication. Generally, it means treatment can continue from 6 months to more than a year. Socio-occupational rehabilitation is an integral part of treatment process and this aspect should be discussed with patient as well as family members. The patient must be assessed comprehensively before planning for termination of treatment. Patient and family members are advised to remain in contact with treatment centre and continue the follow-up visits even after being off-substances. The patient is also clearly advised as well as encouraged to come back as soon as possible in case of relapse.

Substance use treatment and Anti-retroviral therapy

Substance users are often affected by multiple co-morbid medical and psychiatric conditions, including HIV infection. HIV/AIDS is more prevalent in substance use disorder patients as compared to general population. The use of parenteral route and sexual risk factors play a major role. The treatment staff must be aware of issues involved in concurrent treatment of substance use disorders and Highly Active Anti-Retroviral Therapy (HAART) for HIV-infected substance users.

An increasing number of potential interactions between medications to treat substance abuse and HAART have been evaluated. Such interactions can result in diminished efficacy of substance abuse medications or HAART treatment, medication toxicity, or both. Interactions between HAART and methadone may precipitate symptoms of over sedation or withdrawal. Zidovudine (used as part of HAART) toxicity, such as anemia, nausea, and headache, may occur when zidovudine and methadone are used concurrently while no significant interaction has been reported with Buprenorphine. Similarly, no significant interaction of HAART has been reported with Disulfiram and Naltrexone. Evidence is lacking that use of heroin, cocaine, or marijuana interact with HAART. Concurrent use may, however, diminish HAART effectiveness in some persons by diminishing adherence to prescribed regimens.

Responsibilities of nurse in pharmacotherapy

The nurse serve as a key member of the health care team in the both detoxification and rehabilitation treatment. Nurses must know appropriate use of medications. They should be aware about action, indications, interaction with other substances, potential side effects and contraindications.

During detoxification phase

- Remain alert for the signs and symptoms and severity of withdrawal symptoms.
- Maintain 5R's of medication administration: right patient, right time, right dose, right medicine, and right route.
- Monitor the patients physiological status and to provide appropriate medication without unduly alarming the patient.
- Identify the manipulative behavior of certain patients and should not reinforce their substance seeking behavior.

- Careful documentation and proper checking of the medicines should be done in each shift and adequate stocks to be maintained.
- Educate the patients about the duration of treatment and the precautions they have to take while taking medicines (like disulfiram).

During maintenance phase

- Ensure patient renews the treatment regime consulting with the treating doctor.
- Supervise that medications has been taken by the patient properly to avoid misuse (i.e. injecting the tablets after dilution)
- Careful documentation and adequate stocks of medicines to be maintained.
- Educate the patients about the need for medication compliance.
- Assess for any lapses, or relapse- inform the treating physician for further evaluation and management.
- Use harm minimization strategies for IDUs

Conclusion

Pharmacotherapy is required to help control the withdrawal symptoms, treatment of co morbid illness (if any) and to prevent relapse. Medication should be properly chosen, supervised and monitored at regular intervals. Compliance to treatment and regularity of follow-up is crucial to success of any treatment. Treatment goals are multiple and include the medical, social, occupational goals and aims at improving overall quality of life. Pharmacotherapy is required for few months to more than a year depending on the achievement of treatment goals. The achievement of treatment goals is the important criteria to be fulfilled before the termination of long-term treatment.

Suggested reading materials

1. American Psychiatric Association: Practice Guidelines for the Treatment of Patients with Substance Abuse Disorders: Alcohol, Cocaine, Opioids. American Journal of Psychiatry. 1995, 152 (Suppl.): 1-59
2. Blaine JD, ed. Buprenorphine, Alternative Treatment for Opioid Dependence. NIDA, D.C, 1992.
3. Dhawan A, Kumar. Long term treatment of opioid dependence syndrome. In: Lal R (Ed) Substance Use Disorder: Manual for Physicians, National Substance Dependence Treatment Centre, A.L.M.S, 2005
4. Fudala PJ, Charles O'Brien PO. Buprenorphine for the treatment of opioid addiction. In: Lowinson JH, Ruiz P, Millman RB, Langrod JG (eds.) Substance Abuse- A Comprehensive Textbook- fourth edition, Lippincott Williams and Wilkins, USA, Maryland, 2005
5. Fudala PJ, Greenstein RA, Charles O'Brien PO. Alternative pharmacotherapies for opioid addiction. In: Lowinson JH, Ruiz P, Millman RB, Langrod JG (eds.) Substance Abuse- A Comprehensive Textbook- fourth edition, Lippincott Williams and Wilkins, USA, Maryland, 2005.
6. Hughes JR. Nicotine related disorders. In: Sadock BI, Sadock VA (eds.) Comprehensive Textbook of Psychiatry- seventh edition, Lippincott Williams & Wilkins, 2009
7. Jaffe JH, Jaffe AB. Opioid related disorders. In: Sadock BI, Sadock VA (eds.) Comprehensive Textbook of Psychiatry- seventh edition, Lippincott Williams & Wilkins, 2000.
8. Ray R, Dhawan A. Oral Buprenorphine Substitution Therapy. Report submitted to Research Monograph 121. US Department of Health and Human Services Washington, UNODC, RNSA, 2004.
9. Schuckit MA. Alcohol related disorders. In: Sadock BI, Sadock VA (eds.) Comprehensive Textbook of Psychiatry- seventh edition, Lippincott Williams & Wilkins, 2000.

Suggested slide material

Slide 1

Role of nurse in pharmacotherapy

During detoxification phase

- Assess and manage withdrawal symptoms appropriately
- Maintain SR's of medication administration
- Identify the manipulative behavior of certain patients and should not reinforce their drug seeking behavior.
- Careful documentation and stock maintenance
- Educate the patients about the action side effects, duration of treatment and special precautions

Slide 2

Role of nurse in pharmacotherapy (contd.)

During maintenance phase

- Ensure treatment compliance
- Ensure the medicines are not misused
- Careful documentation and adequate stocks of medicines to be maintained.
- Evaluate any lapses, or relapse and do intervention accordingly
- Harm minimization for OUDs

Slide 3

Role of Pharmacotherapy

- Short-term: Control of withdrawal symptoms
- Long-term: Help patient maintain abstinence over a long term.
- Medication may be needed to treat co-morbid illness

Slide 4

Need for Long-term medication

- Addictive disorders are relapsing in nature (renewing drug phenomenon)
- Persistence of strong urge to take substance (Craving).
- Brain changes take a long time to normalize.
- Socio-occupational functioning is regained gradually.

Slide 5

Treatment Goals

- Abstinence (Cessation of drug use)
 - Harm minimization (Reduction in drug use or associated harms)
 - Improvement in Physical and Psychological health
 - Improvement of socio- occupational functioning
 - Reduced involvement in illegal activities
 - Reduced Burden on Family
 - Improved quality of life
- "Achievement of these goals should guide the duration of long-term pharmacotherapy"

Slide 6

Treatment setting-1:

- The treatment can be on out-patient or In-patient basis
- No difference in long-term course and outcome between both settings

Selection criteria for OPD treatment:

- Patients with mild to moderate dependence,
- Medically stable patient
- Good social support
- Patients ready for frequent follow-up in OPD
- Willing to give fluids for examination to confirm abstinence
- Patients with poor motivation and with anticipated disciplinary problems

Slide 7

Treatment setting-2

In-patient settings:

- Those who are unable to abstain on OPD basis,
- Those having severe withdrawals (current or past history)
- Those with medical complications
- Co-morbid psychiatric/medical illness
- Distant patients with poor social support

Slide 8

Phases of treatment

- Phase of Withdrawals
- Maintenance phase

Phase of Withdrawals-1

Goals:

- Treatment of withdrawal symptoms
- Assessment and treatment of medical and psychosocial complications
- Building up of mutual trust and therapeutic relationship with patient

Slide 9

Phase of withdrawal-2

The medications used are as follows:

- Those which have similar pharmacological properties and effects as the substance
- Those which have specific pharmacological properties to suppress symptoms of withdrawal
- Provide general symptomatic relief, e.g. sedatives, anti-emetics, anti-diarrheals and analgesics.

Slide 10

Medications for Phase of withdrawal:

- Alcohol withdrawal: Long acting benzodiazepines (Clonidiazepoxide / Diazepam)
- Opioid withdrawal: Buprenorphine, Dextropropoxyphene, Clonidine
- Benzodiazepines withdrawal: Shift to long acting benzodiazepines and taper
- General: Analgesics/Sedatives/Anti-emetics /Anti-diarrheals

Slide 11

Alcohol-Withdrawal management

- Substitution with Benzodiazepines (diazepam: 20–40 mg; clonidiazepoxide: 40–80 mg)
- Titrate dose as per withdrawal monitoring
- Gradual tapering over next 7-10 days
- Thiamine supplementation
- Monitor for complicated withdrawal: seizures, delirium tremens

Slide 12

Opioid-Withdrawal management

- Divided doses of:
 - 1.2 to 4 mg of buprenorphine OR
 - 6 to 12 capsules of dextropropoxyphene
- Taper after 3rd day
- Gradual tapering (10% daily)
- Sedative – hypnotic; Analgesics

Slide 13

Medications for Maintenance phase:

- Alcohol dependence:
 - A. *Deterrent*: Disulfiram, Calcium Carbimide
 - B. *Anti Craving*: Acamprosate, Naltrexone
- Opioid dependence:
 - A. Opioid Agonist Substitution
 - Methadone (Not available in India)
 - Buprenorphine, Morphine
 - B. Antagonist therapy
 - Naltrexone

Slide 14

Alcohol Dependence-1

- **Disulfiram**
 - Inhibits the enzyme aldehyde dehydrogenase
 - Accumulation of acetaldehyde leads to unpleasant experiences (DER)
 - 250-500mg/day
 - Side effects: drowsiness, gastric irritation and uncommonly hepatotoxicity, peripheral neuropathy, skin reactions and psychoses
 - Informed consent

Slide 15

Alcohol Dependence-2

- **Acamprosate**
 - Reduce craving
 - 333mg 4-6 tsh/day
 - Side-effects: nausea, diarrhea, abdominal pain, irregular heart beat
 - Not to be given in kidney dysfunction
- **Naltrexone**
 - Reduces craving
 - 50mg/day
 - Monitor for hepatotoxicity

Slide 16

Philosophy of Agonist Substitution:

Heroin Minimization:

- **Heroin**: Illicit, medically unsafe, short acting drug of unknown purity/potency, multiple administrations, IV. use, associated criminal activities.
- **Agonist drug**: Medically safe, long acting drug, known purity/ potency, once daily, combined with psychosocial rehabilitation.

Slide 17

Heroin Minimization

- Reduction in illicit drug consumption.
- Avoidance of medical complications due to impurities in street preparations
- Avoidance of the complications of parenteral administration
- Better nutritional and health status.
- Decrease in criminal behavior
- Decreased family burden

- Improvement in social behavior and psychological well being.
- Improvement in Inter-personal and family relationships

Slide 18

Antagonist therapy (Naltrexone)

- Bind to opioid receptors in the brain without opioid like effects.
- Block the euphoric effects of opioids
- 50mg/day
- Side-effects: nausea, abdominal pain, dyspepsia, skin rash and derangement in liver function tests.

Slide 19

Selection criteria for Agonist:

- Long duration of drug use (> 3-5 years)
- Minimal abstinence period or unsuccessful attempts (2 or more)
- No regular occupation
- Poor social support
- Willing to come regularly and give urine for screening for substance use

Slide 20

Selection criteria for Antagonist:

- Young adults
- Short duration of opioid use
- Past history of significant abstinence.
- High motivation
- Professionals like doctors, dentists etc.
- No co-morbid psychopathology
- Good social support

Slide 21

Nicotine Dependence

- **Nicotine Chewing**
 - 24 mg
 - Every 2-3 hourly
 - Gradual tapering over few weeks
- **Nicotine transdermal patch**
- **Bupropion**
 - First Non-nicotine agent for long term therapy
 - Reduces craving
 - 300-600mg/day
 - Onset of action takes 2 weeks
 - Side effects: dry mouth, insomnia, anxiety, tremors and a small risk for seizures.

Slide 22

Conclusion:

- Multiple treatment goals
- Variety of pharmacotherapies available
- Patient should be carefully chosen for a particular pharmacotherapy
- Regular monitoring and compliance
- Long-term pharmacotherapy –few months to more than a year
- Termination of treatment after the treatment goals are met

Annexure 1

CONSENT FOR THE ADMINISTRATION OF DISULFIRAM

As approved by National Institute of Drug Abuse (NIDA)

By accepting disulfiram therapy, I acknowledge the need for assistance in solving a drinking problem. I also understand that, with my full cooperation in this therapy, I am most likely to achieve successful recovery. It has been explained to me and I understand the effects which disulfiram can trigger if I should consume even a small amount of alcohol in any form. These symptoms include flushing, nausea, vomiting, thirst, low blood pressure, and possible convulsions. I understand that this reaction may occur up to 2 weeks after I discontinue disulfiram.

It has also been explained to me that the safe use of this in pregnancy has not been established. I understand that sexually active women taking disulfiram should be practicing a medically effective, reliable method of birth control. I understand that if I were to become pregnant, it is recommended that I terminate disulfiram therapy.

I also understand that my family members will be supervising my medications.

DISULFIRAM ETANOL REACTION: (DEER)

Even a small amount of alcohol taken in any form (vinegar, cough syrup, mouthwash, after shave lotion and back rub) 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, palpitation, giddiness, weakness, sensation of surroundings revolving around you, blurred vision and confusion. Very rarely, in severe reactions there may be a decrease in breathing, shock, acute heart failure, unconsciousness, convulsions and death.

SIDE EFFECTS OF DISULFIRAM

Side effects of Disulfiram taken alone may include drowsiness, numbness in extremities, metallic taste and / or allergic skin reaction. Rarely it may derange liver function test needing regular monitoring of LFT.

SIGNATURE OF PERSON TO RECEIVE DISULFIRAM
DATE & TIME

REFERENCES

SIGNATURE OF WITNESS
DATE

SIGNATURE OF COUNSELING PHYSICIAN
DATE

Morphine sulphate

Therapeutic actions

- Principal opium alkaloid;
- Acts as agonist at specific opioid receptors in the CNS to produce analgesia, euphoria, sedation;
- The receptors mediating these effects are thought to be the same as those mediating the effects of endogenous opioids (enkephalins, endorphins).

Indications

- Relief of moderate to severe acute and chronic pain
- Used in opioid dependence as opioid agonist
- Preoperative medication to sedate and allay apprehension, facilitate induction of anaesthesia, and reduce anaesthetic dosage
- Analgesic adjunct during anaesthesia
- Intraspinal use with microinfusion devices for the relief of intractable pain

Contraindications/cautions

- Contraindications: hypersensitivity to narcotics; diarrhea caused by poisoning until toxics are eliminated; during labor or delivery of a premature infant (may cross immature blood–brain barrier more readily); after biliary tract surgery or following surgical anastomosis; pregnancy; labor (respiratory depression in neonate; may prolong labor).
- Use cautiously with head injury and increased intracranial pressure; acute asthma, COPD, or pulmonary, preexisting

respiratory depression, hypoxia, hypercapnia (may decrease respiratory drive and increase airway resistance); lactation (wait 4–6 h after administration to nurse the baby); acute abdominal conditions, CV disease, supraventricular tachycardias, myxedema, convulsive disorders, acute alcoholism, delirium tremens, cerebral arteriosclerosis, ulcerative colitis, fever, kyphoscoliosis, Addison's disease, prostatic hypertrophy, urethral stricture, recent GU or GU surgery, toxic psychosis, renal or hepatic dysfunction.

Dosage

Dose for opioid addiction 30–120 mg/day
Available Forms: Injection—0.5, 1, 2, 3, 4, 5, 8, 10, 15 mg/mL; tablets—15, 30 mg; CR tablets—15, 20, 50, 60, 100, 200 mg; SR tablets—30, 60, 100 mg

Adverse effects

- CNS: *Light-headedness, dizziness, sedation, euphoria, dysphoria, delirium, insomnia, agitation, anxiety, fear, hallucinations, disorientation, drowsiness, lethargy, impaired mental and physical performance, coma, mood changes, weakness, headache, tremor, convulsions, miosis, visual disturbances, suppression of cough reflex*
- GI: *Nausea, vomiting, dry mouth, anorexia, constipation, biliary tract spasm; increased colonic motility in patients with chronic ulcerative colitis*
- CV: *Facial flushing, peripheral circulatory collapse, tachycardia, bradycardia, arrhythmia, palpitations, chest wall rigidity, hypertension, hypotension, orthostatic hypotension, syncope*
- GU: *Ureteral spasm, spasm of vesical sphincters, urinary retention or hesitancy, oliguria, antidiuretic effect, reduced libido*

or potency

- **Dermatologic:** Pruritus, urticaria, laryngospasm, bronchospasm, edema
- **Local:** Tissue irritation and reduration (SC injection)
- **Major hazards:** Respiratory depression, apnea, circulatory depression, respiratory arrest, shock, cardiac arrest
- **Other:** Sweating, physical tolerance and dependence, psychological dependence

Clinically important interactions

- **Substance-substance**
 - Increased likelihood of respiratory depression, hypotension, profound sedation or coma in patients receiving barbiturate, general anesthesia

Nursing Considerations

- Caution patient not to chew or crush controlled-release preparations.
- Provide narcotic antagonist, facilities for assisted or controlled respiration on standby during IV administration.
- Use caution when injecting SC or IM into chilled areas or in patients with hypotension or in shock; impaired perfusion may delay absorption; with repeated doses, an excessive amount may be absorbed when circulation is restored.
- Reassure patient about addiction liability; most patients who receive opiates for medical reasons do not develop dependence syndromes.
- Take this substance exactly as prescribed. Avoid alcohol, antihistamines, sedatives, tranquilizers, OTC substances.
- Swallow controlled-release preparation (*M/S Contin, Oxycodone SR*) whole; do not cut,

crush, or chew.

- The following side effects may occur: nausea, loss of appetite (take with food, lie quietly); constipation (use laxative); dizziness, sedation, drowsiness, impaired visual acuity (avoid driving or performing tasks that require alertness and visual acuity).
- Do not take leftover medication for other disorders, and do not let anyone else take your prescription.
- Report severe nausea, vomiting, constipation, shortness of breath or difficulty breathing, skin rash, used concomitantly.

1. Disulfiram

Therapeutic actions

- Inhibits the enzyme **aldehyde dehydrogenase**, blocking oxidation of alcohol and allowing acetaldehyde to accumulate to concentrations in the blood 5-10 times higher than normally achieved during alcohol metabolism.
- Accumulation of acetaldehyde produces the highly unpleasant reaction described below that deters consumption of alcohol.

Indications

- Aids in the management of selected chronic alcoholics who want to remain in a state of enforced sobriety

Contraindications/cautions

- **Contraindications:** allergy to disulfiram or other thiazam derivatives used in pesticides and rubber vulcanization; severe myocardial disease or coronary occlusion; psychoses, current or recent treatment with

metronidazole, paraldehyde, alcohol, alcohol-containing preparations (eg, cough syrups, tonics), pregnancy.

- Use cautiously with diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic and acute nephritis, hepatic cirrhosis or dysfunction.

Dosage

- **Available Forms:** Tablets—250, 500 mg. Never administer to an intoxicated patient or without patient's knowledge. Do not administer until patient has abstained from alcohol for at least 12 h.

Initial dosage

- Administer maximum of 500 mg/d PO in a single dose for 1–2 wk. If a sedative effect occurs, administer at bedtime or decrease dosage.

Maintenance regimen

- 125–500 mg/d PO. Do not exceed 500 mg/d. Continue use until patient is fully recovered socially and a basis for permanent self-control is established.
Trial with alcohol (do not administer to anyone > 50 y).
- After 1–2 wk of therapy with 500 mg/d PO, a drink of 15 mL of 100 proof whiskey or its equivalent is taken slowly. Dose may be repeated once, if patient is hospitalized and supportive facilities are available.

Adverse effects

- Disulfiram-alcohol reaction: Flushing, throbbing in head and neck, throbbing headaches, respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitations, dyspnea,

hyperventilation, tachycardia, hypotension, syncope, weakness, vertigo, blurred vision, confusion; severe reactions may include arrhythmias, CV collapse, acute CHF, unconsciousness, convulsions, MI, death.

Clinically important interactions

- **Substance-substance**
 - Increased serum levels and risk of toxicity of phenytoin and its congeners, diazepam, chlordiazepoxide
 - Increased therapeutic and toxic effects of theophyllines
 - Increased PT caused by disulfiram may lead to a need to adjust dosage of oral anticoagulants
 - Severe alcohol-intolerance reactions with any alcohol-containing liquid medications (eg, elixirs, tinctures)
 - Acute toxic psychosis with metronidazole

Nursing Considerations—patient teaching

- Do not administer until patient has abstained from alcohol for at least 12 h.
- Administer orally; tablets may be crushed and mixed with liquid beverages.
- Monitor liver function tests before, in 10–14 d, and every 6 months during therapy.
- Monitor CBC, SMA-12 before and every 6 months during therapy.
- Inform patient of the seriousness of disulfiram-alcohol reaction and the potential consequences of alcohol use: disulfiram should not be taken for at least 12 h after alcohol ingestion, and a reaction may occur up to 2 wk after disulfiram therapy is stopped; all forms of alcohol must be avoided.

- Arrange for treatment with antihistamines if skin reaction occurs.
- Take dose daily; if substance makes you dizzy or tired, take it at bedtime. Tablets may be crushed and mixed with liquid.
- Abstain from forms of alcohol (beer, wine, liquor, vinegars, cough mixtures, sancoos, aftershave lotions, colognes). Taking alcohol while on this substance can cause severe, unpleasant reactions—flushing, copious vomiting, throbbing headache, difficulty breathing, even death.
- Wear or carry a medical ID while you are on this substance to alert any medical emergency personnel that you are on this substance.
- Have periodic blood tests while on substance to evaluate its effects on the liver.
- The following side effects may occur: drowsiness, headache, fatigue, restlessness, blurred vision (use caution driving or performing tasks that require alertness); metallic alteration (transient).
- Report unusual bleeding or bruising, yellowing of skin or eyes, chest pain, difficulty breathing, ingestion of any alcohol.

General Principles of Psychopharmacotherapy

1. The use of pharmacotherapies should not be reduced to one diagnosis—one drug approach.
2. The variables including the selection of medicine and administration; the psychodynamic meaning of substance to the patient and family and environmental influences should be taken into consideration.
3. The patients and relatives must be instructed about the reasons of treatment and expected benefits and potential risks.
4. Medicines must be used in effective dosages for sufficient periods.
5. Subtherapeutic doses and incomplete trials should not be used due to the fear of side effects; may cause harm rather than benefit to the patient.
6. Treatment response and the emergence of side effects must be monitored closely.
7. Appropriate treatment for emergent adverse effects must be instituted as quickly as possible.
8. The treatment, diagnosis and identification of the target symptoms should ideally be carried out when the patient is in a drug-free state for 1 or 2 weeks or weaned slowly for assessment.