

Opioid Dependence: Neuro-Biology, Clinical Features, Diagnosis and Management

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ABSTRACT

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Opioids have been in use since centuries, but there is a growing concern regarding its illicit use among the youth, especially in India. Activation of mesolimbic reward pathway and dysfunction of the frontal inhibitory mechanisms contribute to the addictive nature of opioids. The main goal of the management is detoxification, relapse prevention and adaptive and social rehabilitation. Management comprises of pharmacological and non pharmacological methods. Among the pharmacological methods, opioid substitution treatment (OST) has garnered wide recognition, with Buprenorphine being the most widely used agent. Methadone, naltrexone, clonidine and slow release oral morphine are other agents.

Keywords: Opioid dependence, Neuro-biology, Opioid- related disorders, Clinical features, Management, OST, Harm reduction, Newer approaches, Ethics

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“Anyone who takes opioids on a regular basis will become dependent upon them, meaning they will have to taper off gradually to avoid withdrawal symptoms. But very few chronic pain patients exhibit the compulsive drug-seeking behaviours of someone who is addicted.” – Karen Lee Richards

INTRODUCTION

The earliest reference to opium growth and its use was in 3,400 B.C. when the opium poppy was cultivated in lower Mesopotamia (Southwest Asia) which was called *Hul Gil*. The word opioid is derived from ‘Opium Poppy’ (*Papaver Somniferum*). Worldwide, some 12 to 21 million people use opiates (0.5-0.8%). In India, the prevalence of opiates use ranges from 0.7% to 1.4% in the general adult male population. The national survey published in 2004 estimates the prevalence of current opioid use to be 0.7% in general population. This corresponds to 2 million current opioid users and 0.5 million opioid-dependent people¹. The Drug Abuse Monitoring System,¹ which assessed the primary substance of abuse in inpatient treatment centres found that the major substances were alcohol (43.9%), opioids (26%) and cannabis (11.6%). However, opioid dependence contributed to the highest number of disability-adjusted-life-years lost (9.2 million) and to drug-related deaths

(43.5 deaths/million people aged 15–64 years).^{2,3} The injecting route used to abuse opioids is another cause for worry due to the serious consequences. There are about 12 million injecting drug users (IDUs) globally, who face some of the most severe harms due to drug use, including blood-borne infections and deaths due to overdose.¹

NEUROBIOLOGY OF DEPENDENCE

Drug addiction has been conceptualized as a chronic disease process occurring in the brain, which is modulated by genetic, developmental and environmental factors. Many factors, both individual and environmental, influence whether a person who experiments with opioid drugs persist in taking them in an addicting manner. One of the brain circuits that is activated by opioids is the mesolimbic (midbrain) reward system which brings out the acute, euphorogenic and positive reinforcing effects of opioids.^{4,5} This system generates signals in a part of the brain called the ventral tegmental area (VTA) that result in the release of the chemical dopamine (DA) in the nucleus accumbens (NAc).⁵ This release of DA into the NAc causes the “high” and pleasurable feelings. Feedback from the prefrontal cortex (PFC) to the VTA helps us overcome drives to obtain pleasure through actions that may be unsafe

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or unwise, but this feedback appears to be compromised in individuals who become addicted to drugs.

The locus ceruleus (LC) is also another area of the brain that plays an important role in drug dependence. The reward signals through dopamine mediated transmission is crucial in producing the “high”, focussing attention, and directing behaviour towards the stimuli.^{4,5}

There is also upregulation of cAMP pathway in several different regions of the brain simultaneously, that leads to the diverse symptoms in opioid dependence.⁶

The compulsive drug- seeking nature is due to upregulation of dopaminergic neurons in frontal cortex, while the physical dependence is due to upregulation in the Noradrenergic neurons in the locus ceruleus. Genetic polymorphisms of the opioid receptor $\mu 1$ has been associated with alcohol and heroin addiction in a population from Eastern India.⁷

Once the neurons are upregulated, they become less sensitive to the successive inputs that mediate reward thereby leading to use of higher doses to obtain the “high”, leading to tolerance.

Opioid - Related Disorders

It encompasses opioid use disorders, opioid intoxication & opioid withdrawal.⁸ According to the International Classification of Mental and Behavioural Disorders (ICD)-10, dependence syndrome⁹ has been defined as “A cluster of physiological, behavioral and cognitive phenomena in which use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviors that once had greater value”. It comprises of the following features of which 3 or more must be present for some time over a period of 1 year.⁹

- A strong desire or sense of compulsion to take the substance.
- Difficulty in controlling substance taking behaviour
- A physiological withdrawal state
- Evidence of tolerance
- Progressive neglect of alternative pleasure or interests
- Persisting with substance use despite harmful consequences

CLINICAL FEATURES

Opioid intoxication leads to respiratory depression, pinpoint pupils, cyanosis, cold clammy skin, hypoten-

sion and in severe cases, cardiac arrhythmias and coma may occur.

Opioid withdrawal, on the other hand, leads to dysphoria, irritability, restlessness, general achiness, yawning, perspiration, lacrimation, rhinorrhoea, restlessness, broken sleep. In severe cases, dilated pupils, piloerection (*cold turkey*), hot and cold flushes with visible diaphoresis, nausea, vomiting, diarrhoea, weight loss, fever, increased blood pressure, twitching of muscles, kicking movements of lower extremities.¹⁰

The course of the opioid withdrawal depends predominantly on the half-life of the opioid and withdrawal symptoms usually start to occur when intake is stopped or lesser quantities are taken.

MANAGEMENT

General Principles-Establishing and maintaining a therapeutic framework and alliance, motivation enhancement, assessing safety and clinical status and pharmacological management.^{11,12}

Assessment

- Clinical History
- Clinical Examination
- Investigations
- Instruments

Goals of Management

- Abstinence from using opioids.
- Retention in treatment.
- Reduction in the frequency and severity of substance use episodes.
- Improvement in psychological, social, and adaptive functioning.
- Harm reduction: Reduction of harms associated with drug use without reduction in drug use per use.¹³

Management involves Pharmacological and Non-pharmacological methods as described below:

Pharmacological Methods

Opioid Intoxication: Ensure clear airways and breathing, and other supportive measures. Patient should be ventilated mechanically until opioid antagonist is administered. **Naloxone** is the specific antidote (0.8mg/70kg i.v./s.c initially and may require repeat administration at an interval of 2-3 mins, max- 10mg). It has a short half-life (60 to 90 min). **Nalmefene**,

another opioid antagonist, has a half life of 10 hours and hence given as a single dose (0.5-1mg). Increase in respiratory rate and pupil dilation is observed as signs of improvement.

Management of Withdrawal

Withdrawal of opioid is achieved by detoxification. An ideal agent for detoxification should relieve withdrawal symptoms effectively require minimal monitoring and have negligible side effects and no abuse potential. Various methods are used for opioid detoxification such as

- Ultrarapid (under general anaesthesia or heavy sedation)
- Rapid (over 3-6 days)
- Short term (1-3 weeks)
- Long term (over months)¹⁴

The pharmacological agents used for detoxification are:

Opioid Agents- The most effective approach to treating a patient who has withdrawal is to prescribe a long-acting oral opioid (usually methadone or buprenorphine) to relieve symptoms and then gradually reduce the dose to allow the patient to adjust to the absence of an opioid. While methadone is most commonly used agent in the world, buprenorphine is most often used in India. Buprenorphine is given in the range of 6-32mg/day which is gradually tapered, and is preferred as it has a longer duration of action and minimal withdrawal symptoms during dose reductions.¹⁵

Alpha-2 adrenergic agonists (Clonidine) decreases the noradrenergic hyperactivity associated with opioid withdrawal and reduces autonomic components of withdrawal and is also preferred in detoxification.¹² It is usually given in the doses of 0.4 to 1.2 mg/day. It requires careful monitoring of side effects (particularly hypotension) and is preferred for inpatient setting.¹⁵

Long Term Pharmacotherapy

Agonist maintenance treatment / Opioid Substitution Treatment(OST):

Criteria for determining suitability for OST: long-duration opioid users with severe dependence, with high risk of relapse and for those who are willing to comply with the requirements. Agonist maintenance treatment with opioids (commonly referred to as opioid substitution therapy [OST] in India), has displayed good outcomes in that it helps in retaining the patient in treatment, reducing the use of illicit opioids and other substances,

and in improving the individual's functioning.¹⁶

The drugs commonly employed are Methadone (40-80mg/day), Buprenorphine(6-10mg/day) combination of Buprenorphine and Naltrexone in the ratio of 4:1. Combination of sublingual buprenorphine-naloxone addresses the problem of diversion: have a minimum risk of being injected. Buprenorphine is preferred for outpatient office- based management.¹⁷ SROM (Slow release oral morphine),¹⁸ a natural derivative of opium and a mu-receptor agonist is also used in maintenance treatment and has the advantage of single dosage, decreased sleep disturbance and increased medication compliance. Usual dose is 60mg/day and is given in methadone intolerant individuals.^{17,18}

For younger patients with a smaller duration of opioid use and strong motivation and support, naltrexone is recommended for maintenance in the dose of 25-50mg/day, after obtaining confirmed abstinence.

Harm Reduction

It is defined by the International Harm Reduction Association as 'policies, programmes and practices that aim primarily to reduce the adverse health, social and economic and legal consequences of the use of legal and illegal psychoactive drugs without necessarily reducing drug consumption'. The main objective is to ensure that the drug users are productive and functioning well in their lives, until the treatment works or they grow out of their drug use and can be reintegrated into society. Harm reduction approach is endorsed in the National policies and used for Injecting Drug Users (IDUs) to reduce risk of HIV infection through sharing and reuse of unsafe injecting equipment. Strategies used are :

1. Outreach programs and peer education
2. Needle and syringe programs
3. Drug substitution/Agonist maintenance programs

Non Pharmacological Management

Cognitive-Behavioural Therapy in combination with pharmacotherapy has yielded superior results. Psychodynamic and Interpersonal Therapies, Self-Help and 12-Step Group Therapy are other psychosocial measures. Family and Network Therapy engage the patient's abstinent family & friends in counselling sessions with the patient.¹⁹

Therapeutic Communities-refers to total immersion of the dependent patients in a community with rules and structure. Therapeutic interventions derive from member-member interactions. It's a complete change

of lifestyle where the patients are made to participate in frequent group sessions devoted to mutual criticisms of attitudes and behavior. Deviation from community expectations, devoid of the harsh criticisms by staff or entire community. Currently, referred by criminal justice system in the West.²⁰

NEWER APPROACHES

- Newer formulations of buprenorphine include a depot, a transdermal patch and in a high single oral dose. The depot contains 58 mg of buprenorphine in microcapsules injected subcutaneously. The transdermal patches come in varying strengths and release buprenorphine at a fixed rate. The patch used for detoxification releases buprenorphine at 20 µg/h over a period of 7 days.²¹
- Slow release oral morphine delivers known quantity and purity of morphine in a controlled manner which is shown to be useful in opioid detoxification.²²
- Dihydrocodeine, a semi-synthetic opioid analgesic used mainly as an anti-tussive, has also been utilized for opioid detoxification.²³
- Tramadol, is a synthetic opioid, which acts as a weak µ-opioid agonist, releases serotonin, and is a norepinephrine reuptake inhibitor.²¹
- Buspirone, is a serotonin 5-HT1A receptor partial agonist acting through the serotonin, dopamine, and noradrenergic systems. It is effective in withdrawal at doses of 30-45mg/day.
- Venlafaxine, a serotonin- norepinephrine reuptake inhibitor was used at doses of 300mg/day in opioid dependent subjects.
- Quetiapine, an atypical antipsychotic acting through the dopaminergic and serotonergic pathways was tried for opioid detoxification, with 4 hourly use of 50mg for reducing anxiety, pain and craving.

ETHICAL CONSIDERATIONS

Persons dependent on opioids may vary in their behavioural pattern and mode of dependency to drugs. So the kind of treatment varies with individuals. The treatment should be carried out by the physician with an ethical consideration. The duty of the physician is to save the patient from self- destruction.

While managing Opioid dependence, the *prima facie* duty of a physician is to act in accordance with moral values based on the Principle of Beneficence, Non-

Malfeasance and preservation of human dignity. The physician should give prime importance to the patient's interest. While promoting patient's interest, the physician should also be conscious about the health condition of the patient. By providing proper advice on the patient's health condition, the physician should allow the patient to choose the kind of treatment as per his or her wish. Correction as: the physician should allow the patient and his/ her family to choose the kind of treatment as per his or her wish. In a situation in which the patient is not in a condition to take any rational decision, the physician should give awareness about his health condition and the kind of treatment he needs. Correction as: condition and the kind of treatment he needs to the patient and his/ her family

The treatment procedure and care given to the patient should be beneficial for improving his health condition and should protect the patient from further health or social problems.

It is also the responsibility of the physician to provide justice to the patient. For this, initiatives should be taken from the part of the physician to arrange financial resources to meet the needs and requirements of the patient for carrying out further treatment. Anyway, the Correction as: For this, initiatives should be taken by the Government, the family and the physician to arrange financial resources to meet the needs and requirements of the patient for carrying out further treatment. The treatment given to an opioid dependent should be in such a way that could provide him therapeutic benefits. For this, the physician should gain trust on him through cultivating an effective therapeutic relationship with the patient.^{24,25}

CONCLUSION

Opioid dependence is a chronic, relapsing disorder amenable to medical treatment. Injecting drug use (IDU) is strongly associated with HIV, hepatitis C and other blood borne infectious diseases. In India, opioids are the drugs most commonly injected by IDUs. Main principles of management include Motivation Enhancement, Establishing and maintaining a therapeutic framework and alliance, Assessing safety and clinical status, Pharmacological management and Non pharmacological management alongwith utmost care to ethics. Methadone, Buprenorphine, Naltrexone, Clonidine are the commonly used detoxifying and maintaining agents. Psychosocial interventions include relapse prevention strategies, CBT, family and group therapies.

END NOTE

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Conflict of Interest: None declared

Editor's Remarks: This article educates us about the causes of opioid dependence, its clinical features and the recent concepts in management. Harm reduction approach is well explained. A must read review for clinicians since there are several areas less known to most of us.

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