e-ISSN - 2348-2184
Print ISSN - 2348-2176

AMERICAN JOURNAL OF BIOLOGICAL AND PHARMACEUTICAL RESEARCH

Journal homepage: www.mcmed.us/journal/ajbpr

OPIOIDS AND ITS DERIVATIVES- AN OVERVIEW

Vijaya kumar S[1*] and Sasikala M[2]

[1]Department of Pharmacy Practice, Vels University, School of Pharmaceutical Sciences, Chennai, Tamil Nadu, India.
[2]PG Scholar, Department of General Medicine, Government of Siddha Medical College, Chennai, Tamil Nadu, India.

Article Info

Received 29/09/2014
Revised 16/10/2014
Accepted 11/11/2014

Key words: -
Morphine, Codeine, Delusion, Addiction and Hospital.

ABSTRACT

Opium is an narcotic drug, since it has been used for mankind started centuries ago. It was first cultivated in Mediterranean regions and probably brought by Alexander in 327 BC, to India. Indian opium is produced at Ghazipur and is consumed in India or exported for the US and British trades. Indian opium yields about 10% of anhydrous morphine. The objective of this review is to assist the hospital management of patients with a suspected exposure to opium poisoning by 1) describing the process by which evaluate an exposure to opium derivatives, 2) identifying the predictive factors in Opioid adverse effects. 3) Providing clear and practical recommendations that reflect the current state of knowledge in opium poison management. Our review suggested that evidence based management of opium poisoning patients in the hospital and highlights the importance of preventive measure for opium addiction.

INTRODUCTION

Opium is an narcotic drug, since it has been used for mankind started centuries ago. It was first cultivated in Mediterranean regions and probably brought by Alexander in 327 BC, to India. It is the air-dried milky exudates obtained by incising the unripe capsules of *Papaver somniferum* Linne or its variety album DeCandolle (Family: Papaveraceae). The term opium is from the greek opion, meaning poppy juice; papaver is the latin name for the poppy; somniferum is latin and means to produce sleep. Narcotine was the first alkaloid reported both from opium and among alkaloidal series, to be isolated in 1803 by Derosne. Segin isolated morphine in 1804. Magendi and Bally first introduced it in medical practice in 1818. Gulland and Robinson elucidated the structure of morphine in 1923. In 1833. Robiquet isolated codeine from opium and in 1881. Grimaux reported that codeine is O-methyl derivative of morphine. Merck company isolated papaverine in 1848.The genus papaver has 50 different species, of which six species are found in india viz *P. Somniferum* (Opium Poppy), *P. Nudicaule* (Iceland poppy), *P. Rhoes* (Corn Poppy), P.*orientale*, *P. argemone* and *P.dubium*.

Table 1. Most common name of *Papaver somniferum* in different countries [1]

Languages	Common names
Tamil	Abini
English	Opium, Poppy
Telugu	Abhini, Nalla-mandu
Malayam	Kasha-Kasha-Karappa-Apini
Kananda	Aphimu
Hindi	Afynn
Sanskrit	Ahipehnam
Arabic	Afyun
Persian	Mahanul, Tiryak
Dutch	Afim

The opium cultivation, collection and preparation are controlled under Narcotic Drugs and Psychotropic

Corresponding Author

Vijaya kumar S
Email:- vijayvijay66@yahoomail.co.in

Substances Act, 1985. In India, about 54 thousand hectares of land is under opium poppy cultivation. It is under government control and cultivation of poppy is restricted to Madhya Pradesh, Rajasthan and Uttar Pradesh. The weather conditions affect upto large extent, the yield of opium. Although, temperate climate is the natural requirement of opium poppy. It can be grown with success under subtropical climate in winter season, as there is a favourable effect on yield by cold weather. But extreme cold conditions, including frost, adversely affect the plant and ultimately yield of opium. In short, the best climatic conditions for opium poppy are cool weather without freezing temperature and cloudiness and sufficient sunshine. Opium poppy is grown from November to March Sowing the seeds for which 3-4 kg of seeds per

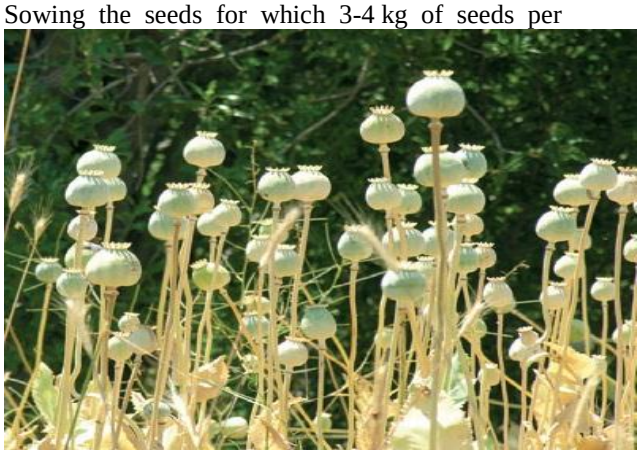

Figure 1.The opium poppy after the flowers has been dropped in the field [18]

hectare are necessary. The seeds admixed with about 3-4 parts of sand are sown. The soil should contain organic matter, nitrogen and should have around pH. After sowing within 3-4months, the plant bears flowers, which are converted to capsules within few days and attain maturity after 15-20days. During the maturity period, the capsule excudes maximum latex which shows a colour change from dark green to light green. Such capsules are incised vertically in the afternoon with the help of specific needle like apparatus called 'nushtur'. It penetrates maximum upto 2mm into the capsule. Because of incisions, latex excudes out and thicknens due to cold weather in night which is eventually scrapped and collected next morning by an iron scoop called charpala. The incisions must remain superficial, so as to maintain the external exudation of latex. The latex is collected in plastic containers. Then, capsules are collected and dried in open areas and further the seeds are separated by beating. The average yield of opium is about 25-26kg per hectare and for seeds, it is from 4-5 quintals per hectare. Opium is exported traditionally from India. [2]. Morethan, 30 different alkaloids have been obtained from opium and its extracts, some of which are alteration products of the alkaloids occurring naturally in the drug. The most important of these are morphine, which exists to the extent of 4 to 21%; codeine, 0.8 to 2.5%; noscapine (formerly narcotine), 4 to 8%; Papaverine, 0.5 to 2.5% and thebaine, 0.5 to 2%. Other alkaloids include narceine, protopine, laudanine, codamine, cryptopine, lanthopine and meconidine. Opium also contains from 3 to 5% of meconic acid, which exists free or in combination with morphine, codeine, and other alkaloids. It forms rhombic prisms that are soluble in water and alcohol and give a red color in solutions of ferric chloride. The color is not altered when diluted hydrochloric acid is found only in opium, this test may be used for the detection of opium. The total ash yield of opium is from 4 to 8% with about 0.55% of acid insoluble ash. Opium in its normal, air-dried condition yields not less than 9.5% of anhydrous morphine. Therefore, narcotic drugs are generally classified as

A. Natural opium alkaloids : It includes (I) Morphine (II) Codeine

B. Semi-synthetic opium alkaloids : It includes drug like (I) Apomorphine (II) Heroin (Diacetyl morphine) (III) Dihydromorphine

C. Synthetic morphine drugs: It includes (I) Pethidine (II) Methadone [3]

EPIDEMIOLOGY

In Persia (Iran) the exudation is scraped off with a knife and collected in a small bowl or on a poppy leaf; it is then mixed and made up into rectangular brick-shaped cakes about 10×5×7cm. Each brick, which is wrapped in paper, usually red in colour, weighs about 1 lb, and 160 of them are packed in a case for export. In Turkey (Asia Minor) a special cutter is used; this consists of a wooden handle, about 18cm.Long, with a flat end in which are embedded seven small knives, the tips of which project about 1.5mm, so that incisions cannot be made too deeply . The cutter is drawn around the equator of the capsule thus making seven parallel incisions from which the latex exudes. The incision may be repeated after a lapse of two or three days and sometimes the capsule are incised three times. The scrapings are massed into balls of various sizes, wrapped in poppy leaves and packed with Rumex fruits for transport to Istanbul, where they are mixed in a mill and moulded into uniform sub-cylindrical cakes about 9cm, high and 14cm in diameter, each weighing about 2 kilos; they are packed forty in a case. [4] During the reign of Shah Mohammad Reza Pahlavi (1941-1979), Iran was a major producer of drugs, and opium was openly available in pharmacies. Opium production in Iran was halted following the Islamic Revolution in 1979. Today, no licit or illicit cultivation of narcotic plants is reported to take place in the territory of Iran, nor do reports cite the existence of illicit drug manufacturing in the country. Nevertheless, one cannot completely rule out the possibility of the existence of limited heroin processing on the main trafficking routes

from Afghanistan and Pakistan and toward the western border of Iran. A large part of the opium seized by law enforcement authorities is used by the national pharmaceutical industry for manufacturing licit drugs, mainly codeine. [5] There are different ways of opium consumption: inhalation (which is the most common way to begin recreational use), oral, and intravenous. Opium consumption through inhalation is normally done through a Vapour or Sikh-sang or through a special form of opium called sheereh. As they become tolerant to the inhalational route, opium addicts tend to resort to the oral and intravenous routes gradually. Opium absorption and blood level of its main sub extract, i.e. morphine, are different in the foregoing routes of consumption. Chinese opium once of considerable commercial importance has not been available in this country since the communist government came to power in china more than 30 years ago. Although the people's republic of china has not reported to the international narcotics control board during this period, the domestic production and use of narcotic drugs are strictly controlled. Chinese opium occurs as flat globular cakes usually wrapped in paper and contains from 4 to 11% of morphine. Approximately 285,000 kg of opium, with a market value in excess of $5million are imported into the united states annually. Indian opium is produced at Ghazipur and is consumed in India or exported for the American and British trades. It is presently our main source of opium. It usually occurs in soft cakes that weigh about 5kg each. These cakes are shipped in plastic bags. Indian opium yields about 10% of anhydrous morphine.

ADULTERANTS

Fragments of the capsules the pulp of figs and other fruits, tragacanth, beeswax, powdered cumin seed, starch, and such inorganic substances as clay,sand,stone,lead piping,and lead bullets have been found in opium. Starch is not usually admixed with Turkish opium.[6]

MEDICINAL CHEMISTRY

The basic structure of morphine and side chains of the derivatives. The Opioid are composed of six membered saturated heterocyclic rings forming the phenanthrene nucleus to which is attached a piperidine ring. The structure represents the prototype for all opiods except methadone and meperidine although the more important opiate alkaloids exhibit a phenanthrene nucleus, the majority of the derivatives have the isoquinoline ring structure. Esterification of the phenolic functions, such as in the formation of diacetylmorphine, results in a compound with increased lipid solubility and increased potency and toxicity. Morphine is glucuronidated in the liver at the phenolic hydroxyl group (C_3). Protection of that group with a methyl group, as occurs in codeine and other codeine derivatives such as oxycodone, renders the molecule less susceptible to glucuronidation and decreases the first-pass effect in the liver. It is for this reason that codeine and its derivatives retain activity following oral administration to a greater degree than does morphine. However, the glucuronidation of morphine at the hydroxyl moiety in C_6 leads to an active metabolite, morphine 6 glucuronide, which contributes to the activity of morphine and extends its duration of action. [7]

Opioid receptors

Opioid receptors and their precursor mRNAs are distributed throughout the brain and spinal cord. It has been shown in schematic diagram of figure 2 and 3. [7]

TOXICOKINETICS

Morphine is rapidly absorbed from an oral dose and from i.m and s.c. injections, peak plasma levels occur a 15 to 60 min , respectively. Morphine is metabolized extensively, with only 2 to 12% excreted as the parent molecule, while 60 to 80 % is excreted in the urine as the conjugated glucuronide. Heroin is rapidly biotransformed, first to monoacetyl morphine and then to morphine. Both heroin and monoacetylmorphine disappear rapidly from the blood ($t_{½}$ =3 min, 5 to 10 min, respectively). Thus, morphine levels rise slowly, persist longer, and decline slowly. Codeine is extensively metabolized, primarily to the 6-glucuronide conjugate. About 10 to 15% of a dose is demethylated to form appear in the urine after codeine ingestion. [8].

Morphine drug-drug interaction shown in Table 2. [9]

DIAGNOSIS

The diagnosis in a case of poisoning can be made from the 1) History 2) Physical Examination 3) Laboratory Evaluation

1. History

- Most important indicator of toxic ingestion. Careful history regarding involved toxins, amount of drug and timing should be recorded.
- Information regarding prescription medication, over the counter drugs and illicit substances of abuse should be obtained.
- Friends, relatives and other involved healthcare providers should be questioned and medications identified.
- Medication found on or near the patient should be examined and pharmacy on the medication label should be called to determine the status of all prescription medication

2. Physical examination

- Needle marks, Dermal scars (suggestive of addiction)
- Hypothermia

3. Laboratory evaluation

- Evidence of hypoglycaemia

➢ Most opiates can be detected in urine or blood by radio-immunoassay, gas chromatography, or high performance liquid chromatography.[10]

USES [14]

It serves as an analgesic, a hypnotic, and a narcotic and checks excessive peristalsis and contracts the pupil of the eye.

Powered opium is used in making dover's powder and camphorated opium tincture and is combined with other agents in antidiarrheal preparations.

Poppy seeds are used in baking (poppy seed rolls). They contain about 50% of a fixed oil (Poppy seed oil), which is used in some parenteral formulations by artists as a drying oil and also for food and salad dressings.
Poppy seed oil cake is used as a cattle food.

Naloxone: It is effective against all opiates including pentazocine, but is not very effective against buprenorphine. The usual initial dose is 1.2mg for an adult and 0.4mg for a child. The best route of administration is IV. Since the effect of a single bolus dose of naloxone is usually short lived, repeated doses are required. E.g: Narcotan, 2mL ampoules of 20mcg/mL.

Naltrexone: It is a long-acting opiate antagonist which can be administered orally. It is usually used for treating opiate addiction. The dose is 50mg/day orally, which may have to be continued for several weeks or months. Eg: Naltima 50mg tabs.

Nalmefene: It is a naltrexone derivative with pure opiate antagonistic effects, and has a longer duration of
than naloxone in acute opiate poisoning. It is usually given intravenously beginning with 0.1mg, and if withdrawl reaction doesnot occur, 0.5mg is administered, followed by 1mg in 2 to 5 minutes (SOS).

COMPLICATION

Faniya shigakova (2013) reported that female opium addicts of post abstinent period of heroin morbid attraction exacerbation was found characterized with affective, behavioral and sonic disturbances. However, four clinical variants, such as, emotionally labile (44.0%), depressive (24.0%), dysphoric (16.0%) and restless (16.0%) have been observed, emotionally labile type Divsalar Kouros et al 2010 reported that, chronic consumption of opium and heroin can change serum FBS, Electrolytes, and protein and lipid profiles. Opium addiction may chances of increasing the risk of infectious diseases (especially HIV), and also increase in risk of cardiovascular diseases, osteoporosis, or kidney and hepatic malfunctions. [15.17]

MANAGEMENT OF OPIUM POISONING [10]

Supportive care

➢ Maintenance of patient airway circulation
➢ Endotracheal intubation and assist ventilation support

Factors that predict opiod adverse effects include:

1. Drug related factors there is little evidence suggesting that any one opiod agonist has a substantially better adverse effects profile than any other.
2. Route- related factors There is limited evidence to suggest differences in adverse effects associated with specific routes of systematic administration.
3. Patient- related factors there is evidence to suggest that there is inter-individual variability in sensitivity to opiod-related adverse effects; the variables include genetic susceptibility, the presence of co-morbidity and age.
4. Dose-related factors dose response relation is most evident with the CNS adverse effects of sedation, cognitive impairment, hallucinations, myoclonus, and respiratory depression, although there is still inter-individuals variability in dose responsiveness to these effects; nausea and vomiting are common at the start of therapy but are then unpredictable.
5. Starting doses and escalation The adverse effects of morphine, especially cognitive impairment, occur transiently and abate spontaneously; there are no reports of a relation between the starting dose of morphine or dose escalation and the occurrence of nausea, vomiting or delirium.
6. Drug interactions Adverse effects of concurrent medications may be synergistic or cumulative with those associated with opiods. [16]

POSTMORTEM FINDINGS [10]

➢ Cerebral oedema
➢ Tattooing (a common feature of the drug subculture)
➢ Emaciation, Unkempt appearance
➢ HIV and Hepatitis are common among intravenous drug abusers
➢ Gross pulmonary oedema

Injection marks, dermal abscesses, scarring, fossae, forearms, back of upperlimb, neck, groin and ankles

Table 2. Fatal dose of common opiates derivatives [10]

Opiate	Usual fatal dose	Usual therapeutic dose (in mg)
Morphine	200mg	10 to 15
Codeine	800mg	10 to 60
Heroin	50mg	-
Crude Opium	500mg	-
Pethidine	1gm	50 to 150
Methadone	100mg	5 to 10
Pentazocine	300mg	30 to 60
Propoxyphene	1g	100 to 150
Diphenoxylate	200mg	10 to 20

Table 3. Clinical features [11-13]

System effects	Exposure	
	Acute	**Chronic**
Gastro intestinal	Vomiting, Abdominal pain	Decrease in gastric motility increases gastric emptying time and reduces absorption of other drugs, Constipation
Lung	Non-Cardiogenic pulmonary edema, Bradypnoea	Mu- receptors agonists depress respiration in a dose dependent manner and can lead to respiratory arrest within minutes
CNS	Loss of consciousness, Sedative effects, Release of hormone from both pituitary and the hypothalamus, Convulsions	Decrease the release of dopamine, thus increasing release of Prolactin, Unusual mood swings, Amnesia, Confusion, Coma
Liver	----------	Congestion of liver with enlargement of hepatic lymph nodes, Hepatitis
Heart	(Higher dose of morphine) Hypotension, feeble tachycardia	Premature atherosclerosis (Cardiac ischemia)
Renal	Urine output diminishes, Acute renal failure	Constriction of urinary sphincter can lead to painful urine retention in some patients
Musculoskeletal effects	Some patients feel a dysphoric effect upon the administration of opiods, which is most likely mediated by the sigma receptor, Rhabdomyolysis	Opioids suppress the perception of pain by eliminating or altering the emotional aspects of pain and inducing euphoria and sleep with higher dose
Eyes	Pinpoint papillary response	Miosis is due to disinhibition of the Edinger-Westphal nucleus in the cortex resulting in increased papillary constrictor tone.
Skin	Hypothermia, with cold, clammy skin	Pallor, Dermal scars (from subcutaneous and intravenous abuse) and dermal abscesses

Table 4. Morphine (drug - drug interaction)

Category	Drug Interaction	Mechanism	Management
Mild	Ritonavir	By the use of morphine and ritonavir, ritonavir will induce the hepatic enzymes responsible for the glucronidation of morphine and there prediction is morphine serum levels will increased	No confirmatory clinical evidence of this interaction and no published data shown.
Moderate	Metoclopramide	Metoclopramide increases the rate of gastric emptying so that the rate of morphine absorption from the small intestine is increased. Both drugs act additively on opiate receptors to increase sedation.	Exploited in anaesthetic practice, but the increased sedation may also represent a problem if the morphine is being given long term.
	Rifampicin	Rifampicin increased the clearance of the morphine by 49% and its analgesic effects were abolished. The presumed reason is that the rifampicin increases the metabolism of the morphine so that it is cleared from the body much more quickly and its effects are lost.	To use an increased dosage of morphine in patients treated with rifampicin.
	Secobarbital	Seco & Morphine depressed respiration when given and prolonged depression occur when given together	Diazepam is an alternative tranquilizer and sedative drug which appears neither to depress respiration nor to add to the respiratory depressive effect of pethidine
	Tricyclic Antidepressants (Desipramine,	Desipramine increased and prolonged morphine analgesia and confirm the value of desipramine	It is an useful interaction but the possibility of increased morphine toxicity should also be born in mild

	Clomiprarmine, Amitriptyline)		whether other TCA's behaves similarly is uncertain.
	Cimetidine/Ranitidine(H2-blocker)	Studies with human liver, microsomal enzymes have shown that metabolism of morphine is not affected by cimetidine/Ranitidine. The isolated case of interaction remain unexplained	The isolated cases sited here under line the importance of monitoring the concurrent use of morphine and H2 blockers.
	Oral Contraceptive	The estrogen component of the contraceptive increases the activity of one of the liver enzymes concerned with the metabolism of the morphine	The dosage of morphine would need to be virtually doubled to achieve the same degree of analgesia.
	Dexamfetamine	Its increased the analgesic effect of morphine and reduces to some extent its respiratory depressant effect. Methyl phenedate increases the analgesic effect and reduces the sedation	There would be seems advantage in using this drug incombination
Major	Food	Food increases the bioavailability of oral morphine and raises the serum levels	The inference to be drawn as that pain relief is likely to be increased if the morphine is given with food.
	Cyclophosphamide Or Chlormethine Lidocaine Or Chloraprocaine	Toxicity of cyclophosphamide or chlormethine is increased by morphine or pethidine Morphine given as an IV bolus doesnot alter lidocaine serum levels given as a continuous IV infusion chloroprocaine can reduce epidural morphine analgesia when compared with lidocaine	They need to re-evaluated the concurrent use of these drugs in man Chloroprocaine should be avoided if epidural morphine therapy is used.
	Cisapiride	No clinically relevant interaction are apparent with morphine 20mg cisapiride was found to increase the serum levels of morphine	No clinically relevant interaction are apparent with morphine
	Esmolol	Morphine can rise the serum levels of esmolol	This drug should be use cautiously until more confirmation is known.
	Iproniazid & Parstelin & Tranylcyclopromine	No changes in BP, PR and state of awareness when given as test doses of up to 4mg morphine or test doses of up to 40mg pethidine (Meperidine)	Naloxone proved to be a rapid and effective treatment in one of the cases cited.
	Isocarboxazid and MAOIs (Phenelzine)	Increases in levels of 5-HT within the brain causing the serotonin syndrome	It would be imprudent to give pethidine to anyone an MAOIs or shortly after it has stopped. unless they are known not to be sensitive.
	Ketamine	The respiratory depressant effects of ketamine and morphine may be additive	Ketamine is a respiratory depressant like morphine but less potent and its effects can be additive with morphine
	Mexiletine	Absorption of mexiletine is depressed in patients following a MI and depressed and delayed if used concurrently.	This can limit its value as an anti-arrhythmic agent during the first few hours following an interaction.
	Moclobemide	Mechanism is Unknown	Moclobemide was stopped on the morning of surgery in a patient who was anaesthetized with propofol and later isoflurone in nitrous oxide and oxygen.
	Neuromuscular blockers (Pancuronium bromide)	Hypertension and tachycardia when given pancuronium after induction of anaesthesia with morphine and nitrous oxide and oxygen	Pancuronium can antagonize the vagal tone induced by morphine, thus allowing the BP & heartrate to raise so ketamine can be given which produce additive effect with morphine.
	Promethazine	It has potent sedative effect which would be expected to be additive with CNS depressant effects of the narcotics	Dosage adjustment necessary

Figure 3. Hypothesized opioids receptors have been cloned (μ,δ and Ƙ receptors) in the brain and spinal cord

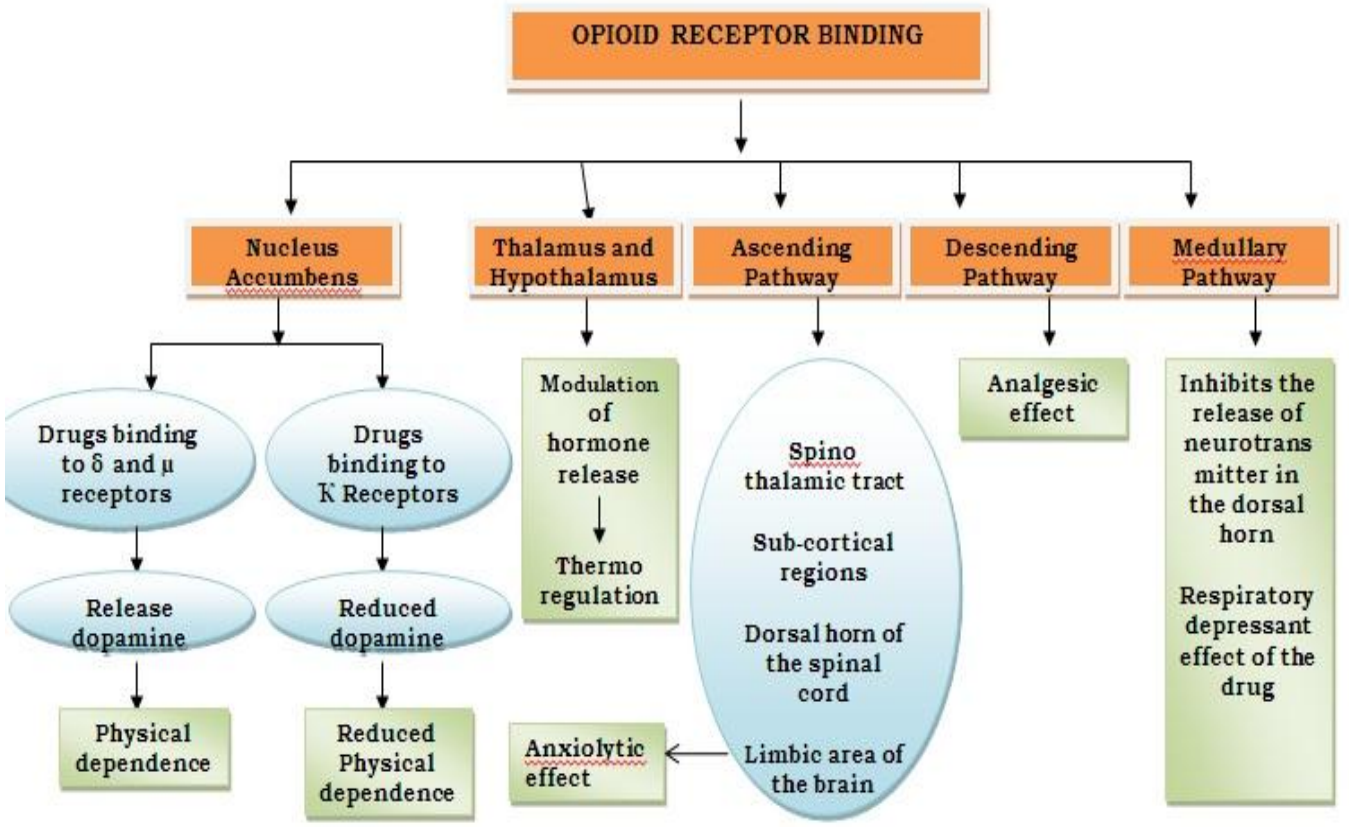

Table 5. Pharmacological therapy for opium poisoning

Antidote	Acute exposure	Nature	Chronic exposure
Naloxone	Buprenorphine, Butorphanol, Dextromethorphan, Heroin, Hydrocodone, Levorphanol, Oxycodone, Oxymorphone, Pentazocine	Semisynthetic	Gradual withdrawl of opiate
	Codeine, Morphine	Natural	Substitution therapy with methadone begun at 30 to 40mg/day, and then gradually tapered off
	Diphenoxylate, Fentanyl, Pethidine (Meperidine), Propoxyphene, Tramadol, Loperamide, Methadone	Synthetic	A beta-adrenergic blocker like propranolol (80mg) is said to be quite effective in relieving the anxiety and craving associated with opiate addiction, but has no effect on physical symptoms. Buprenorphine or naltrexone can also be used
Benzodiazepines	Convulsions	Synthetic	Psychiatric Counseling
Physostigmine Salicylate (0.04mg/kgIV) has been suggest, if opiate antidotes are not available	Respiratory depression	Synthetic	Tranquillizers or bed time sedation if necessary

CONCLUSION

Our review suggested that evidence based management of opium poisoning patients in the hospital and highlights the importance of preventive measure for opium addiction. This can be done through a variety of public policy measures, including regulatory, financial and educational approaches. This is a long-term approach, Due to the mixed cultural in our country, dealing with the sequelae of opium abuse will continue to be a significant challenge in developing countries.

REFERENCES

1. Murgesan MKC, Gunapadam (2003). Siddha Materia Medica Part-I. Indian Medicine- Homeopathy division, (7th ed.), 25-26.n
2. Kokate CK, Purohit AP, Gokhale SB (2004). *Pharmacognosy,* (26th ed.). Nirali Prakashan. pg. 473-475.
3. Atul K, Singh Uppal PP. Concise course in pharmacology and toxicology. (1st ed.), S.Vikas and Company (Medical Publishers), India. pg. 38-40.
4. Wallis TE (2005). *Textbook of Pharmacognosy*. (5th ed), CBS Publishers & Distributors. Newdelhi. pg. 442-445.
5. Aliverdinia and Pridemore (2008). *European Journal of Crime, Criminal Law and Criminal Justice*, 16, 155–170.
6. Varro E. Tyler, Lynn R. Brady, James E Robbers (1988). *Pharmacognosy* (8th ed.) lea & Febiger, Philadelphia, USA Pg. 229-250.
7. Charles RC, Robert ES (2003). Modern pharmacology with clinical application. (6th ed.), 316-319.
8. Opiods and Derivatives (2004). Clinical Toxicology: Principles and Mechanisms, 121-131.
9. Ivan H Stockley (2008). Drug Interactions 8th edition. Pharmaceutical Press, Londan. 62-70.
10. Pillay VV (2010). Textbook of forensic and toxicology (15th ed.), Paras Medical Publisher, India. pg 514-520.
11. Eve Griffin, Paul Corcoran, Linda Cassidy, Amanda O'Carroll, Ivan J Perry (2014). Brendan Bonner. Characteristics of hospital-treated intentional drug overdose in Ireland and Northern Ireland. *BMJ Open*, 4, e005557
12. Asgary S, Sarrafzadegan N, Naderi GA, Rozbehani R. (2008). Effect of opium addiction on new and traditional cardiovascular risk factors: do duration of addiction and route of administration matter? *Lipids in Health and Disease*, 7, 42.
13. Sadeghian S, Graili P, Salarifar M, Karimi AA, Darvish S, Abbasi SH. (2010). Opium consumption in men and diabetes mellitus in women are the most important risk factors of premature coronary artery disease in Iran. *Int J Cardiol*, 141(1), 116-8
14. David S, Patrick T, Anouar T, Nilesh C, James G. (2014). Opioid Use is Associated with Decreased Quality of Life in Patients with Crohn's Disease. *The Saudi Journal of Gastroenterology*, 20 (3), 182-187.
15. Divsalar K, Haghpanah T, Afarinesh M, Mahmoudi ZM. (2010). Opium and Heroin Alter Biochemical Parameters of Human's Serum. *The American Journal of Drug and Alcohol Abuse*, 36, 135–139.
16. Aronson JK. (2006). Meyler's side effects of drugs; the international encyclopedia of adverse drug reactions and interactions (15th ed.) 2386-2387.
17. Mahdi N. (2012). Opium and the Heart: Common Challenges in Investigation. *The Journal of Tehran University Heart Center*, 113-114.
18. Faniya S (2013). Analysis of changes in personality of female opium addicts in correlation with clinical-dynamic characterization of drug morbid attraction. *Medical and Health Science Journal*, 14, 1, 35-39.