

## A Review on Crisis of Opioid Addiction and Its Treatment

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**ABSTRACT:** *Mimosa pudica* L., also known as touch me not, live and die, shame plant, and humble plant, is a prostrate or semi-erect subshrub native to tropical America and Australia. It is also found in India. It is heavily armed with recurved thorns and has delicate, soft leaflets that are grey green in colour and fold and droop at night or when touched and cooled. The active ingredients and pharmacological activity of the legume family *Mimosa pudica* Linn were attempted to be reviewed in the current study. The entire *Mimosa pudica* plant is particularly beneficial for a variety of pharmacological and biological processes. *Mimosa pudica*'s roots and leaves primarily exhibit the plant's highest levels of pharmacological action, including anti-diabetic, antitoxin, antihepatotoxin, antioxidant, and wound-healing properties. A scientific foundation for the medicinal applications of this plant has been established by these pharmacological research. Reviewing the pharmacological, phytochemical, and therapeutic aspects of the plant *Mimosa pudica* was the goal of this paper.

**Keywords:-** *M.pudica*, anti-ulcer, phytochemistry, pharmacology.

### I. INTRODUCTION

Opioids are substances obtained naturally, semi-synthetically or synthetically to relieve pain and often bind to the same cell receptors as opium to create effects that are similar to narcotics (such as sedation, pain relief, slowed breathing, and euphoria). Having the narcotic effects that make opiates so potent: of, involving, or being an opioid. Sometime opioid-containing drugs are misused by persons for their other purposes. The misuse of narcotic drugs produces addiction. For the treatment of opioid or narcotic addiction, naloxone is the right drug of choice. If the suitable strategy can be used. Seen that the misuse of opioid drugs decreases and opiate drugs by physicians also decrease. However, heroin overdose deaths have sharply climbed since 2011. For Thankfully, there

are effective treatments for opioid use disorders, such as methadone, buprenorphine, and naltrexone.<sup>[1]</sup> Opioid painkillers are often safe when taken as directed by a doctor for a brief period of time. They can be abused (taken in a different method or in a bigger quantity) since they can elicit exhilaration. Regular use can result in addiction, overdose events, and fatalities.<sup>[2]</sup> After prescribing any opioid-containing drug, a physician should guide the patient for their proper use as per new rules and regulations because patients unintentionally become addicted to that drug. The drugs that come under the opioid or narcotic class are Codeine, Fentanyl, Heroin, Hydrocodone, Morphine, Oxycodone. The 1990s saw a dramatic rise in the number of prescribed opioids as well as a significant relaxation of prescription guidelines, which led to the current opioid crisis. It has been evident over the last few years that these medications have harmful side effects, such as opioid dependence, abuse, diversion, and mortality. As a result, shorter courses and lesser dosages are now being prescribed.<sup>[3]</sup>



Fig. No. 1 Six most addicted opiates

## II. HISTORY

Opium is obtained from ripped pods of opium poppy flower of papaver somniferous. It is used from 3000 B. C. early by Greek, Arabian and Egyptian.<sup>[4]</sup> The opioid is potent pain relieving drug used in wars. In order to treat injured soldiers, the use of opioids first gained popularity in the US in the early 1860s. These soldiers received morphine treatment, and many of them later acquired morphine dependence and addictions. In 1898 a Bayer Company claim that heroin is also potent pain relieving medicine and not habit forming.<sup>[5]</sup> Addiction means when something that was once enjoyable becomes something you cannot live without. Doctors define as the unnecessary craving for some drug, boost energy and excitation are called as addiction. Also when you take medicine continuously and after few days the drug stop showing action at normal dose are called drug Tolerance. This is commonly occur when the drug deposited on the receptor site. Once tolerance is developed the person is drive to increase dose.<sup>[6]</sup> So that they can feel good. There is no doubt that our country is in a state of crisis. How did opioid addiction get started? Let us examine the history of opiate addiction. There is reliable evidence of opium use as far back as 3,400 B.C. The opium poppy was called "joy plant," and it spread from Mesopotamia to Assyria, Egypt and the Mediterranean. In 460 B.C., Hippocrates acknowledged its usefulness. Alexander the Great introduced it to Persia and India, and Arab traders took it to China. The Opium Wars were fought in China from 1839 to 1860.



Fig. No.2 Opium plant

Morphine was discovered in 1803 and commercial manufacture began in 1827 with Merck & Co. By the time of the Civil War, morphine and other opiates were commonly utilized. Following the war, an alarming proportion of veterans became hopelessly addicted. In 1874, morphine was used to

create heroin for the first time. It was heralded as a miracle medicine as a cough suppressor. In the early 1920s, doctors were concerned about rising rates of drug addiction. In 1924, heroin was declared illegal.<sup>[7]</sup>

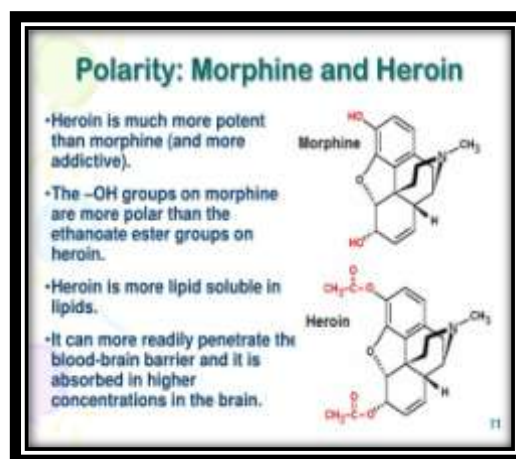


Fig. No. 3 Morphine and Heroin

In its recently released "World Drug Report 2020," the United Nations Office on Drugs and Crime (UNODC) noted that "total opioid usage in India is anticipated to have grown five-fold in contrast to prior estimates from a study carried out in 2004" at a time when an alarming spike in drug misuse has been seen in India. According to the UNODC, a recent significant drug use study in India revealed that in 2018, 23 million individuals, or 2.1% of the population aged 10 to 75, had used opioids in the previous year. The most popular opioid in the population under study is heroin, which is followed by opium and prescription opioids used for non-medical purposes.

According to a 2019 drug use study in India, approximately 1% of persons aged 10 to 75 had abused prescription opioids in the previous year, and an estimated 0.2% of people (2.5 million people) experienced drug use disorders linked to prescription opioids. According to a UNODC report, tramadol, morphine, buprenorphine, and pentazocine are the most frequently abused opioids in India. A range of "negative outcomes such as drug use disorders, mental health problems, HIV infection, hepatitis-related liver cancer and cirrhosis, overdose and early death" were mentioned in the study as major health effects of drug use. According to the UN research, those who start using drugs and go on to develop problems often go through a number of phases, from first use through escalation, maintenance, and finally dependency or addiction.<sup>[8]</sup>

**CLASSIFICATION OF OPIOID DRUGS<sup>[9]</sup>**

1. **Endogenous Opioids:** These are the opioid actually made in human brain.

**Example:**Endorphins, Endomorphism, Dynorphins, Enkephalins

2. **Natural Opioids:** These are the opioid are obtained from natural sources. Also called alkaloid opioids.

**Example:**Morphine, Codeine, Thebaine.

3. **Semi-synthetic Opioids:**These opioids are man-made but obtain from natural sources.

**Example:**Hydromorphone, Hydrocodone, Oxycodone, Heroin.

4. **Synthetic Opioids:** These are the drug obtain in laboratory or other place by man.

**Example:** Fentanyl, Pethidine, Levorphanol, Methadone, Tramadol, Dextropropoxyphene

**CLASSIFICATION ON THE BASIS OF RECEPTOR BINDING<sup>[10]</sup>**

1. **Opioid Agonist:-**Drugs known as opiate agonists function by binding to opiate receptors and simulating the body's natural opiates to lessen pain and increase pleasure.

2. **Opioid Antagonist:-**Drugs called opiate antagonists are used to relieve pain because they stop an agonist's activity.

**TYPES OF OPIOID RECEPTOR**

In human body commonly three types of receptors are present. each of them has unique effect and specific distribution regions of brain and other area of body.

1. **Mu:-**Mu receptors are directly link to mood, pain and rewards triggers. The drug connected to the Mu receptor can give relief from pain, change mood physical activeness and affect respiratory action. Generally most of the drugs are Mu agonist. This means that they activate the action of the Mu receptor.

They are located at Mesenteric plexus, Brain, Spinal cord, Sub-mucosal plexus.

2. **Delta:-**Delta receptors are connected to the mood. In previous seen that blocking of delta receptors causes anxiety and depression in mice. This could mean that delta receptor play role in person's mood.

They are located at Mesenteric plexus, Brain.

3. **Kappa:-** The kappa opioid receptors are also stimulated by some opioid medications. Mood and reward responses appear to be impacted by the kappa receptor. Additionally, there is a history of pain alleviation, dysphoria, and an increase in urine from opioid that activate the kappa receptor.

They are located at Mesenteric plexus, Brain, Spinal cord.<sup>[11]</sup>

Receptor	Clinical Effect	Location
Mu( μ)	Analgesia changes, smooth muscle tone , sedation, mood alteration, nausea/vomiting	Mesenteric plexus , Brain, Spinal cord, Sub-mucosal plexus
Delta(δ)	Decrease colonic transit time	Mesenteric plexus, Brain
Kappa( k)	Central analgesia, decrease colonic transit time, visceral nociception antagonist	Mesenteric plexus, Brain, Spinal cord

**Table No.1 Opioid Receptors**

**OPIOID ADDICTION AND HOW THEY PRODUCE ADDICTION**

Opioid addiction is something that may happen to users of these medicines readily quite. It may come after opioid dependency, which is a physiologic reaction to the presence of opioids and the commencement of withdrawal when the

body's level of opioids drops. Although opioid addiction is common, it is not a given. Opioid dependency is inevitable.

Like other disease opioid addiction is also consider as a brain disease. Those produce psychological and physical dependency of drug. Opioids alter the brain in ways that result in a

variety of harmful, destructive behaviors. Despite the issues it creates in her life, an opioid addict constantly pursues and consumes these narcotics with increasing vigour. Opioids are highly addictive in nature. Opioids may cause addiction in humans, whether they are legally prescribed medications like heroin or illegal narcotics like morphine, Vicodin, codeine, or oxycodone. Addiction and dependence of some drug is based on the nature of drug, not the nature's of person. Opioids are use for a therapeutic purpose. For relieving pain. They also produce a pleasant happy sensation. This are the reason people take opioid containing medicine in the first place. These don't guarantee addiction, though.

There are some reason which produce opioid addiction.

- Natural opioids are produced by the body and brain (endorphins are among them).
- We produce our own opioids, thus our brain and body are covered in opioid receptors.
- The brain and body cease manufacturing these vital neurotransmitters and hormones when we take any kind of opioid for any reason because they believe we don't need to manufacture our own.
- Now, instead of the naturally occurring opioids that were produced in our bodies, the opioid receptors are bound by the opioids we consume or utilise.
- Since there are no natural opioids to take their place when we stop using painkillers, heroin, etc., the brain and body start to suffer opioid withdrawal. This is reliance.
- Because the opioid withdrawal symptoms are unpleasant, we start taking them again.
- In order to stimulate our brain's reward system, which reduce pain and feel high, and to prevent the unpleasant withdrawal symptoms that start as soon as the drug levels in our system drop, we consume more opioids nowadays.
- Because of the high physiological need for and response to opioids, addiction has already started, and without assistance and medication, it is likely to worsen and persist.

After addicted to opioid person may misuse the prescription given by physician. They use that prescription for their bad purpose. [12, 13, 14]

### SYMOTOMS OF OPIOID ADDICTION

The following are typical opioid addiction indications and symptoms:

- Feeling down
- Headache
- Pine point pupil
- significant decrease of weight
- Cramping
- Diarrhea
- joint discomfort or muscle pain
- nausea or diarrhea
- Headache
- withdrawing or isolating oneself from friends and relatives
- financial struggles brought by usage
- irrational mood swings
- inability to pay attention<sup>[15]</sup>

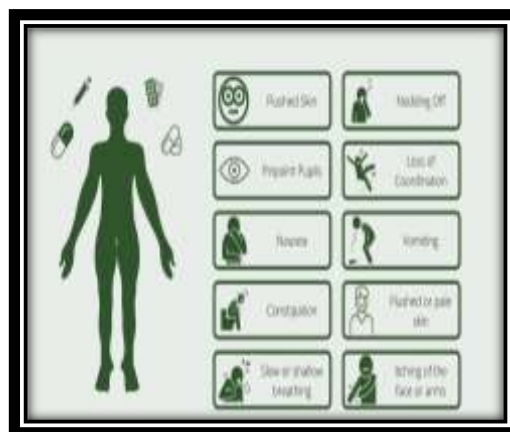


Fig.No.4 symptoms of opioid addiction

### WITHDRAWAL SYMPTOMS OF OPIOID

Opioid withdrawal symptoms are generally occurring after stopping of the opioid drug. It can last up to 10 days, but is most often between 3-5 days. It causes very troubling symptoms with life threatening. The following symptoms are observed during drug withdrawal.

❖ **Early symptoms include:**

- Agitation
- Muscle aches
- Restlessness
- Anxiety
- Increased tearing
- Runny nose
- Excessive sweating
- Inability to sleep

❖ **Later stage symptoms include:**

- Diarrhea

- Abdominal cramping
- Nausea and vomiting
- Skin goose bumps
- Dilated pupils
- Rapid heartbeat
- High blood pressure<sup>[16]</sup>



Fig.No.5 Withdrawal symptoms

### STEPS TO AVOID OPIOID ADDICTION

Following these strategies can help keep you on a safe and successful route if you have determined that opioids are necessary to treat your pain after an injury, surgery, or sickness but you are concerned about establishing a habit.

1. **Communication with doctor:-**If doctor prescribe opioid medicine. Patient or any other come with patient should ask question to doctor why they prescribe this medicine. Take all information about that medicine and it's side effect. Should talk with doctor freely and clear all doubts.
2. **Replace opioids with other drug:-** If opioid medicine is replace with other medicine like for example opioid used as pain reliving medicine but non-steroidal anti-inflammatory drug (NSAID) produce same action and relief from pain. Then opioid is replaced with NSAID.
3. **Follow the rules if opioid contain medicine is necessary:-**According to NIDA following rules should follow while taking opioid containing drugs.
  - Avoid combining opioids with other drugs or alcohol, especially sedatives like Xanax or Ambien.
  - Do not share or sell your opioids; keep them safely stored.
  - If you have any adverse effects, tell your doctor right away. You should also talk to

your doctor before stopping or changing your medication.

4. **Take less dose of medicine:-**doctor prescribing opioids containing medicine. Than must tell the doctor to prescribe less dose of drug. In case you need additionally, if an opioid is necessary for you, it should only be prescribed for one to two weeks at most, as beyond that time, the likelihood of dependency increases significantly. Ask your doctor if you still need pain medication if you've been taking it for more than a week.
5. **Don't ignore your physical and mental health:-**Anxiety and sadness can be brought on by physical discomfort or made worse if they already exist. Therefore, it is necessary to continue taking any recommended drugs. Additionally, while taking opioids, you might want to think about attending therapy sessions.<sup>[17]</sup>

### TRETMENT OF OPIOID ADDICTION

Now a days, effective medication or treatment are available to cure opioid addiction. There are mainly three medicines are used such as buprenorphine (Suboxone, Subutex), methadone, and extended release naltrexone (Vivitrol), are effective for the treatment of opioid use disorders. Methadone and buprenorphine are referred regarded as "essential drugs" by the World Health Organization.<sup>[18]</sup> Following drugs are used in treatment of opioid addiction:

#### 1. METHADONE:-

Methadone is potent synthetic analgesics. It acts on Mu receptor antagonist.  $\mu$ -opioid receptor (MOR) agonist and N-methyl-D-aspartate (NMDA) receptor antagonist. And potent MOR agonist through the release of neurotransmitters involved in pain transmission, methadone imitates the actions of the body's endogenous opioids, endorphins, and enkephalins.<sup>[19]</sup> The goal of replacing illegal opioids with the long-acting opioids used in OAT is to delay the onset of withdrawal symptoms for 24-36 hours after dose, hence lowering cravings and drug-seeking behaviors. By lowering crime rates, imprisonment, the use of illegal opioids like heroin or fentanyl, and eventually marginalization, OAT usage is also meant to contribute to social stability<sup>[20]</sup>.

- **MOA:-** Binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression.

Methadone has also been shown to have N-methyl-D-aspartate (NMDA) receptor antagonism.

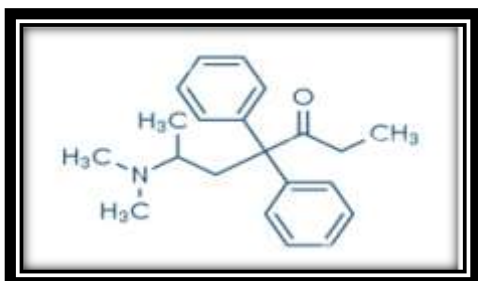


Fig.No.6 Methadone

**DOSE:-**

- 1) Orally: 2.5mg every 8 to 12 hours quantity increases with patient condition.
- 2) Parentally: IM, IV, Subcutaneous with 2.5 to 10 mg every 8 to 12 hours

**USE:-**

- 1) detoxification
- 2) pain management. [21]

**2. BUPRENORPHINE:-**

Buprenorphine is also a synthetic analgesic used in the treatment of acute pain, chronic pain and opioid dependence. It acts as a partial agonist at the mu receptor and a high affinity antagonist on Delta and Kappa receptors. This is an approach to treating addiction that involves utilizing a drug (such as buprenorphine or methadone) to replace a more potent full agonist opioid (such as heroin). For individuals receiving addiction therapy, it is an effective way to treat opioid dependency, lessen cravings, and enhance quality of life. It enables the patient to avoid many of the unpleasant opioid withdrawal symptoms, resulting in the development of a medication regimen that patients are more inclined to follow, lowering morbidity and mortality. [22]

- **MOA:-** The Central nervous system mu opiate receptors are where buprenorphine has high affinity binding to provide its analgesic effects. It also exhibits mild kappa antagonist and partial mu agonist action. Because it is a partial mu agonist, it first acts as an antagonist before reaching a plateau in its analgesic effects at higher dosages.

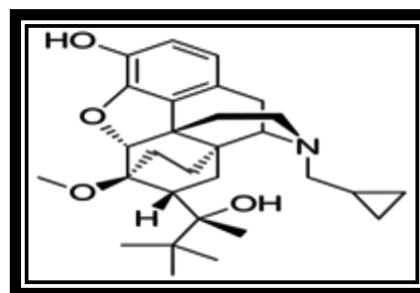


Fig.No.7 Buprenorphine

**DOSE:-**

- Sublingual route:- 16mg/day tablet  
Parentally:- 0.3 mg every 6 to 8 hours

**USE:-**

- 3) Opioid dependence.
- 4) Pain management. [23]

**3. NALTREXONE:-**

It acts as a Delta and Kappa receptor antagonist. Naltrexone is a prescription medication used to treat alcohol use disorder and opioid use disorder. It helps you stop using these substances and remain off them. Naltrexone shouldn't be administered to an opioid-dependent person before detox. [24] The drug naltrexone was created in 1965 and was given medical approval in the United States in 1984. It is also used to treat obesity under the trade name Contrave. [25]

- **MOA:-** It acts as an agonist of mu receptor and a weak antagonist of Delta and Kappa receptors. By preventing opioid addiction and physiologic dependency on opioid users, naltrexone suppresses the effects of opioids. To reduce ethanol intake, naltrexone alters the hypothalamic-pituitary-adrenal axis. Exogenous opioids are used for pain relief treatment. This medicine produces euphoria at higher doses. Opioid overdose, coma, and respiratory impairment can result after an. Although they also impact mu, delta, and kappa opioid receptors, opioids primarily operate through the mu receptor. Artificial opioid antagonists can change how opioids interact with these receptors. Opioid use disorders can be treated with naltrexone, an antagonist that competes with opioid receptors.

**DOSE:-**

- 1) Orally :- 25mg / hr. (if no withdrawal signs)
- 2) Parentally:- 30mg (IM,IV)

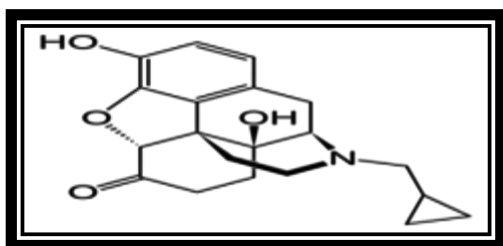





Fig.NO.8 Naltrexone

USE:-

- 1) Opioid use disorder
- 2) Alcohol use disorder
- 3) Heroin use disorder
- 4) As a antidote of opioid. [26]

MARKETED PREPRATION OF MEDICINE [27]

MEDICINE	MARKETED PREPRATION	DOSAGE FORM
Buprenorphine	Probuphine (implant), generics	
Methadone	Generics(tablet)	
Naltrexone	Vivitrol(injection)	

III. CONCLUSION

This brings us to the conclusion that opioid-containing medicines are utilised for analgesic therapy, but their abuse leads to addiction, which is the leading cause of illness and disability. Opioid receptors are found in our bodies; everyday opioid medication use activates these receptors, resulting in opioid cravings. Overuse of opioids causes symptoms that damage the patient's physical and mental health, and can be fatal. Some techniques are used to reduce the abuse of opioid analgesics and other opioid-containing drugs. For the treatment and management of opioid addiction, effective medications such as methadone, buprenorphine, and naltrexone, or a combination of these drugs, are used. Another method is to substitute another analgesic medicine for the opioid. If an opioid-containing analgesic is required, relevant information must be obtained from the doctor. If you utilize a high dose to recover quickly, you will develop tolerance. For drug addicts, intolerance and prejudice are

significant barriers to treatment. Everyone has the same level of access to health care, education, employment opportunities, and social inclusion. Investment in drug addiction brain research must continue and expand to include social science, prevention, treatment, and policy research. The study's findings should be used to develop evidence-based policies to lessen the burden of drug addiction. Recent advancements in the treatment of drug addiction have created difficult ethical issues that scientific and governmental institutions must address as a priority.

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