

Review article:

A Review on Opioid Dependence, Mechanism and Treatments Used: Option of Treatments: Modern versus Alternative Medicine

Nor Zidah Ahmad¹, Khairi Che Mat², Nasir Mohamad³, Rohayah binti Husain⁴, Nor Hidayah Abu Bakar⁵, Nur Husna Zakaria⁶, Siti Norhajah Hashim⁷, Liyana Hazwani Mohd Adnan⁸, Mohamad Halim Mohamad Shariff⁹

Abstract

Opioid dependence is one of the severe social problems encountered by civilization nowadays. Prior to the illicit use of opioid, an abundance of research had been done in order to understand the molecular and cellular action of the opioid. In spite of that, the actual cellular mechanism remains controversial. Hence, this review is targeting on the mechanism of opioid dependence in a biochemical pathway and treatments available either via drug medication or the use of natural remedies to treat opioid dependence.

Keywords: Opioid dependence; calcium channel blocker; alternative treatment; modern treatment

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Introduction

Chronic opioid had become a threat to the healthcare problems, despite of all the headway in medicinal field such as improvement in diagnostics and pharmacotherapy. It is noted that the effort in opioid prevalence had causes a great annual economic burden; almost USD 100 billion, due to the loss of workforce efficiency from the affected individuals¹. Insufficient treatments or mismanagement can further cause additional suffering to individuals suffered from chronic pain, but may also cause other adverse effects including delay in recovery, changes in neuroplasticity, depression, suicide and opioid

addiction^{1,2}

In clinical pathway of medication field, opioids were commonly used to induce analgesic during surgery to act as an anesthesia, cough suppression and diarrhea suppression³. By the right dosage used, opioid helps to reduce the intensity of pain signals reaching the brain areas that control emotion, thus reducing the painful stimulus¹. Unfortunately, the pure use of opioid was misused, causing bigger problems in society. This illicit use of opioid had led to the damage of body systems such as severe respiratory depression, constipation and in most serious cases, death⁴.

1. Nor Zidah Ahmad
2. Khairi Che Mat
3. Nasir Mohamad
4. Rohayah binti Husain
5. Nor Hidayah Abu Bakar
6. Nur Husna Zakaria
7. Siti Norhajah Hashim
8. Liyana Hazwani Mohd Adnan
9. Mohamad Halim Mohamad Shariff

Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), 20400 Kuala Terengganu, Terengganu Darul Iman, Malaysia. Email: nzidahahmad@gmail.com & nurhusnazakaria92@gmail.com, hajah_gk@yahoo.com, liahazwani@gmail.com & halimshariff89@yahoo.com, drnasirmohamadkb@yahoo.com, khairicm@unisza.edu.my, rohayah@unisza.edu.my & norhidayahabubakar@unisza.edu.my

Correspondence to: Nor Zidah Ahmad, Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), 20400 Kuala Terengganu, Terengganu Darul Iman, Malaysia.

In the 19th century, the use of opiates and cocaine were almost uncontrolled. It had been prescribed and used in large quantities for various diseases. Early in the 20th century, cocaine became related to crime, which led to anxiety over the use of opiates. In 1909, the use of opium in medicine had been allowed, but it is prohibited in smoking. Later in 1914, the Harrison Narcotics Tax Act was enacted to regulate the import, export, manufacture and distribution of opium or cocaine. In 1919, the Supreme Court confirms the Harrison Narcotics Tax Act, which states that doctors cannot set up supplies of opiate maintenance to addicts. At that time, addiction is not considered as a condition of illness thus, doctors who set opiates to filtered drug addicts, lose their medical license or, in some cases, imprisonment. Those addicts were punished for crimes, which leads to an insufficient treatment to treat the addiction. The advocacy year for humanitarian treatment of the bottom-line illnesses and professional organizations, along with the published articles on the efficacy and safety of opioid in the treatment of pain, led to the use of severe pain laws that promote opioid therapy for chronic pain including non-cancerous pain.^{5,6}

In order for further understanding, the basic root of definition of addiction terms must be known. Amongst them are physical tolerance and dependence, which are often associated with the regular or longer-term use of opioids. Chronic use of heroin, oxycodone, and other morphine-derived drugs causes brain abnormalities, which lead to opioid dependence (the need to keep taking drugs to avoid a withdrawal syndrome) and addiction (intense drug craving and compulsive use of the drug)⁷. Opioid dependence occurs when body relies on substance for normal functioning⁸. Opioid dependence is an adaptive state of the body when an isolated interference appears in the body system⁹. During the administration of an opioid, these substances specifically and chemically attach to μ -opioid receptors (MOR), which is opiate-sensitive neuron area¹⁰. The linkage of these chemicals to the MOR receptors trigger the same biochemical brain processes that reward people with feelings of pleasure when they engage in activities that promote basic life functions, such as eating, working and exercising⁷.

During the long-term use of opioid, this substance abuse generally leads to the body system damage, lack of nutrition and a low physical and mental health. Medications are needed in order to recover body to the normal state. Modern medication such as methadone, buprenorphine, naloxone and naltrexone

had been used to treat opioid dependence. But, none of these treatments are curative. These medication works by blocking opioid effects, thus diminish withdrawal symptoms and craving⁽¹¹⁾. In spite of that, the action of these medications is only temporary, and frequent intake of the medication is a must to avoid withdrawal effect.

In contrast to the modern medicine, alternative medication containing high nourishing nutrient can be helpful in some way to deal with chemical imbalances resulted from a long-term substances addiction. Opioid dependency is a serious illness that involving certain spiritual, psychological and social aspects of the affected person. Natural remedies such as plant-based nutrient (honey, nigella sativa, ginger, curcumin, dates, etc), high-content mineral water such as zam-zam water were often used due to the effectiveness that had been proven by the scientific evidence. Herbal medicines from plant sources had been proven to contain a lot of biological active compounds that synergistically can provide a potentiating effect¹².

Understandings of opioid dependence are not only based on the modification of opioid receptor during the drug metabolism, but it clearly requires explanation during the activation of the opioid receptor. Furthermore, combination of existing medications with psychosocial therapies, have proven efficacy in reducing aspects of opioid addiction. Unfortunately, the complex mechanisms of this opioid dependence are still inconsistent and agreement cannot be achieved due to variation in mechanism involved. Thus, further research and study must be done to clearly understand regarding the mechanism and pathway of opioid dependence.

Opioid dependence and mechanism

The diverse biological effect of opiates, from analgesia to addiction, occur due to the action of opioid, mediated by the activation of specific opioid receptors from G protein-coupled receptor family (GPCR); mu (μ), delta (δ), kappa (κ) and opioid receptor like-1 (ORL-1)¹³. The body systems give the same effect, similar to the action of endogenous opioid peptide when opioid binding occur¹³.

Studies reported that on agonist binding, opioid receptors coupled to G proteins and affect several signal transduction pathways, including inhibition of adenylyl cyclase to produce second messenger cAMP and Ca^{2+} channels, activation of inward-rectifying K^+ channels, transient increases in intracellular Ca^{2+} levels, and activation of phospholipase C and mitogen-activated protein kinases extracellular

signal-regulated kinases 1 and 2^(9,14-19). The activation of MOR causes the hyperpolarization of post-synapse, due to the inhibition of neurotransmitter release, thereby causes an analgesic effect¹⁷.

Prolonged use of opioid will lead to the symptom of tolerance, physical dependence, and addiction. These conditions occur due to the lost of drug's inhibitory effect after the chronic exposure of opioid⁷. Chronic opioid exposure causes the induction of adenylyl cyclase and cAMP-dependent protein kinase A, where with a sudden decrease of opioid intake, affected enzyme decrease and withdrawal affect appear²⁰⁻²². One of the findings from²³ had suggested that up-regulation of cAMP pathway by protein kinase A (PKA) might play an important role in the development of opioid tolerance.

One of the factors that have been extensively studied regarding the opioid dependence is the calcium channel blocker. A preliminary study from²⁴ shows that voltage-gated calcium channel had been affected by the activation of mu-opioid receptor (MOR) activation. Study regarding calcium channel blocker shows the assumption that it controls opioid dependence and withdrawal syndrome via L-type voltage-dependent calcium channel antagonist such as verapamil, diltiazem, and felodipine^{25,26}. Neuronal L-type calcium channels are important in the regulation of activity-dependent gene expression²⁷. As quoted from study by²⁷, they investigate the inhibitory effect of Ca²⁺ influx via L-type calcium channel on gene expression of the steroidogenic acute regulatory protein. they found out that the blocking of the calcium channel had resulted in an increase of cAMP-induced protein and progesterone production in MA-10 Leydig cells.

Recollection from the past study²⁸ also had reported that daily injection of rats with morphine enhance the cytosolic protein kinase C (PKC) in the medulla region but not in the membrane fraction. This study had suggested that the upregulation of PKC in a specific area may contribute to morphine tolerance and dependence.

Modern Treatment for Opioid Dependence and Addiction

The clinical study had provided two general treatment paths to choose, either opioid maintenance treatment or detoxification²⁹. Agonist and partial agonist medications are commonly utilized for both maintenance and detoxification purposes. While antagonist medications are used to accelerate detoxification process and prescribed post-detoxification assist in preventing relapse.

Successfulness in a combination of treatment can be determined from the outcomes; whether patient have achieved a level of retention in treatment of opioid and other drug use²⁹.

Methadone

Methadone is a μ OR agonist that helps in correcting the compulsive use of opiate drugs and in return give the individuals a productive normal life. Methadone occupies the brain receptor sites affected by opioid drugs. Due to the long half-life and duration of action of methadone, the abstinence syndrome is delayed and prolonged but less severe than that from a shorter-acting opiate such as heroin³⁰. Methadone is eliminated from the body system via metabolism process occur in liver and kidney³¹. Methadone acting via several ways such as blocking the euphoric and sedating effects of opiates relieves the craving for opiate and relieves symptoms such as withdrawal from opiates³².

Generally, opioid-addicted individual requires less than 30 mg/day methadone to reduce the withdrawal symptoms for the first time intake³¹. Most patients require a dose of 60-120 mg/day to achieve optimum therapeutic effects of methadone³². Patients with high dose intake of methadone (>80 mg/day) shown a more effective effect compared to the low dose intake³¹.

Naloxone & Naltrexone

Both naloxone and naltrexone are medication commonly used in opiate addiction treatment. These drugs act by binding to the opioid receptors in the body, thus blocking the opiate receptors and prevent the body from responding to the other opiate. Consumption of opiate antagonist causes individuals to inhibit the effect of opiate as it will block the body's normal response to these drugs as well as endorphins that may also be released when such drugs are administered³². A daily dose of naltrexone (50 mg) will block the pharmacologic effects of 25 mg IV heroin for as long as 24 hours, and increasing the dose extends its duration of action to 48 hours with 100 mg and 72 hours with 150 mg²⁹.

Buprenorphine

Buprenorphine, a semi-synthetic opioid derivative is a partial μ -opioid agonist. In 2002, U.S Food and Drug Administration (FDA) approve a sublingual tablet (Subutex® and Suboxone®) as a medication to be used in the treatment of opioid dependence³³. In opioid addicts, buprenorphine has the advantage to produce sufficient agonist effect to enable individual discontinue the illicit use of opioid and promoting treatment retention among opioid abusers³⁴.

Buprenorphine effects produce the typical opioid effect and also the same side effect, but its maximal effect is less than those of full agonist opioids such as heroin and methadone. Despite its property as a partial μ -opioid agonist, buprenorphine has a ceiling effect on its agonist activity where after a certain point of intake, taking more will not increase any of the drug effect³⁵. When comparing between buprenorphine and methadone treatment therapy, Whelan & Remski³⁵ review show that a flexible dose of buprenorphine was statistically less effective than methadone in retaining patients in treatment although it.

Alternative treatment

Nigella sativa

Since ancient time, *N. Sativa* has a role such as to treat infectious disease or metabolic disorder. A recent study on *N. Sativa* shown that it has many pharmacological effects such as anti-inflammatory, antioxidant, analgesics and immune-protective properties as such reported in several studies^{36, 37}. Many medicinal properties of *N. Sativa* seeds extracts and/or its oil, are attributed to a quinone compound called thymoquinone (TQ)³⁸.

Most of the medicinal properties of *N. sativa* have been contributed by its seeds extracts or oils. The chemical composition of *N. sativa* is widely studied and the compounds found therein, especially TQ, carvacrol, p-cymene, t-anethole and 4-terpinol was proven to have potent antioxidant activities. Several studies have attributed this attenuation of oxidative stress by *N. sativa* to the free radical scavenging properties of *N. sativa* and provided evidence of increased expression of antioxidant genes³⁹. *N. sativa* decreases hepatic lipid peroxidation and increases activities of catalase, Glutathione-S-transferase, adenosine deaminase, myeloperoxidase by normalizing glutathione (GSH) and nitric oxide (NO) levels due to TQ activity⁴⁰⁻⁴². TQ has been shown to suppress the ferric-nitriacetate-induced oxidative stress and prevent oxidative injuries⁴³.

Time frame studies on *N. sativa* since two decades ago focused a lot on the effect of *N. sativa* extract and its active compound to help in supplemented modern medication in treating opioid dependence, tolerance. *N. sativa* is believed to mediate in blocking the calcium channel via its active compounds. Calcium channel blockers have been proved to be effective in opioid withdrawal syndrome^{44, 45}.

A study from Hosseinzadeh *et al.*³⁸ stated that since TQ is the major constituent of *N. Sativa* oil, it can be hypothesized that the inhibitory effect of *N. Sativa* works due to the neuroprotective effects of

TQ on opioid-induced tolerance and dependence. Administration of single doses of TQ (20 and 40 mg/kg, i.p.) 30 minutes before the injection of naloxone (2 mg/kg, i.p.) on the fourth day, significantly decreased the number of jumps in morphine-dependent animals ($p < 0.05$ and $p < 0.001$, respectively). In addition, repeated administration of TQ at the doses of 20 and 40 mg/kg, 30 minutes before the injection of morphine during the 3-day administration schedule, significantly decreased the number of jumps in morphine-dependent mice. This proved that result from Hosseinzadeh *et al.* study show TQ prevent the induction of physical dependence to morphine and attenuated the severity of the signs of withdrawal syndrome in morphine-dependent mice.

Honey

Honey had been used traditionally to heal the wound, cough and sore throat (46, 47). Honey consists of a compound such as carbohydrate, proteins and minerals⁴⁸. Honey also contains many bioactive compounds such as gallic acid, kaempferol, ellagic acid, caffeic acid and chrysin which serve as an antioxidant, analgesic effect, antibacterial and anti-allergic activities⁴⁹⁻⁵¹.

In morphine dependence and tolerance study, within the important factor concerning the use of honey are the role of oxidative stress and antioxidant level via the contribution of its bioactive compounds. *In vivo* study of honey on rats shows that honey has a strong analgesic effect in a test of acetic acid formalin writhing test and hot plate test of 100, 200 and 500 mg/kg of Sidr honey given with a dose-dependent analgesic effect⁴⁶. In one of the study, it is found that 1-10 mg/kg of ellagic acid tested on hot plate that use short thermal of heat stimulus to have an analgesic effect^{52, 53}. A study by⁵⁴ shows a significant test on tail flick latency, where treatment of 5, 30 and 100 mg/kg of caffeic acid did not give any prevention at early phase but later on, antinociception significantly increase at late phase.

Holy Zam-zam water

Treatment of opioid dependence with Holy Zam-zam water is one of the new discovered researches which are still ongoing. Zam-zam water has a special physique and advantageous water according to Al Zuhair & Khounganian⁵⁵. Zam-zam water has a different quantity of minerals such as calcium, magnesium salts, lithium and zinc when compared to other type of water. It has a slightly higher content of these minerals and more significantly it contains fluoride which is an effective germicidal action.

Research on the interaction between mineral

supplement, opioid dependence and tolerance done show that one factor that can cause dependency is the lack of a single vitamin or mineral supply in body⁵⁶⁻⁵⁸. Those minerals had been studied and show a positive result in alleviating opioid dependency, although an exact mechanism cannot be confirmed^{59, 60}.

Conclusion

Opioid drugs have both advantages and disadvantages based on the individual intention of use. Prescription of opioid without proper prescription will cause harmful effect to the users, in most cases causing drug abuse. Physician consultations are highly recommended for the right dosage of drug intake. Recent studies on the structural and molecular biology of opioid receptors can promise a significant cure to treat dependency and addiction with more selective actions.

Ethical clearance: This article was approved from the ethics Committee of Universiti Sultan Zainal Abidin (UniSZA), 20400 Kuala Terengganu, Terengganu Darul Iman, Malaysia prior to submission.

Conflict of interest:

The authors declared no conflict of interest with respect to the authorship and/or publication of this paper.

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Authors' Contributions:

Data gathering and idea owner of this study: Nor Zidah Ahmad, Khairi Che Mat

Study design: Nor Zidah Ahmad, Nasir Mohamad, Rohayah binti Husain

Data gathering: Nor Zidah Ahmad, Nor Hidayah Abu Bakar, Nur Husna Zakaria

Writing and submitting manuscript: Nor Zidah Ahmad¹, Siti Norhajah Hashim, Liyana Hazwani Mohd Adnan

Editing and approval of final draft: Nor Zidah Ahmad, Mohamad Halim Mohamad Shariff

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