REVIEW OF LITERATURE
Chronic pain is a pain that persists longer than normal stipulated time of cure, for which prescription analgesics are the preferred choice of treatment globally. Long-term prescription opioid use for the treatment of chronic pain can lead to abuse and addiction.

**Opiates & Opioids:**

Conventionally, the term ‘opiate’ indicates both naturally occurring substances and semisynthetic drugs which are derived from them (e.g. Heroin), whereas the term ‘opioid’ describes totally synthetic drugs (e.g. pethidine) with similar properties. But with the discovery of opioid receptors, the term ‘opioid’ describes collectively naturally occurring alkaloids, semisynthetic derivatives and totally synthetic drugs.

Discovery of various opioid receptors has helped understanding the mechanism of actions of various opioids a better way. These receptors are specialized sites on the cell membrane, with a very specific shape to which opioids binds. Three major categories of opioid receptors have been identified in various nervous system sites and in other tissues. They are mu (µ), kappa (κ) and delta (δ). A fourth receptor NOP (nociception opioid receptor), has also been identified. It has high sequence homology to these three opioid receptors (µ, δ, κ). Opioids do not bind to NOP receptor with high affinity, although it has structural similarity with opioid receptors. Each of the three major receptors has now been cloned. All are members of G protein-coupled receptor and show significant amino acid sequence homologies. Multiple receptor subtypes have been proposed based on pharmacologic criteria, including µ1, µ2; δ1, δ2; and κ1, κ2, κ3. All the three types of receptors are found on presynaptic nerve terminals and they have inhibitory effect on transmission across synapses, by reducing the release of neurotransmitters. Since an opioid may
function as an agonist, partial agonist or antagonist at more than one receptor subtype, it is expected that these agents are capable of diverse pharmacologic effects. One of the important action of opioids i.e. their ability to induce analgesia but depending on the patient as well as condition, not necessarily the most important action of this class of drugs (loperamide for diarrhoea, codeine for cough…) is mediated by supraspinal activation of µ receptors and by the activation of κ receptors in the spinal cord. Opioids produce analgesic action not only through central action, but also through activation of peripheral opioid receptors by local application which was proven by promising results seen in patients undergoing arthroscopic knee surgery.[19]

Euphoria – a pleasant floating sensation with lessened anxiety and distress, miosis, respiratory depression and decreased gastrointestinal motility are the other opioid effects due to stimulation of µ receptor, whereas stimulation of κ receptor is often associated with dysphoria. The effects of δ stimulation have not been yet fully established.

Endogenous ligands of opioid receptors i.e. the opioid peptides are termed as endogenous opioid peptides. They possess opioid like pharmacological properties. There are three distinct ‘families’ of endogenous opioid peptides. They are 1) the pentapeptide–enkephalins, 2) the endorphins, 3) dynorphin with 31 amino acids. The endogenous opioid peptides are derived from three major precursor proteins: prepro-opiomelanocortin, prepro-enkephalin and prepro-dynorphin. The prepro-opiomelanocortin contains met-enkephalin sequence, beta-endorphin and several non-opioid peptides such as ACTH, beta-lipoproteins and melanocyte-stimulating hormone. Prepro-enkephalin contains six copies of met-enkephalin and one copy of leu-enkephalin. Both of them have slightly higher affinity for δ receptor than for µ receptor. The endogenous peptides endomorphin-1 and endomorphin-2 has high affinity towards µ receptor. These endogenous
opioid peptides are secreted from immunocytes. They occupy opioid receptors on sensory nerves and produce analgesia by inhibiting either the excitability of these nerves or the release of excitatory pro-inflammatory neuropeptides (e.g. substance P). In contrast to the analgesic role of leu- and met-enkephalin, an analgesic action of dynorphin A – through its binding to κ receptor remains controversial. Chronic agonist action at μ or κ receptors can cause tolerance and physical dependence within the neural systems which are affected by these receptors. Thus precipitation of withdrawal syndrome is either due to withdrawal of agonist drug after a long period of administration, or due to its displacement by an antagonist. μ (mu) receptor physical dependence produces severe withdrawal manifestations with intense drug seeking behaviour. There is little cross tolerance between the different receptors so that a drug with κ (kappa) agonist properties cannot suppress the withdrawal syndrome caused by a μ agonist withdrawal. The outstanding property of opioid analgesic is to cure pain. Severe, constant pain is usually relieved with opioids, whereas sharp, intermittent pain does not get controlled effectively by opioids. The pain associated with cancer and other terminal illnesses are effectively treated by using opioid analgesics. The acute, severe pain of renal and biliary colic requires stronger opioids.

There are two components of pain perception. They are nociceptive component and affective component. The nociceptive component is an unpleasant sensation evoked by noxious thermal, chemical or mechanical stimuli and conveyed to CNS by ascending pathways. The chemical stimuli acting on nociceptor to cause pain are substance P, neurokinin A and B, bradykinin, serotonin, histamine, prostaglandins, ATP, and capsaicin. The affective component is the psychological response towards pain and conveyed from CNS to dorsal horn by descending
pathways. There are two types of pain pathways. They are the ascending and descending pathways. The ascending pain pathway transmits pain impulses from the dorsal horn of the spinal cord to the medulla, midbrain, thalamus, limbic structures and cortex. The pain activates the terminals of primary afferent neuron fibres (Aδ & C) which enters the spinal cord. The Aδ fibre alerts the person about the presence and location of intense and sharp somatic pain. Based on this, the person may use withdrawal reflexes to avoid noxious stimuli. The slow conducting C fibres mediate the motivational –affective (mood) response towards dull aching visceral pain (e.g. pain related to myocardial infarction), or burning neuropathic pain (e.g. pain of trigeminal neuralgia, diabetic nephropathy), thereby enable the person to bear with the pain, experience the discomfort and modify his/her emotional reaction to the pain. The descending pain pathway control pain transmission through dorsal horn by applying inhibitory effect on dorsal horn transmission. The descending neuronal tracts from periaqueductal grey (PAG) activate nucleus raphe magnus (NRM), and releases serotonin and enkephalin from NRM at substantia gelatinosa (SG) of dorsal horn to inhibit ascending pain transmission. From loculus ceruleus (LC), there is release of nor-epinephrine that also inhibits pain transmission from dorsal horn.

Opioid analgesics activate the descending PAG, NMR and LC neuronal pathways and also activate opioid receptors in the spinal cord and SG. They reduce both sensory and affective (emotional) components of pain. Neuropathic pain is less responsive to opioids than is nociceptive pain. The analgesic action of opioids is probably due not only to their direct action at one or more sites within the nervous system, but also to the way in which they make pain more tolerable. This in turn is related to the euphoriant effect i.e. their ability to induce a state of
mental detachment and feeling of wellbeing. However, dysphoria, an unpleasant state characterized by restlessness and malaise, may sometimes occur in some individuals.

Opioids also cause sedation, drowsiness and mental clouding. There is little or no amnesia. Sleep is induced by opioids more frequently in the elderly than in young, healthy individuals. In standard analgesic dose, opioid disrupts normal rapid eye ball movement (REM).

All the opioid analgesics can produce significant respiratory depression by inhibiting brainstem respiratory mechanisms at medulla. The respiratory depression is dose related and mediated by \( \mu_2 \) receptor. Respiratory depression by opioids is not accompanied by depression of medullary centres controlling CVS functions. Therefore, respiratory depression by opioids is well tolerated. Opioid induced respiratory depression remains one of the most difficult clinical challenges in the treatment of severe pain. Higher doses cause respiratory arrest, unconsciousness and death.

Opioids also control cough by suppression of cough reflex. Suppression of cough reflex occurs at doses lower than that required to produce analgesia or respiratory depression. Codeine particularly has advantage in persons suffering from pathologic cough. However, cough suppression by opioids may allow accumulation of secretions and thus lead to airway obstruction and atelectasis.

The opioid analgesics initially activate the brainstem chemoreceptor trigger zone, later depress vomiting centre. Thereby produce emesis. There is role of vestibular component to nausea as vomiting occurs more frequently in ambulatory patients than in recumbent patients after giving potent opioid analgesic such as morphine.
Constriction of pupils (pin point pupil) is seen with practically all opioid agonists. It is due to $\mu$ and $\kappa$ receptor induced stimulation of third cranial nerve nucleus. It has no direct action on radial or circular muscles of iris. Even in highly tolerant addicts, miosis is seen.

Constipation is a well-recognized effect of opioids which does not diminish with continued use. That means tolerance does not develop to opioid-induced constipation. This action is mediated through $\mu_2$ opioid receptor effect on CNS and also action on enteric nervous system. In the large intestine opioid diminishes propulsive peristaltic waves and increases tone which delays passage of faecal mass and allows increased absorption of water leading to constipation. This action of opioid accounts for their use in antidiarrheal preparation.

Opioids constrict the urinary sphincter causing difficulty in urination (true for mu receptor agonists but not for kappa receptor agonists); on the other hand contract the detrusor muscle, causing urgency to urinate, which often is very troublesome to the patient. $\mu$ Opioids have been found to have antidiuretic effect in humans. Opioids also enhance renal tubular sodium reabsorption.

According to WHO, tolerance\cite{20} is ‘a reduction in the sensitivity to a drug following its repeated administration in which increased doses are required to produce the same magnitude of effect previously produced by a smaller dose’. Although development of tolerance begins with the first dose of an opioid, tolerance normally does not become clinically apparent until after 2-3 weeks of frequent exposure to therapeutic doses. However ultra-potent opioid remifentanil have been shown to induce tolerance within hours. A very high degree of tolerance develops to the actions
of opioids that cause analgesia, mental clouding and respiratory depression (slow and shallow breathing) so that these effects of opiates are not apparent even when the individual is consuming a very high daily dose—as long as that dose level has been reached gradually. It is possible to produce respiratory arrest in a non-tolerant person with a dose of 60mg of morphine, whereas in addicts who are maximally tolerant to opioids, as much as 2000 mg of morphine taken over a period of 2-3 hour may not produce significant respiratory depression. Tolerance to sedating and respiratory effects of the opiates dissipates within a few days after the drugs are discontinued. Tolerance to emetic effect may persist for several months after withdrawal of drug. The degree of tolerance and rate of its development as well as disappearance differ among different opioid analgesics and among individuals using the same drug, for e.g., tolerance to methadone develops more slowly and to a lesser degree than to morphine. However, little or no tolerance develops to the action of opiates on the pupil of the eye or on the bowl so that the same individual usually displays a typically constricted pupil and suffers from constipation as well as to convulsing effect. Cross tolerance develops between different opioids. That means if an individual has become tolerant to the effects of heroin, he or she can take large doses of any other opiate but not of other classes of drugs. If heroin is withdrawn, the resulting abstinence syndrome can be relieved by the administration of any opiate but not by any other type or class of drug. Morphine and its congener’s exhibit cross tolerance not only with respect to their analgesic actions but also to their euphoriants, sedative and respiratory effects. However the cross tolerance existing among the μ receptor agonists can often be partial or incomplete. This clinical observation has led to the concept of opioid rotation, which has been used in the treatment of cancer pain. A patient who is experiencing decreasing effects of one opioid analgesics is rotated to a different opioids (morphine to hydromorphone) thereby experiences significantly improved analgesia at a reduced
overall equivalent dosage. Another attitude is to ‘recouple’ opioid receptor function through the use of adjunctive nonopioid agents. NMDA receptor antagonists (ketamine) have shown promise in preventing or reversing opioid induced tolerance in both animals and humans. The novel use of δ receptor antagonist with μ receptor agonist is also emerging as a strategy to avoid the development of tolerance.

Physical dependence is ‘an adaptive state manifested by intense physical disturbances when the drug is withdrawn’. The development and severity of physical dependence on opioids depends on the particular opioid being taken, the dose and the duration of chronic administration; but becomes apparent only if regular administration of the drug ceases. While opioids are being taken there is no subjective evidence of the existence or the severity of physical dependence. The symptoms and signs of the abstinence syndrome develop if the drug administration is interrupted, or in the presence of antagonists. Severity of abstinence syndrome is a measure of degree of physical dependence. As tolerance to opioids develops, the daily dose is increased, and the severity of dependence increases too. Beyond its ceiling effect, further increase of dose has little effect on the degree of physical dependence. Degree of physical dependence varies from opioid to opioid. Codeine and Dextropropoxyphene, even in high dosage, do not cause physical dependence to match that caused by morphine or heroin.

The signs and symptoms of opioid abstinence syndrome are graded from grade 0 to grade 3, depending on the severity. These are importantly drug craving, anxiety, drug seeking behaviour, running eye and noses, restless sleep, gooseflesh, muscle twitching, hot and cold flushes, loss of appetite, irritability, increased pulse as well as respiratory rate, weight loss etc. The time of
onset, severity and duration of abstinence syndrome depend on the drug previously used and biological half-life of opioid. An opioid with short duration of action, such as heroin, has an abstinence syndrome of earlier onset, shorter duration and greater intensity than the longer acting drug like methadone. Intensity of signs as well as symptoms of withdrawal increases with increased dosage of opioids. With morphine or heroin, withdrawal signs usually start within 6-10 hours after the last dose. Peak effects are seen at 36-48 hours, after which most of the signs and symptoms gradually subside. By 5 days, most of the effects have disappeared, but some may persist for months. In case of meperidine, the withdrawal syndrome largely subsides, within 24 hours, whereas with methadone several days are required to reach the peak of the abstinence syndrome, and it may last as long as 2 weeks. The slower subsidence of methadone effects is associated with a less intense immediate syndrome, which is reason for its use in the detoxification of heroin addicts. A transient abstinence syndrome can be induced in a subject physically dependent on opioids by administering naloxone or other antagonist. Within 3 minutes after injection of the antagonist, signs and symptoms similar to those seen after abrupt withdrawal appear, becomes maximum in 10-20 minutes and largely settling after 1 hour.

Psychological dependence is the ‘feeling of satisfaction and a psychic drive that requires periodic or continuous administration of the drug to produce pleasure or to avoid discomfort’.[21] Psychological dependence on opioid is severe & accounts for the desire and craving for drugs that eventually disrupt the addict’s life, which may become wholly devoted to obtaining more drugs. There are various factors that promote compulsive use of opioid drugs. They are euphoria, indifference to stimuli, and sedation. The addict also experiences abdominal effects that have been linked to an intense sexual orgasm.[22] Craving[23] is a fundamental component of psychological dependence and implies a constant preoccupation with the drug with instructive
thoughts and obsessive thinking about everything to do with it—particularly its desired effects and the need to obtain it. When craving is severe, drug seeking behaviour dominates daily activity. Drug seeking behaviour involves literally searching for drugs, different activities—both legal and illegal, to obtain money to buy them, identifying the source of supply, purchasing them etc. Unfortunately, psychological dependence does not end when drug withdrawal has been achieved. It persists long after the abstinence syndrome has been subsided.

The intensity of withdrawal symptoms depends on physical condition of the user, type of drug abused, amount of drug intake and duration of abuse. Feeling of unpleasantness, body aches, pains all over the body, diarrhea, dilated pupil, insomnia are the common withdrawal symptoms of opioids which is discussed earlier. On the other hand, extreme fatigue, voracious appetite, moderate to severe depression, disturbed sleep are prominent withdrawal symptoms of stimulants such as oral amphetamines and snorted cocaine. Depressants such as sedative hypnotics, barbiturates, benzodiazepines, alcohol exhibit tremors, insomnia, irritability, restlessness, hallucinations, convulsions, and delirium tremens as major withdrawal symptoms. Withdrawal symptoms are not reported by hallucinogens such as lysergic acid diethylamide (LSD), phencyclidine, mescaline, psilocybin. While, Loss of appetite, irritability, tremors, sleep disturbances, prominent psychotic symptoms, depression are characterized as important withdrawal symptoms of cannabis/marijuana.

Comorbidity of substance abuse and mental health problems is at the heart of drug abuse in much of the world. Drug use disorders (abuse / dependence) often co-occur with other mental illnesses such as depression, anxiety, or schizophrenia. Population surveys show a high rate of co-
occurrence, or comorbidity, between drug abuse and other mental illnesses. Results from the South African Stress and Health (SASH) Survey shown significant associations between substance use and mood and anxiety disorders, with a particularly strong relationship between cannabis use and mental disorder. The high prevalence of comorbidity between drug use disorders and other mental illnesses does not mean that one caused the other, even if one appeared first. According to reports from NIDA research report series (NIH Publication Number 10-5771, revised September 2010), substances of abuse can cause abusers to experience one or more symptoms of another mental illness. Reports from the Epidemiologic Catchment Area (ECA) study, the National Comorbidity Study (NCS), and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) establishes high prevalence of SUDs in those with mood disorders. Of these, the NESARC survey provides the most comprehensive, up-to-date data on psychiatric comorbidity. On the other hand, mental illnesses can lead to drug abuse. Individuals with overt, mild, or even subclinical mental disorders may abuse drugs in the form of self-medication. Both drug use disorders and mental illnesses are caused by some of the common factors such as overlapping genetic vulnerabilities, underlying brain deficits, etc.

**Global scenario:**

Physicians treating patients for chronic pain have limited means of determining whether a person is taking medications as prescribed or are not consuming extra medication. Over the past few decades, the prescription of opioid analgesics for the treatment of pain has increased globally from 75.5 million to 209.5 million. Estimates from the U.S. National Survey on Drug Use
among Households (NSDUH) from 1990 to 2006, reflect trends of increasing self-reported recent abuse of prescription opioids. Total cost of prescription opioid abuse in the United States was $8.6 billion in 2001 and this continues to grow. Direct health care cost for people who use opioids non-medically alone is more than eight times than those who do not use them for non-medical purposes. There are two major population based surveys on college students and younger adults of US population, which also supports the trends in increasing pattern of prescription opioid abuse among them. They are ‘National Household Survey on Drug Abuse’ (NHSDA) and ‘Monitoring The Future’ (MTF). The NHSDA, conducted by the Office of Applied Studies, Substance Abuse and Mental Health Services Administration, surveys a representative sample of households aged 12 years and older in the United States. On the other hand, the MTF study, which was conducted by the University of Michigan, with funding from the National Institute on Drug Abuse (NIDA), is an on-going study of the behaviours, attitudes, and values of American secondary school students, college students, and young adults since 1975. In 1991, the study was expanded to include 8th and 10th graders from representative samples of middle schools and high schools.

Based on the 1997 National Household Survey on Drug Abuse, it is estimated that 36.5 per cent of the Nation’s household population aged 12 and older, had used an illicit drug at least once in their lives and 13.9 million people had used an illicit drug sometime in the month prior to the survey. According to report, 60 per cent had used only marijuana, 20 per cent had used marijuana and some other illicit drug, and 20 per cent had used a drug other than marijuana in past month. 1997 NHSDA showed that a prescription opioid – codeine was the most prevalent illicit drug used, after marijuana. Illicit use of analgesics, hallucinogens, inhalants, and
stimulants were also reported. This study also reported that illicit codeine use among those ages 12 and older has consistently been much higher for males than for females among US population. 30 per cent of the household population aged 12 and above, reported smoking cigarettes within the month prior to the 1997 NHSDA. The mean age at which persons started use of marijuana, cocaine, inhalants, hallucinogens, heroin, and daily cigarette smoking has decreased over time since the survey began, whereas the mean age of first use of alcohol and cigarettes has remained stable. [31] Apprehension for drug use among young people is supported by the findings from the December 1998 Community Epidemiology Work Group (CEWG) meeting, which is the major national surveillance system in the US, supported by NIDA. According to their report benzodiazepines and codeine (prescription opioid) abuse are emerging in US populations. Benzodiazepines abuse has been reported in Boston, Chicago, San Francisco, Seattle, and Texas and is used by heroin addicts mainly. On the other hand in Boston, Detroit, San Diego, San Francisco, and in Texas, codeine abuse is emerging as a major problem. Comparative data on 8th, 10th, and 12th grade students surveyed in 1997 and 1998 in the Monitoring the Future (MTF) Study reported a decrease in the proportions of young people using most illicit drugs including prescription opioids; the exceptions were crack cocaine and tranquilizers.

According to the MTF study, in 2009, hydrocodone was the most used substance after alcohol & marijuana among 12th grade students in United States and although its use fell significantly in 2010 to 8%, hydrocodone remains one of the most widely used illicit drugs among 12th graders. Whereas in 2008, methadone was implicated as the principal drug in 27 per cent of drug- related deaths among 16-24 year-olds in the United Kingdom.
In 1975, when MTF began, 55% of young people had used an illicit drug by the time they left high school. This figure increases to 66% in 1981 then declined to 41% in 1992. From there it rose to 55% in 1999, and then declined gradually to 47% in 2007 through 2009, and stands at 49% in 2012. There has been no significant change in use of other illicit drugs between 2011 and 2012. But, heroin use without using a needle declined significantly in 8th (down by 0.3%) and 12th grades (down by 0.4%), and remained unchanged in 10th grade in 2012.

MTF-2012 report also revealed that there is sharp increase in the use of narcotic drugs i.e. prescription opioids other than heroin in recent years. Significant use is reported only in 12th grade, because researchers considered that the data from 8th and 10th graders to be of questionable validity. Increase in OxyContin use observed in all grades from 2002 (when it was first measured) through 2011. MTF-2012 reported an increase in OxyContin use in all grades from 2002 through 2011. MTF-2014 reported a significant drop in OxyContin use among the 8th graders. Annual prevalence in 2014 was 1.0%, 3.0%, and 3.3% in grades 8, 10, and 12, respectively. On the other hand, use of Vicodin, remained fairly steady at somewhat higher levels since 2002, until its use declined after 2009 in all three grades till date. MTF-2014 reported declining use of number of illicit & licit substances, this decline is mainly due to a decrease in annual prevalence of marijuana in 8th, 10th, and 12th graders.

Other than younger adults, women drug abusers are more likely than men to report psychiatric problems, (mental disturbances, suicidal behaviour) and histories of ‘physical, emotional, and/or sexual abuse’ which put them at greater risk of abuse of drugs. A retrospective study
by Traci C Green et al.\textsuperscript{[13]} on participants of 18 years and older attending substance abuse treatment centres across the United States, who completed the Addiction Severity Index-Multimedia Version\textsuperscript{®} (ASI-MV\textsuperscript{®}) Connect, revealed that there are gender differences persists at the most fundamental levels of prescription opioid use and abuse and women were more likely than men to report use of any prescription opioid in the past 30 days (29.8\% females vs. 21.1\% males, \(p<0.001\)) as well as abuse of prescription opioids in the past 30 days (15.4\% females vs. 11.1\% males, \(p<0.001\)). A Canadian study suggests that women between 12-16 years old in detention compare to men in detention of the same age are more likely to report injecting prescription opioids.\textsuperscript{[35]}

Non-medical use of prescription opioids remains a major problem in the Americas. According to world drug report 2011, there are over 40 per cent of global opioid users in North America. This is because there is widespread non-medical use of prescription opioids in the North America which rose between 2002 and 2006, then fell was recorded until 2008 and rose again in 2009. In 2006, a behavioural surveillance study in Canada, reported injection morphine use in Canada.\textsuperscript{[36]} In 2009, 1.9 million people in the USA were diagnosed with substance abuse or dependence on prescription opioids and prescription opioid misuse was reported at 0.5\% in Canada.\textsuperscript{[37]} In US, the non-medical use of prescription opioids (4.9\%) now show higher annual prevalence rate than cocaine (1.9\%). Among prescription opioids, oxycodone’s non-medical use was reported to rise since 2005 in US and it was also observed that codeine based preparations are among the commonly abused prescription opioids in south and Central America. World Drug Report 2011 also reported high prevalence of non-medical use of prescription opioid in Costa Rica, Brazil and Chile. Increased incidences of overdoses from prescription opioid by 175\% from 2001 to 2006 in
US has also been reported by both National prescription Drug threat Assessment 2009 report and National Drug threat Assessment 2010 report.[38]

Opium poppy—the parent drug grows largely in the South-East Asia and Middle-East i.e. Afghanistan, Iran, Myanmar, Thailand, Turkey etc. as well as in other parts of the world. Opium crop failure due to a disease of the opium poppy in Afghanistan in 2010 as well as heroin shortage in some European countries in 2010-11 might be the possible reasons for rapid build-up of parallel illicit market for prescription opioids. This encourages users to shift from heroin to other substances like desomorphine, acetylated opium and prescription opioids such as fentanyl and buprenorphine. Replacement of heroin by fentanyl was reported by Russian federations. [8] According to UNODC report, opioids remains the dominant drug type accounting for treatment demand both in Asia and Europe.

According to annual report 2010 of European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [39], among European countries, only Denmark, Estonia and Finland show substantial non-medical use of prescription opioids than heroin, whereas benzodiazepines are the commonly abused there. Northern Ireland reports highest abuse of prescription opioids. Some of the European countries such as Estonia and Finland reported incidences of shift from heroin to prescription opioid mainly fentanyl and buprenorphine. EMCDDA annual report 2015 indicated high substance abuse related admission due to prescription opioids. A 75 percent of substance abuse related admission due to fentanyl in Estonia and 58 percent of drug abuse related admission due to buprenorphine in Finland were reported. [40]
According to UNODC report, seven out of fifty four African states reported an increasing trend in the use of opioids and opioid along with cannabis were the two main substances contributing to demand for treatment for illicit drug use. In South Africa, an average of 6.9% of people at substance abuse treatment reported prescription opioid as either their primary or secondary substance of abuse. Annual Reports questionnaire (ARQ) data by UNODC evidenced non-medical use of buprenorphine and pentazocine in Africa.

2012 World drug report indicated that cannabis, opioid (mainly heroin) and amphetamine type stimulant (ATS) are the major substance of abuse in Asia and there is an increasing trends of non-medical use of synthetic prescription drugs in Middle East. NIDA, UNODC and SAMHSA reports identified several drug use characteristics in Middle East such as decreasing age of starting drug use, increasing number of IDUs, more women drug users, contribution towards spread of HIV/AIDS.

Population based survey in Taiwan from 2002 to 2007 reported increased consumption of transdermal fentanyl and oral morphine. The first national study on secular trends and characteristics of pethidine use in Taiwan conducted during 2002-2007, observes declining trends in the prevalence of pethidine users. An increasing proportion of pethidine prescriptions from clinics, outpatient settings and operation patients with cancer diagnoses was also noted. Similar trend of pethidine use was also reported in Israel from 2000-2008. Nepal which shares border with India, also reported significant use of prescription opioids such as dextropropoxyphene, buprenorphine and propoxyphene non medically. According to Mapping and Size Estimation of Most at Risk Population survey, Nepal reported 30,000-34,000
(nearly 0.18 per cent of the adult population) injecting drug users among which most of them uses buprenorphine and propoxyphene non medically.\[47\]

**Indian scenario:**

Historical aspects:-

The traditional drugs of use in India were cannabis (bhang, ganja) and opium since ancient times. Their use has been continuing in rural areas of northern states of India. The Indian Hemp Drugs commission reviewed and discussed medical evidence given by 335 physicians throughout India from Bengal, Assam, North-Western Provinces, Punjab, Central Provinces, Madras, Bombay, Sind, Burma, and Berar regarding physical, mental and moral effects of marijuana. The Indian Hemp Commission Report (1893-94) states that occasional bhang use was almost universal in India and only 5% of the regular users were heavy users. In last few decades, there is rapid increase in the use of alcohol, tobacco and drugs. Since early 80’s, heroin brown sugar effectively displaces opium and cannabis as the major substance of abuse. This was mainly due to stringent effects of Narcotics and Psychotropic Substances act 1985.\[48\] India ranks second to Afghanistan in licit production of opium. Opium was transported to India in the ninth century by Arab traders via the west coast and was primarily used for the medicinal purposes. By the next century, its use spreads all over the country. By the end of 14th century along the west coast at Cambay and Malwa full production and cultivation of opium has started. By 1757, the British East India Company started increasing revenue by cultivating opium mainly in Bengal. By the early 80’s India became the main opium producing country and became the only supplier of licit opium for the world’s requirements. Legally cultivated opium was being diverted and converted
into heroin by the 80’s-90. In the beginning of 90’s there were nearly five million opium addicts and 750,000 to one million heroin addicts in India. ICMR bulletin\textsuperscript{[49]} also reports that since ancient times, opium was being used by wrestlers in battle fields to increase physical strength. This bulletin also states that in industrial areas of Kolkata, Mumbai, women factory workers used to give opium mixed with sweets to their children’s to keep them docile. Opium is often mentioned in the Materia Medica section of Sharangadhar Samhita and Bhavaprakash and found in eight Ayurveda preparations such as Karpua rasa, Ahiphenasava, Brihat Gangadhar churna, Markandeya churna, Dugdha vati, Grahanikapta rasa (Rasendra sara sangraha), Akrakaravadi churna (Sarangadhara) and Sambhunath rasa (Bhaishajya tantra) in last two centuries. In the 19\textsuperscript{th} century, smoking of opium became popular in India compare to oral consumption of it. By 1959, the sale as well as consumption of opium was completely prohibited by the government of India except for registered addicts. Various other substances other than opium, such as hypnotics, sedatives, stimulants, hallucinogens were being popular among younger population by the latter half of twentieth century. During the late 1980’s and early 1990’s, buprenorphine became very popular and its injectable form became popular throughout India.\textsuperscript{[49]}

Indian epidemiological studies:

There are four major national surveys and five thematic studies which were carried out among general populations of India to determine the prevalence and pattern of major substance of abuse including prescription opioids amongst them. Each study differ in methodology.
Among these the first systemic study done on Indian population was National Household Survey on Drug and alcohol abuse (2000-2001). The National Household Survey (NHS) determines the prevalence of lifetime as well as current abuse of various licit and illicit substances for the country as a whole and studies the socio demographic correlates of drug abuse, where data were collected from 40,697 males aged 12-60 years in 25 states of India. National Household Survey on Drug and Alcohol Abuse, Government of India, observed the prevalence of opioids abuse of 0.7% after alcohol (21.4%) and cannabis (3%) among adult males.\(^{15}\) The second major survey was National Family Health Survey (NFHS). It is a house to house survey. NFHS-3 (2005-2006) did not provide any information on prescription opioid abuse, whereas it provides information only about alcohol and tobacco use.\(^{50}\)

The Drug abuse monitoring system (DAMS) evaluated the primary substance of abuse in inpatient treatment centres (de-addiction centres) which were funded by Ministry of Social Justice and Empowerment, Ministry of Health and family Welfare as well as various NGO’s. They reported that alcohol (43.9%) was the major substance of abuse (n=16942) followed by opioids (26%). 14 per cent had used drugs through the injecting route at some point in time and about 9 per cent could be called current (used within last month) IDUs.\(^{15}\)

The Rapid Situation Assessment (RSA) attempted to obtain data from inaccessible drug users in the community. It measures the pattern of substance use. Study was conducted by United Nations Office of Drugs and Crime (UNODC) in 2002 among 4648 drug users in 14 urban areas in India showed that cannabis (40%) was the major substance of abuse followed by alcohol (33%) and opioids (15%). However, the proportion of IDUs was higher in four major metros and Imphal.\(^{16}\)
A Rapid Situation and Response Assessment (RSRA) of drugs and HIV among 5800 male drug users in India revealed that among prescription opioids, injection buprenorphine (76%) was primarily abused followed by propoxyphene (64%).[17]

A Rapid Assessment Survey of 1865 women drug users by 110 NGOs across the country revealed that 25% currently were heroin users, 18% used dextropropoxyphene, 11% used opioid containing cough syrups and 7% used buprenorphine. 25% respondents had history of lifetime injecting drug use. 87% concomitantly used alcohol.[51]

The NHS, DAMS and RAS had unique and exclusive information on various aspects such as socio demographic information, drug use pattern, sexual behaviour and knowledge on AIDS, on drug abuse from the particular city / state / region. Information on reasons for drug use is available from both the NHS and the RAS survey. Detailed information on injecting drug use in the form of reasons of use, reasons for shifting to IDU, frequency of sharing, cleaning habits, etc. is available from the NHS and the RAS surveys.

There are five focused thematic studies which were carried out on Indian population. They are Drug Abuse among Women, Burden on Women due to Drug Abuse by Family Members, Drug Abuse among Rural Population, Availability and Consumption of Drugs in Border Areas and Drug Abuse among Prison Population.
The study on Drug Abuse among Women studied individual characteristics, household characteristics and social support systems available to and accessed by women drug users from Delhi, Mumbai and Mizoram (Aizawl). This study included 75 women drug abusers enrolled in a snowball sampling technique from these cities. The Mumbai sample consisted of women drug users involved in sex work, the Delhi sample comprised mostly working women, and the Aizwal sample was constituted by women drug abusers in treatment. The women were mostly in their 3rd and 4th decades. Half the respondents from Mumbai and Delhi were illiterate. Very few had received any technical or professional training. Thirty one per cent of the women across the sites were single, 32% were separated or divorced. While a majority of women from Aizawl lived with their families of origin, Mumbai had a large number of women who had run away from home at an early age and were entrapped in the flesh trade. Friends had introduced drugs initially to 48% of the respondents, whereas in 16%, introduction to drug use was by the husband or partner. Thirteen per cent of women from Mumbai reported initiation of drug use on account of humiliation, shame, anger and powerlessness as a response to their situation. With the married women from Delhi, marital conflict and abuse of prescription pharmaceuticals (including prescription opioids) was a common initiation factor of drug abuse. Most of the women were using heroin or brown sugar. Other common or concomitant drugs of abuse were propoxyphene, alcohol, tranquilizers, cough syrups and cannabis. Propoxyphene was most preferred substance of abuse in Aizawl. IDU was reported in 41% among respondents. Study also stated that women from Aizawl who injected propoxyphene for their peers were able to receive their drug supply in exchange for ‘fixing’ their peers. Injecting drug users from Mizoram were regularly hospitalised for overdose and treatment of abscesses. There was reporting incidences of both physical and psychological problems associated with their drug use. About 10 had suffered miscarriages or
undergone medical terminations due to their drug use. Among Aizawl women, family cohesion was better than women respondents of Delhi and Mumbai. Domestic violence was often reported by non-drug abusing husbands of the women. Sexual intimacy within the relationship was reported as poor, as was emotional closeness. The drug abusing women received little support from their relatives, husbands or friends. In all three cities, specific issues that interfered with treatment included concerns for children unattended at home, fear of exploitation, fear of withdrawal, and a lack of supportive systems.

In the study on Burden on Women due to Drug Abuse by family members, adult women who were living with an affected close family member who was a current regular user of drug(s) (opioid and prescription opioids) other than exclusively alcohol or tobacco from various treatment centres, community or workplace of nine Indian cities were interviewed. This study indicated that women, both as substance users and partners of users were vulnerable to HIV infection through the sexual route.

Another thematic study on Availability and Consumption of Drugs in Indian Border Areas explored drug trafficking across the international borders of India (three sites at India - Pakistan border and one site at India – Nepal border, one site at India – Bangladesh border, one site at India – Srilanka border, two sites at India – Myanmar border) and availability and consumption of various drugs in these border areas. It examined both supply and demand of various drugs in these sites. Study revealed that 40 per cent reported using drugs through injectable routes. Injecting drug use was reported mostly from Tuensang (Nagaland) and Moreh (Manipur) on the Indo-Myanmar border. There were a few IDUs at Tuticorin (Tamil Nadu)-Indo-Sri Lankan
border, Sonauli (Uttar Pradesh) on the Indo-Nepal border and Lalgola, (West Bengal) on the Indo-Bangladesh border. The primary drug of abuse in Tuensang, Moreh and Attari (Punjab, Indo-Pakistan border) was heroin and propoxyphene. At times of inadequacy due to mainly heroin drought or escalating cost of heroin, they shift to injectable pharmaceutical drugs. In Tuticorin, pentazocine injection was prevalent. At Sonauli, Lalgola, and to a lesser extent in Attari, injectors used a cocktail of buprenorphine and antihistamines. At Moreh and Tuensang (Indo-Myanmar border), many injectors reported overdose and reuse of syringes and needles. Seizure statistics as well as information from other sources also states that there is rapid increase in the use of the Tamil Nadu shore around Tuticorin as a staging point for heroin shipments to Sri Lanka. According to Narcotic Control Board, geographical proximity and ethnic links contribute to smuggling between coastal southern India, especially the southern Coromandel Coast and the north-western coast of Sri Lanka by sea, mainly by small craft. The smuggling of pharmaceuticals from India, especially prescription opioids such as dextropropoxyphene, injectable buprenorphine, and codeine based cough syrups as well as diazepam and nitrazepam is a major concern for India’s neighbours, particularly Bangladesh, Nepal and Sri Lanka. During 2002, law enforcement authorities on the Indian side of the border seized 300,000 bottles of Phensidyl. 

IDU in India was initially acknowledged in the north east states of Manipur and Nagaland, mainly due to their proximity to the ‘Golden Triangle’ –Burma, Thailand, and Cambodia. In the Northeast Indian states of Manipur and Nagaland there has been an on-going HIV epidemic among injecting drug users (IDUs) since the mid-1990s. Of the eight north eastern states – Assam, Meghalaya, Sikkim, Tripura, Arunachal Pradesh, Manipur, Mizoram and Nagaland –the
last four share a common international border with Myanmar, the world’s second largest illicit opium producing country. Heroin – commonly referred to brown sugar, enters the north eastern states from their respective borders with other Indian states as well as from Myanmar. Ephedrine, a precursor for the manufacture of Amphetamine Type Stimulants also moves into Myanmar from India. In mid-2006 a cross-sectional survey among 200 injecting drug users (IDUs) was undertaken in collaboration with local NGOs in (Imphal) Manipur and (Dimapur) Nagaland. According to their study, the primary drug of abuse was injection dextropropoxyphene (spasmoproxyvon) (65.5%), followed by heroin (30.5%). This study also states that injection drug use started at 20 years of age and there were evidences of significant peer influence. Among North East Indian states, Manipur has high prevalence of HIV among IDUs as evidenced by a study conducted by Agarwal AK et al.[54] where 100 blood samples were collected from Manipuri women of which seven were migrant from Myanmar. The HIV prevalence among IDU community sex workers of Manipur was found to be 9.4 times higher than non IDU community sex workers.

**Information from Sikkim:**

Sikkim, a small mountainous state in the eastern Himalayas, observed great changes in its political structure, social structure, economic life and cultural values during the past hundred years. The state borders Nepal to the west, China's Tibet Autonomous Region to the north and east, and Bhutan to the southeast. The Indian state of West Bengal lies to the south. Sikkim with a population of 6.11 lakh [55] is a multi-ethnic state, inhabited by ethnic population of Lepchas, Bhutias and Nepalese. Lepchas are traditional inhabitants of Sikkim, whereas Bhutias and
Nepalese (approximately 70% of Sikkim’s population) have migrated from Tibet and Nepal, respectively. Sikkim was annexed to India as its 22nd state in 1975. As a result, a lot of migration took place from other parts of India, with introduction of new substances of abuse including prescription opioids. A retrospective study by Bhalla et al [56] on patients with history of current drug use seeking emergency services for any medical or surgical consequence incident to substance abuse in Sikkim from July 2000 to June 2005 revealed that the primary substance of abuse was alcohol (77.8%), followed by opioids (14.8%) mainly injection dextropropoxyphene and pentazocine. National Family Health Survey-3 (2005-06) by Govt. of India has shown a significant increase in alcohol abuse in Sikkim among both males (45.4%) and females (19.1%) of 15-49 yrs. age group from its previous report of NFHS-2. In order to control or regulate the use of drug and controlled substances with abuse potential being misused by addicts and traffickers, to make stringent provision to deal with the ever increasing phenomena abuse of medicinal preparations -‘Sikkim anti-drug Acts (SADA)’ was launched in 2006. There are many reports of arrests under SADA Act from both rural as well as urban areas of Sikkim, for consuming or carrying illicit substances including prescription opioids, barbiturates etc. This also shows a growing trend towards alcohol and drug abuse and addiction.