Review Article

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Pain management in hospitalized patients with long term opioid use

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Abstract

This study aims to provide a discussion on pain management challenges in opium addict patients. Pain and addiction are complicated with each other, and their managing requires more clinical consideration. The number of opioid abusers has grown rapidly through the Iranian population, and it seems that opium is the drug of choice in addicted patients. Due to illegal sources of procurement, the purity of substances is suspicious, and it makes pain management more challenging in the field of medication choosing. Although hospitalized patients should receive their daily opioid dose in morphine equivalent, there is no equal value for such substances using in Iran. This concern is not limited to the selection of the treatment, but withdrawal symptoms, relapse causes, drug interactions, and comorbidities are also essential and various in patients. Therefore, pain control should individually be started and proceed based on each one's response.

Keywords: Addicted Patients, Opioid, Pain.

1. Introduction

Pain management has become a challenging concern in a patient with long term opioid use, whether therapeutic or illicit origin. The number of opium users has been drastically increasing due to both misperceptions of opioid medications and the recreational use of substances (1). Despite the availability of non-opioid options for managing all acute pain, opioids are continually selected as the main treatment for severe acute pain in both opium-addicted and non-addict patients (2). Pain and addiction are closely related and complexly affected managing the other. So there is a concern that addicted patients are more likely to receive subtherapeutic pain management and consequently require special clinical consideration (3). Clinical consideration for this population can be discussed in several areas: The first area is the mistrust of addicted patients. Despite that patient with addiction probably requires higher doses of pain medications because of opioid-induced hyperalgesia and tolerance, they often hide their condition due to social stigmatization associated with being introduced as an addict. Besides, there is a concern of opiophobia by practitioners that overtreatment of pain may cause respiratory and CNS depression in current opioid users and relapse in previous addicted ones. All can lead to inadequate pain management and extra suffering.

On the other hand, pain statements may be fabricated by addicts to gain euphoria of opioids, and fear of withdrawal symptoms appearance due to delayed or omitted prescription can mislead the medical team for pain control. The next area is related to the pharmacological effects of substances. Opioid abuse can interferences the pain pathophysiology process and reduces the adherence of such patients to pain drug therapy. Moreover, drug interactions between illicit substances and pain killers should be investigated to elect appropriate schedules for the patient's status. Finally, addiction-related complications and comorbidities are

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considered as an area of attention for every practitioner (4, 5).

In this review, we discuss pain management challenges in opium addict patients.

2. Substance abuse in an Iranian population

Iranian population has catastrophically suffered from addiction. Due to the geographical location of Iran and shared borders with Afghanistan and Pakistan, illicit substances have widely smuggled and been more easily accessible in the Iranian population (6). There is no accurate estimate of the epidemiology and extent of substance abusers owning to a denial of addiction and fear of law enforcement (7). Most statistics on the prevalence and incidence of addiction in Iran are received based on the Ministry of Health (MOH) and the Iranian Drug Control Headquarters (DCHQ) reports. In this regard, in 2007, it reported that 1.2 million people using illicit substances, the equivalent of 2.4% of the Iranian population (6). Based on data from the United Nations Office on Drugs and Crime in 2011, this portion did not change much, and the estimation of opioid dependents was 2.3% of the Iranian population aged between 15 and 64 year-old (8). The data illustrated that most of the abusers were male. According to Narenjiha et al. report in 2007, Opium was the main substances of abuse in Iran, followed by Shireh (extracted and concentrated alkaloids from opium by evaporation), Neurjezik, Crystal methamphetamine, and Hashish (9) While in 2013 A.Nikfarjam *et al.* results represent that the most common type of drug abused was opium followed by shire, crystal methamphetamine, hashish, crack, stimulants (methamphetamine, LSD, and ecstasy) and injecting drugs (6). Opium, crack, and shireh are often smoked or ingested and rarely injected, while heroin is sniffed, smoked, or injected intravenously or subcutaneously (7). Although inpatients should receive their daily opioid dose in morphine equivalent, there is no equal value for substances illegal using in Iran. The drugs are abused in Iran, and other countries in the middle and south of Asia may prepare incorrectly, and non-standardly result in not be able to define each component accurately. Further, pain control should individually be started and proceed based on each one's response.

3. Pathophysiology of pain in addicted patients

Pain is an unpleasant sensation caused by a series of complex communications between different neurons. Both peripheral nerves and the central nervous system (CNS) are involved, and it consists of four steps including Transduction (Conversion of harmful stimuli to action potential and electrical signals at nociceptor sites), Transmission (propagation of electrical impulse through the neurons from peripheral to spinal cord and brain), Modulation (descending inhibition from the thalamus and brainstem and interneurons in the dorsal horn), and Perception (brain and spinal cord conscious awareness) (10). Addiction is an acquired brain adaptation characterized by compulsive drug use regardless of its consequences. Many physiologic states of addiction occur gradually as a result of repeated drug use, leading alteration in neural interactions within analgesia and reward brain regions. Opioid effects of analgesia, reward, and euphoria are produced by predominantly activation of mu (μ) opioid receptors, which are accumulated in brain regions that regulate pain perception and reward pathways, which can motivate pleasure and wellbeing. Mu opioid receptors in other regions of the brain are responsible for different effects of opioids such as respiratory depression and miosis (11). Chronic use of addictive drugs may alter nociceptor input, neuronal excitation, signal transmission, modulation, and finally, pain perception that gradually reduces the drug effects and causes opium-induced hyperalgesia and tolerances (4). Opium induced hyperalgesia is a state results from nervous exchanges in N-methyl-D-aspartate (NMDA) and opioid receptors under the mechanism of neuronal sensitization, neuro-inflammation, DNA hypermethylation, and histone deacetylases while tolerance is a phenomenon occurs by receptor desensitization, down-regulation, and internalization leading to decrease of drug's effect over the time which is represented as higher requirement of pain medication (1, 12).

4. Assessment

Due to the stigma of being labeled as an addict, clinical professionals have often been misinformed, and pain management in substance

abusers has become a great challenge (5). Therefore developing behavior of trust and confidence between the clinicians and patients plays a crucial role. For additional validity to self-report, testing on biologic samples is also recommended. The study of urine is preferred for drug screening because of easy availability and somewhat noninvasive collecting. The detection timing of different substances differs from 2 to 3 days. So the success of detection is much dependent on its frequency and should be performed at least weekly to evaluate the current use of opioids. Random rather than scheduled testing is more acceptable because of the higher detection rate and recognition of drug use immediately after sampling (13). Patients also require a comprehensive evaluation by the family for the history of substance abuse, material type, amount, frequency, duration, the timing of the last dose, and route of administration (1, 12). Moreover, psychiatric comorbidities, especially personality and mood disorders and concomitant alcohol abuse, are common in opioid users and correlated in these individuals with addiction (5, 12). The severity of substance abuse can periodically be evaluated, accompanied by psychiatric disorders. Long term substance abuse, especially opioids and cocaine are common in several psychiatric problems (major depression, anxiety, psychosis, and personality disorders) (14). Both conditions may exacerbate each other so that many psychiatric problems might be secondary to addiction and finally can complicate pain management (15). Patients with a mood disorder may experience more severe pains; hence, in such cases, monitoring of the social condition, treatment of psychiatric symptoms, and interventions by a behavioral therapist are crucial. Other coexisting medical problems, including cardiovascular, gastrointestinal, and infectious diseases, are also common in substance abusers that can mislead the clinical team. Disorders like hypertension dilated cardiomyopathy, reduced gastrointestinal motility, gastroesophageal reflux disease (GERD), hepatitis, and AIDS may limit drug choices and affect patient compliance for pain management. Difficulty in vein access is another in-hospital challenge care of addicted patients that can affect medication choices (12). With due attention to all aspects, an optimal pain treatment protocol necessitates a comprehensive knowledge of pharmacotherapy to differentiate therapeutic and illicit users and prevent the overdose as well as withdrawal syndrome as well as optimal pain management (5). The best medical schedule should be verified, and doses of all drugs must be adjusted according to patient condition and response.

5. General pain treatment

Generally, therapeutic strategies for pain are defined as pharmacologic options, physical techniques, behavioral therapies, neuromodulation, interventional, and surgical approaches. Pharmacologic strategies are widely used in the management of pain and including non-opioid analgesic agents, alpha2 adrenergic agonists, antidepressants, antiepileptic drugs, muscle relaxants, NMDA receptor antagonists, and topical analgesic agents (16). The selection of medication varies depending on the type of pain. For example, neuropathic pains refer to pain caused by direct stimulation, and damaging of the peripheral or central nervous system be initially treated with antidepressants and anticonvulsants (gabapentin and pregabalin) (10, 16). However, opioids should be considered as an alternative to first-line options, but they may be started earlier in severe discomfort. In such pains, patients mostly require a combination of high dose opioids, antidepressants, and anticonvulsants. Comparing to neuropathic pain, nociceptive pain is caused by damage to other body structures and generated by stimulation of the C group fibers. The pharmacologic guidelines primarily recommend non-narcotic and non-opioid agents. Opioid analgesics are recommended as second-line options due to limited evidence of benefit for nociceptive pains (10), and they should be considered only for patients with an estimated low risk of substance abuse (16). Some guidelines can be helpful in the selection of pain medication and summarized in table 1.

6. Acute pain management in addiction patients

The main goal of acute pain management in addicted patients is to provide instant pain relief while preventing withdrawal symptoms and relapse or exacerbating opioid disorders (5). Due

Table 1. Pain management recomendations.

Presenting condition	Recomendation	References
Cancer pain	Mild: Non-opioid (Acetaminophen, Aspirin, NSAIDs) ±Adjuvant Moderate: Weak opioid (Codein, Tramadol, etc.) ±non opioid ±adjuvant Sever: Strong opioid (Morphin, Fentanyl, etc.) ± non opioid ± adjuvant	World Health Organization (WHO) analgesic ladder (17)
Low back pain	NSAIDs (In lowest effective dose & for short duration) ± Acetaminophen Weak opioids ± Acetaminophen (only when NSAIDs is contraindicated) Acetaminophen is not recommended alone The opioid is not routinely recommended for managing acute low back pain The opioid is not recommended for managing chronic low back pain Antidepressants & anticonvulsants are not recommended	National Institute for Health and Care Excellence (NICE) (2016)(18)
Post operative pain	Moderate to sever: Acetaminophen ±NSAIDs ±Opioid	National Institute for Health and Care Excellence (NICE) (2016)(19)
Tension -Type Headache	Aspirin Or Acetaminophen Or NSAIDs The opioids are not recommended for the acute treatment of tension-type headache	National Institute for Health and Care Excellence (NICE) (2015)(20) British Association for the Study of Headache(BASH) (2010)(21) International Headache Society (2018) (22)
Migraine	Triptan (Alone or with NSAIDs or Acetaminophen) NSAIDs Acetaminophen The opioid should not be administrated in acute migraine pain	National Institute for Health and Care Excellence (NICE) (2015)(20) British Association for the Study of Headache (BASH) (2010)(21)
Cluster headache	Oxygen and/or a subcutaneous or nasal triptan Acetaminophen, NSAIDs, opioids, ergots or oral triptans are not recommended.	National Institute for Health and Care Excellence (NICE) (2015)(20)
Sprains and Strain	First line: Acetaminophen Or topical NSAIDs 48 hours after injury: Oral NSAIDs (if necessary)	National Institute for Health and Care Excellence (NICE) (2016)(23)
Trigeminal neuralgia	**Carbamazepine**	National Institute for Health and Care Excellence (NICE) (2016)(24)

to opioid-induced relapse in addicted patients, adequate pain relief may not be achieved, and appropriate monitoring is essential (5). The nature of the patient's addiction affects pain management. For opioid-dependent patients, the determination of morphine equivalent dose of their opioid intake is recommended. (Table 2) (1, 12, 25). It is calculated by following equation:

Equation 1:

Oral Morphine Equivalent Daily Dose=Current Opioid Dose * Conversion factor.

The patients should receive their baseline opioid to avoid withdrawal symptoms and more additional opioid doses to provide analgesia. By focusing on co-morbid physiological disorders may better meet treatment goals and improve patient outcomes. Therefore, a combination of non-opioid analgesics, including acetaminophen, NSAIDs, anticonvulsants, and antidepressants, provide a multimodal approach for pain control (5). For patients on long term transdermal or implantable pumps, patch and pump should be continued, and other short-acting analgesics must be added with consideration of agonist-antagonist reactions. Also, in the long term methadone abusers, the maintenance dose should be administrated, and poly-opioid therapy is recommended for acute pain (26). Opioid-dependent patients require high dose opioids compared to opioid naïve individuals, with precise side effect monitoring (5). Opioid rotation between either methadone or oxycodone and fentanyl may be required in patients with poor

Table 2. Opioid Dose Equivalence.

Opioid	Unit	Conversional Factor	Half life
	Oral		
Morphin	mg/day	1	2-4h
Tramadol	mg/day	0.2	2-4h
Codeine	mg/day	0.15	3-4h
Oxycodone	mg/day	1.5	3-4h
Hydromorphone	mg/day	5	8-16h
Oxymorphone	mg/day	3	2-3h
Hydrocodone	mg/day	1	2-3h
Methadone	1-20mg/day	4	8-59h
	21-40mg/day	8	
	41-60mg/day	10	
	Sublingual		
Buprenorphine	mg/day	40	37
	Rectal		
Oxycodone	mg/day	1.5	
	Transdermal patch		
Buprenorphine	mcg/h	2	26
Fentanyl	mcg/h	3	16
	Parenteral		
Morphine	mg/day	3	
Oxycodone	mg/day	3	
Hydromorphone	mg/day	15	
Codeine	mg/day	0.25	
Pethidine	mg/day	0.4	2.5-4h
Fentanyl	mcg/day	0.2	2-4h
Sufentanil	mcg/day	2	164min

Table 3. Heroin and morphine dose schedule.

Heroin dose (mg)	The morphine maintenance dose (mg)	
	20	30
0-6.24	20	30
6.25-12.49	10	20
12.5-24.99	0	10
+25	0	0

pain control and opioid associated side effects with a high dose of morphine (26). Related to concern of liver toxicity, there is a recommendation of opioid only use compared with a combination of opioid and acetaminophen in patients need higher doses (1). Recently, a trend of transition with prescribed opioids to heroin has been grown in some countries. As the prices have been decreasing, heroin abusers are on the rise. Heroin is rapidly metabolized to morphine while not bound to the opioid receptor itself. For this reason, morphine dose reductions should be considered according to the following schedule (Table 3) (27):

7. Conclusion

There are several challenges faced by substance abuse in pain management. Access to ideal pain relief is complicated by opioid addiction. Inadequate pain management, withdrawal care, relapse concern, and comorbidity considerations are essential. Although there is a pivotal point to distinguish the addiction severity as an equal morphine dose, the limited data on the exact formulation and purity of substances using in Iran makes pain management even more complicated. So pain management in substance abusers should be patient-specific based on a pharmacotherapist integration to achieve optimal patient care outcomes. Patients should be individually referred to a pharmacotherapist, before, during and after their treatment course for medication and substance reconciliation, assessment of adherence to therapy, medication monitoring especially high- dose of opioid, recommendation for regimen modification, follow up the drugs adverse effects and comorbidities, consideration of high risk for opioid misuse and consulting to opioid adjustment or discontinuation. According to the personalized approach and based on recent interests, detection of genetic correlation and pharmacogenetic tests can also optimize the outcomes as future directions.

Conflict of Interest

None declared.

8. References

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