Review Article

Opioid Therapy and its Side Effects: A Review

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Introduction

"Then Helen, Zeus' daughter, bethought her of another matter. She drugged the wine with an herb that banishes all care, sorrow, and ill humor. Whoever drinks wine thus drugged cannot shed a single tear all the rest of the day, not even though his father and mother both of them drop down dead, or he sees a brother or a son hewn in pieces before his very eyes. This drug, of such sovereign power and virtue, had been given to Helen by Polydamna wife of Thon, a woman of Egypt, where there grow all sorts of herbs, some good to put into the mixing-bowl and others poisonous. Moreover, everyone in the whole country is a skilled physician, for they are of the race of Paeeon."

HOMER, THE ODYSSEY, Book IV

The earliest medical use of opium possibly refers back to around 3500 BCE by Sumerians.[1,2] They called it Hul Gil, which means the "joy plant".[1] Opium is an air-dried milky exudate obtained by incising the unripe capsules of the opium poppy, *Papaver somniferum* (Papaveraceae), one of the oldest medicinal plants.[3] The knowledge of opium passes from Sumerians through Assyrians and Babylonians to the Egyptians. The descriptions found on the Egyptian Ebers Papyrus (1500 BCE) shows the application of opium seeds as a remedy to prevent excessive crying of children and treatment of pain.[2,4] The word opium has been suggested to be of Greek origin, from "*opos*" (juice) and "*opion*" (poppy juice).[1] Homer, the Greek author of "The Odyssey" refers to opium as an intoxicating, pain-relieving and sleep inducing substance in around 850 BCE. Hippocrates (460–377 BCE) has also mentioned the poppy juice in opium wine in his drafts.[1]

Opium is one of the 41 ingredients in Mithridatium, "a universal antidote to all poisons", made by Mithridates VI, king of Pontus in 120 BCE.[5] He became king at the age of 13 after his father was assassinated by poisoning. He sought a compound of different antidotes to protect himself against all poisons and he finally came up with Mithridatium.[5] The formula has been changed with some modification, including addition of viper's flesh and a higher percentage of opium, by Andromachus, Nero's physician, and named as Andromachus Theriac comprising 55 ingredients. Theriac is of Greek origin, meaning "from wild animal" which has become synonymous with panacea or universal antidote in some other languages. In the second century CE, Galen, the physician of great Roman Emperor Marcus Aurelius, inherited the formula from his predecessor and named it Galene, which means "tranquility".[5] The Antidiarrheal qualities of opium were mentioned by the great Persian physician and philosopher Avicenna (980–1037 CE). Avicenna has reported opium use, as *narcotic,* was so common in Khorasan (northeast of Iran) and Bokhara (southwest of Uzbekistan) in his time.[6] He became the father of "soothing syrups" by advising "to mix some poppy with food of children, who do not sleep properly".[6,7] Arab travelers brought opium to China (and India) during the later T'ang Dynasty (618–907 CE).[6] At that time, Chinese elites used opium mainly to control dysentery.[1] Sometimes between the tenth and thirteenth centuries, opium made its way from Asia Minor to Europe. Paracelsus (1493 – 1541), introduced a concoction of deodorized opium tincture "laudanum" (from Latin *laudare* – to praise) as an analgesic and shortly after, Sydenham (1624–1689) reintroduced Mithridatium (Venetian Treacle) as a therapy for the plague in England.[1,5]

The opium puppy is an annual herb with an erect stem containing five to eight capsules with a white, red, or purplish flower on their top, depending on the opium puppy variety (*album*, *nigrum* or *glabrum*). For example, the variety *album* has white seed and flower and is mainly cultivated in India.[1] A white latex oozes on incision of any part of the plant. To collect opium, ripening capsules are incised with several incisions, often horizontally, by a single three- to six-bladed knife. The exuded milky latex rapidly darkens to a brownish or blackish color on air exposure and becomes solid, which is called "raw opium" after collection. This raw opium is dried further at a temperature not exceeding 70°C and powdered, for medical use. Powdered opium should contain 10 to 10.5 percent of anhydrous morphine.[8] The International Narcotics Control Board of the United Nations has regulated cultivation and production of opium poppy and presently, India is the only country that produces opium to meet the world's medical need of opium. Other countries like Australia, France, Spain, Ukraine and Turkey are authorized to cultivate opium poppy exclusively for its seed and straws.[1]

Opium is a mixture of several chemical substances. It is comprised of two major parts; nonalkaloidal constituents including water (5–20%), sugar (20%) and several simple organic acids, the principal one being meconic acid (poppy acid; 3–5%),

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a dicarboxylic acid; and alkaloids (alkali-like), which are weak "salifyable" basic compounds, present mainly in form of meconic (or other simple plant acid) salts, comprising 25% of the opium structure. Although there are more than 40 different alkaloids in opium structure, almost all quantitative alkaloid content of opium is comprised of six alkaloids, including: Morphine (4–21%); Codeine (0.8–2.5%); Thebaine (0.5–2.0%); Papaverine (0.5–2.5%); Noscapine (Narcotine; 4–8%); and Narceine (0.1–2%).[1,3] Further to basic properties, only morphine and narceine display acidic properties, due to the tertiary amine in their molecular structure.[3]

Morphine (from Morpheus- Greek god of dreams) is the first alkaloid that was isolated from opium by Friedrich Wilhelm Adam Serturner, in 1817.[2] Morphine seems to be the most potent analgesic, narcotic, euphoric, and addictive alkaloid with the most diverse effects among other alkaloids and it is responsible for almost all prototypic opioid effects such as analgesia, euphoria, mental clouding, sedation, pupillary miosis (oculomotor nerve parasympathetic stimulation), respiratory depression and cough suppression, antidiuresis and urinary retention, nausea and vomiting, bradycardia and vasodilation, constipation and biliary retention, and histamine release.[3,9] During the 1830s, morphine became a very common analgesic and during the American Civil War, its use increased along with the use of opium tincture and opium powder. The Civil War left many wounded veterans addicted to morphine, to the extent that the name "soldier disease" was coined to call the dependence of these soldiers on the drug. Consequently, scientists tried to find a more potent and non-addictive derivative of opium. In 1874, a British pharmacist, Alder Wright, synthesized diacetylmorphine (diamorphine) through acetylation of morphine, seeking a non-addictive alternative to morphine. He called it "heroin" because of its "heroic" qualities as an analgesic. Unfortunately, this product showed much higher addictive capacities with the same analgesic potency.[2,9]

Codeine has valuable antitussive action and can also produce a morphine-like analgesic effect, though at one-tenth of morphine's potency.[3] The analgesic effect of codeine could be explained by the conversion of 10% of administered codeine to morphine through O-demethylation process.[1] Thebaine is almost devoid of analgesic effect and has mixed morphine agonist-antagonist effects. However, thebaine can be used as a substrate to produce other semisynthetic derivatives.[3] Although Papaverine has little or no analgesic or hypnotic properties, it directly relaxes smooth muscles, independent of muscle innervation, especially in larger blood vessels, including coronary, systemic peripheral, and pulmonary arteries. It can also depress electrical conduction and irritability of myocardium, as well as prolonging myocardial refractory period.[1,3] The original name of Narcotine was changed to Noscapine due to the absence of narcotic and analgesic properties in this alkaloid. However, Noscapine has good antitussive activity and probable antitumor properties, through binding to tubulin and consequently, arresting tumor cells at mitosis.[3]

At the present time, apart from a very limited application of some opium compounds-- "Laudanum" (deodorized opium tincture), "Paregoric" (camphorated opium tincture with antidiarrheal effects) and Papaveretum (opium concentratum used as an operative analgesic), opium is medically used only as a starting material. Instead, opium's purified alkaloids (morphine and codeine) and their semisynthetic derivatives (oxymorphone, oxycodone, hydromorphone, hydrocodone) as well as wholly synthetic opioids (mepridine, methadone, fentanyl, pentazocine) are largely used.[1,8] Opioids (or opiates) are used for treatment of different medical conditions like diarrhea and cough, but they are mainly used to relief pain as analgesics. Opioids are used as analgesics in anesthesia, acute pain, chronic cancer pain and more recently, unrelieved chronic nonmalignant pain like neuropathic pain, osteoarthritis, back pain, phantom limb pain, and sickle cell anemia ischemic pain. In 1986, the World Health Organization (WHO) introduced a simple recommendation for pain management, which became known as WHO analgesic three-step ladder.[10] The idea is that based on the severity of pain, one should consider adding opioids to the pain management strategy. In this ladder, there are three steps; the first is mild pain which is treated by non-opioid analgesics, including paracetamol and NSAIDs; the second is moderate pain that is treated by adding weak opioids like codeine and tramadol; and the third step is severe pain which can be treated by adding strong opioids like morphine. This ladder was proposed when the drug regulations and the consequent increased stigma and fear, had made the physicians reluctant to prescribe opioids and the patients unnecessarily suffered from pain before dying of incurable diseases. In fact, the goal of such a recommendation was to relieve the pain of terminally ill patients, even if there is a risk of addiction or an inevitable increased risk of mortality.[11] Over the past three decades and after successful management of acute pain and pain due to cancer or terminal diseases, the prescription of opioids for treatment of chronic nonmalignant pain has increased dramatically. For instance, the annual prescriptions of opioids increased from 458 to 591 per 10000 individuals in Canada, from 1991 to 2007.[12] The global opioid/morphine equivalent consumption has also increased from 3.6 to 62.4 mg/capita between 1980 and 2014.[13] Unfortunately, there are several complications related to opioid therapy, such as opioid receptor related side effects, abuse/addiction and aberrant drug-related behaviors leading to increased mortality. For instance, mortality related to prescribed opioid analgesics increased by 3.6 folds from 1999 to 2007, in the United States and an estimated 1.4 to 1.9 million Germans were addicted to prescription drugs in 2009.[14]

Side effects and complications

In 1973, using radiolabeling ligand method, stereospecific opium binding sites (receptors) in the central nervous system were demonstrated.[15–18] The presence of opioid receptors in the human body made the scientists think that there should be some endogenous opioid compounds which use these receptors as their target. In 1975, it was shown that brain extracts contain two pentapeptides (Tyr-Gly-Gly-Phe-Met or Met-enkephalin; and Tyr-Gly-Gly-Phe-Leu or Leu-enkephalin) that inhibit acetylcholine release from nerves innervating the guinea pig ileum.[19–21] Up until now, three distinct families of endogenous opioids, with distinct anatomical distributions and characteristics, have been identified; endorphins, enkephalins, and dynorphins.[1,2] In spite of their common pentapeptide amino-terminal (Tyr-Gly-Gly-Phe-Met/Leu),[1] each family is derived from a specific precursor (proopiomelanocortin for endorphins, proenkephalin for enkephalins and prodynorphin for dynorphins), which is encoded by a distinct gene.[22–24]

In the early 1990s, opioid receptor families were cloned, which made it possible to demonstrate the corresponding mRNA for each

opioid receptor family.[25–30] According to the International Union of Basic and Clinical Pharmacology Receptor Nomenclature Committee (NC-IUPHAR), four classes of opioid receptors are named as follows; mu opioid receptor (MOP), delta opioid receptor (DOP), kappa opioid receptor (KOP) and nociceptin/orphanin FQ (N/OFQ) receptor (NOP).[31] Although there are some overlaps, each endogenous opioid family has the high-affinity interaction with one type of opioid receptors, in a way that endorphins (1 and 2) have the highest affinity to MOP, enkephalins (Leu- and Met-) to DOP, dynorphins to KOP and N/OFQ to NOP.[31,32] Opioid receptors are members of G-inhibitory-protein coupled 7-transmembrane receptor (GPCR) superfamily.[33] The activation of opioid receptors mediates the inhibition of adenylate cyclase, increase in K+ conductance through opening of the potassium channels (induces cellular hyperpolarization) and inhibits the opening of voltage-dependent calcium channels, which subsequently inhibits the release of the excitatory neurotransmitter (e.g. acetylcholine, serotonin, vasoactive intestinal peptide and nitric oxide) and synaptic activity.[1,2,34] Opioid receptors are distributed in two major systems: the central nervous system—brain and spinal medulla; and the enteric nervous system (ENS), which regulates gastrointestinal and urogenital motility.[1,35] Receptors have been found in alveolar cells,[36] immune cells[37] and sertoli cells.[38]

Depending on the receptor localization, the interaction between exogenous opioids and opioid receptors can result in several different effects, either desirable or non-desirable, i.e. side effects or adverse events. Analgesia, as mentioned earlier, is the most important desired effect of exogenous opioids, which results from their interaction with opioid receptors in the central nervous system. The effects can also be categorized into two groups of acute and chronic effects. Acute effects are seen after single dose or a short period of continuous administration of the opioid drug.[8] Among acute effects, analgesia, cough suppression and temporary constipation (to treat diarrhea) are the main medically sought while euphoria and mood elevation are the main non-medically sought effects of exogenous opioids. Other acute effects like drowsiness, nausea and vomiting, loss of appetite, reduced body temperature and urinary retention are opioid-induced side effects. Chronic effects are those resulting from prolonged continuous or frequent drug use. They are mainly the prolongation and exaggeration of acute effects, except for those on CNS die to adaptive capacity of brain, i.e. tolerance.[8] Loss of weight and chronic constipation, for instance, are chronic consequences of loss of appetite and temporary constipation.

Opioid-induced gastrointestinal system adverse events

Although opioid induced constipation (OIC) is the most common adverse event of long term opioid therapy (40%–95%), the adverse events on GI system result in a more generalized condition, which is called the opioid induced bowel dysfunction (OIBD).[4,39,40] A constellation of symptoms comprises the manifestation of OIBD, like dry mouth, gastro-esophageal reflux, vomiting, bloating, abdominal pain, anorexia, hard dry stool, straining to pass bowel movements and incomplete evacuation.[35,40] The innervation of the GI system is comprised of two main parts; visceral afferents, mediating conscious sensation together with autonomous system nerves to the CNS; and second, the enteric nervous system (ENS)—the "brain" of the gut, controlled and regulated by two major plexuses: the myenteric plexus (which controls intestinal motor activity) and the submucosal plexus (which controls secretory and absorptive activity).[35] Mu-, kappa- and delta-opioid receptors are found in the GI tract. While mu-opioid receptors are mainly distributed in myenteric and submucosal neurons, kappa-opioid receptors are localized only in the myenteric plexus.[41] Activation of opioid receptors by opioid administration inhibits secretion of several regulatory neurotransmitters of GI tract, which leads to discoordination of GI tract motility.[34,42] Spastic achalasia-like esophageal dysmotility, for instance, is the result of non-peristaltic esophageal contraction with incomplete relaxation of the lower esophageal sphincter after opioid administration.[43] In the small and large intestine, these imbalances lead to increased segmental contraction and decreased propulsive forward peristalsis, which manifest clinically by constipation, gut spasm and abdominal cramps.[35] Further to GI tract dysmotility, gut secretion is also influenced by opioid administration. The inhibition of acetylcholine release causes decreased saliva production that is clinically perceived as dry mouth.[44] In addition, direct activation of MOP in the ENS inhibits VIP secretion and subsequently decreases pancreaticobiliary secretion and gut absorption and hence, harder and drier stool.[34,45–47] Sphincter dysfunction is another adverse event caused by opioid administration. Although incomplete lower esophageal sphincter relaxation causes spastic achalasia-like symptoms, as mentioned earlier, its decreased tone due to its dysfunction increases the risk of gastroesophageal reflux.[43,48] Incidentally identified common bile duct (CBD) dilatation by abdominal imaging, e.g. ultrasonography, which is mainly representative of malignant diseases in normal population, is a well-known benign phenomenon among long-term opium users, resulting from opioid-induced dysfunction of the sphincter of Oddi.[49–51] Radmard *et al.* showed a significantly increased diameter of CBD in long-term opium users compared to non-users (data not yet published). The constriction of the sphincter of Oddi can also manifest clinically by biliary colic and epigastric discomfort and pain.[35] Opioid-induced nausea and vomiting (OINV) is seen in 9% to 27% of patients.[52,53] Although the exact mechanism is not clearly identified, it is believed that central opioid receptors play the major role.[35]

Despite several other opioid-induced adverse events like nausea and sedation that develop tolerance and decrease in frequency and severity after longer period of use, OIC does not develop tolerance.[54,55] For this reason, further to recommending high fiber and liquid dietary regimens and increasing physical activity, co-prescription of laxatives is an obligation whenever opioid therapy is commenced.[56,57] However, the efficacy of such treatments is limited, mainly because they do not target the mechanism by which opioids cause constipation, like delayed GI transit and secretion.[35] Furthermore, laxatives themselves can cause several GI side-effects, such as bloating and abdominal fullness.[58,59] According to the results of PROBE1 survey, 81% of chronic pain patients treated with opioids experienced constipation, despite concomitant use of laxatives.[40] They found that the constipation was most often reported as severe and that a third of patients had missed, decreased or stopped opioid use due to insupportable bowel movement difficulties.[40] A new class of drugs for treatment of OIC that antagonize only the MOP in the gut wall without antagonizing central opioid receptors, called peripheral acting mu opioid receptor antagonists (PAMORAs), have recently been approved. Methylnaltroxone, the first of these drugs was approved

by FDA in 2008 for OIC treatment in cancer patients and in 2014 in chronic non-cancer pain patients. More recently, oxycodone-naloxone extended release, an agonist-antagonist combined medication for long-term management of chronic non-cancer pain and OIC has been approved.[60] While oxycodone induces both analgesic effect and OIBD through activating central and peripheral opioid receptors, orally taken naloxone antagonizes only the MOP located in the gut wall due to its limited systemic bioavailability (<3%; extensive first-pass hepatic metabolism) and subsequently counteracts the digestive side-effects of oxycodone.[60]

Opioid-induced hormonal changes

Opioid endocrinopathy (OE) is the result of opioid effects on at least two major hormonal systems, the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis. The latter is named as the opioid-induced androgen deficiency (OPIAD).[61–63] Use of opioids decreases the serum levels of several hormones like testosterone (both total and free),[64] estrogen and progesterone,[65,66] luteinizing hormone (LH),[66,67] gonadotrophin releasing hormone (GnRH),[68] dehydroepiandrsoterone (DHEA) and dehydroepiandrsoterone sulfates (DHEAS),[63] adrenocorticotropin hormone (ACTH) and corticotropin-releasing hormone (CRH) and cortisol,[69] and increases the serum levels of growth hormone (GH), thyroid stimulating hormone (TSH)[67] and prolactin (PRL).[70,71] These alterations are reported in both men and women, in all forms of administration, including oral, transdermal, intravenous and intrathecal administration and also among illicit opium users, where the alterations are reversible, either by abstinence or naloxone.[65,72–77] The hormonal side effects of consumption of prescribed opioids or illicit opiates are manifested in men by sexual dysfunction, depression and decreased energy level and in women by oligomenorrhea or amenorrhea.[4,67] While these symptoms are proposed to be associated with the hypogonadism and likely hypogonadotropic hypogonadism, Hallinan *et al.* showed that testosterone levels account for little variance in measures of sexual dysfunction.[78] Notwithstanding, these symptoms can be almost completely resolved by testosterone replacement therapy.[66,79] Opioids can cause hyperglycemia and worsening of diabetes, possibly through decreased insulin secretion. It is also suggested that opioid use can increase the risk of metabolic syndrome through increased insulin resistance and induction of hypogonadism.[67] Finally, opioid administration has been shown to be correlated to osteoporosis and increased risk of pathologic fracture, possibly through androgen-based reduction in bone density.[80–83]

Opioid-induced immunologic alterations

Exogenous and endogenous opioids interact with both innate and adaptive immune systems through both central (hypothalamic-pituitary-adrenal axis and the autonomic nervous system) and peripheral opioid receptors, by influencing cytokine release, as well as direct effects on opioid receptors located on immune cells.[4,37,84,85] While endogenous opioids, like endorphins induce immunoactivation, exogenous opioids have been shown to cause immunosuppression by inhibitory effects on both humoral and cell-mediated immune responses.[4] However, the activation of different opioid receptors might have different and sometimes inverse effects on the immune system. For example, MOP activation decreases NK cell activity, while activation of DOP increases NK cell activity.[4] It seems that different opioids can affect the immune system differently.[86] For instance, methadone has been reported to be less immunosuppressive than morphine.[87] The effect of opioids on the immune system might be able to alter a variety of human body responses involving immune system, such as the response to stress, infection and malignant transformations.[37] It has been reported that opiate consumption in HIV infected patients can be associated with exacerbation of the infection and also increased viral load.[88] The association between opium use and several cancer types, such as esophageal, gastric, laryngeal, lung, bladder and pancreas cancers has been demonstrated in several researches.[89,90] Since pain itself can impair the immune function, treating chronic non-cancer pain by opioids can lose its benefice if satisfactory pain relief is not achieved.

Opioid-induced cardiac adverse events

Through histamine release and subsequent vasodilation, opioid use can be associated with hypotension, which is partially reversed by H1-blockers but completely by naloxone.[4] Parasympathetic stimulation by opioids can be associated with bradycardia and in case of methadone, especially in high doses, can be associated with QT prolongation and torsade de pointes ventricular tachyarrhythmia.[91,92] It has been shown that methadone-related QT prolongation is mainly associated with its (R)-enantiomer which has 50 times more analgesic potency than its (S)-enantiomer.[4] The mechanism by which methadone can cause QT prolongation and torsade de pointes is suggested to be the blockage of human ether-a-go-go-related-gene (hERG) channel.[93] It is therefore recommended to perform routine EKGs for patients treated with methadone and especially be prudent when other drugs and conditions predisposing to QT prolongation, such as CYP3A4 inhibitors and also hypokalemia or diminished liver function are present.[94] The opioids are however supposed to have cardioprotective effects through ischemic preconditioning (IPC), an endogenous protective mechanism, by which a brief period of ischemia or hypoxia protects a cell, e.g. cardiomyocyte, against injury from a subsequent more prolonged stressful insult.[95] It has been shown that this protective mechanism can be mimicked by activation of delta- or kappa-opioid receptors and that the infarct size (area-at-risk of ischemia-reperfusion injury) was significantly reduced by IV or intrathecal morphine preconditioning.[96–98]

Tolerance, physical dependence, abuse and addiction

Tolerance, adaptive changes of the nervous system in the form of "drug-opposite changes", is one of the common complications of opioid therapy. Opioid tolerance develops after repeated administration of opioids and results in reduced analgesic potency over time and the need to increase the dose of opioid to maintain equipotent analgesic effect. Tolerance can be categorized into two major categories: pharmacological (physiological) or learned (psychological). Pharmacological tolerance has two classes: dispositional (pharmacokinetic) and functional (pharmacodynamic). Dispositional tolerance refers to the increased ability of an organism to metabolize and distribute the drug in the body. Functional tolerance is defined as decreased dose-

response at the receptor site due to changes in neural functioning like receptor downregulation or receptor desensitization.[99] One of the suggested plausible mechanisms for opioid receptor desensitization involves N-methyl-D-aspartate (NMDA)-receptor cascade.[100–103] Functional tolerance can be either acute, when it develops to the effects of the first/second drug administration or chronic, when it persists after prolonged exposure. Psychological or learning tolerance also can be divided into two distinct groups: operant (instrumental) and associative (classically conditioned) tolerance. Operant tolerance is the acquisition of specific skills or responses that compensate for the disruptive effects of a drug on task performance. On the other hand, associative or classically conditioned tolerance is acquired when environmental stimuli reliably paired with drug delivery become conditioned stimuli that elicit conditioned responses that reduce drug effects. Physical dependence is development of an altered physiological state (drug-opposite changes) that in response to stopping the use of opioids, reacts by autonomic and somatic hyperactivity, which is called opioid withdrawal syndrome.[4] Since tolerance and physical dependence were considered as the driving force to support the street addicts' abuse of opioids, physicians were reluctant to prescribe opioids. However, there is no study to show that a similar phenomenon happens if opioids are prescribed to treat chronic pain. It should be noted that the tolerance developed to one opioid does not necessarily make the patient tolerant to another and that starting a new opioid analgesic at the equianalgesic doses as the previous can lead to overdose.[4] Hence, it is recommended that the new opioid should be started on 50% to 75% less than the previous morphine equivalent dose.[104] Addiction, "a sustained high level of use for non-medical purposes that the user is unable to stop",[8] is one of the major concerns of physicians for treatment of chronic non-malignant pain with opioids. While the rates of opium addiction can reach very high amounts, the addiction rate in prescribed opioid users seems to be low.[8,105] Fishbain *et al*, through a structured evidence-based review, demonstrated that the rate of abuse/addiction can reach 3.27% among chronic pain patients receiving chronic opioid analgesic therapy, and can be as low as 0.19% among patients with no previous history of abuse/addiction.[105] The rate of aberrant drug-related behaviors (ADRBs), behaviors that can operationally indicate the development of addiction (e.g. stealing or borrowing drugs from others),[106] was as high as 11.5%, but among preselected patients without history of abuse/addiction the rate dropped to 0.59%. Finally, illicit drug use was seen in 14.5% of chronic pain patients.

Other adverse events and complications

There are several other opioid adverse events, including but not limited to, opioid induced hyperalgesia (OIH), sedation, sleep disturbances, impaired memory and psychomotor performance and bladder dysfunction.[4] Opioid-induced abnormal pain sensitivity shares several cellular mechanisms with neuropathic pain and opioid-induced tolerance, like NMDA-receptor-mediated cellular mechanisms. While repeated administration of opioids induces tolerance through desensitization of NMDA-receptors, it can also lead to a pro-nociceptive process by sensitization of receptors.[99] It seems that, regardless of the pain progression, both desensitization and sensitization contribute to decreased efficacy of long-term opioid therapy.[107]

Conclusions

The prescription of opioids for treatment of chronic non-cancer pain has increased during the last three decades.[14] However, there is no strong evidence in the literature to reliably prove either the efficacy or the safety of long-term opioid therapy for chronic non-malignant pain.[108] Even some studies have shown that the risks of opioid therapy outweigh its benefits.[109] Only in the United states, deaths associated with prescribed opioid analgesics increased by more than 3 times from 1999 to 2007, which is now more common than mortality from HIV or alcoholic liver diseases.[14] While most of these deaths are directly due to addiction and overdose, the other causes of deaths associated with opioid use should not be overlooked.[110] We have previously shown that long-term opium use, even in low doses, can be associated with increased mortality, not only from overdose, but also mortality due to circulatory diseases, several cancers, digestive diseases, respiratory diseases and infections.[110,111] While the mechanisms of opioid-induced adverse events can all suggest these increased risks, there was no other previous study to demonstrate the clinical significance of opioid-induced adverse events in a relatively longer period, e.g. several years. There are several recommendations on methods of opioid therapy and criteria for chronic pain patient preselection.[104] While considering the risk of addiction/overdose, prophylactic treatment and monitoring of OIC and opioid rotation against tolerance development to one opioid are very important, one should consider the possibility of increased risk of mortality from causes other than overdose and also take long-term side-effects of opioid therapy into consideration in future recommendations. Until then, it might be prudent to prescribe opioid analgesics for treatment of chronic non-malignant pain for as few patients as possible and only for cases in which other solutions were not successful.

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