



MONITORING OPIOID MISUSE: CHEMICAL ENTITIES AND TECHNOLOGICAL ADVANCEMENTS IN THE MANAGEMENT OF PAIN

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ABSTRACT

Opioids fall into the classification of analgesic agents used in healthcare set up. Opioid crisis in America is considered as the national level health crisis. On an average five persons in United States of America died due to opioid addiction or overdose of opioids. This crisis not only exists in America but a global complication as well. Frequent use of opioids has led to the “Opioid Use Disorder” a commonly used term at healthcare settings. As a technology era, there are a number of innovative technologies to curb this problem. These technologies help the patients and the patient parties to closely monitor and send alerts about the opioid misuse. Scientist have developed these technologies by investing lot of time and cost for the benefit of the patients. However, these technologies are unknown to people and should reach out to the public for appropriate use. Training and educating the patients and their care givers on these technologies is an ideal way to help them combat this disorder.

Keywords: Opioid abuse, Healthcare, Digital technology, recent developments, Innovations

1. Introduction

Opioid drugs fall under the category of analgesic agents which is obtained from opium poppy plant. These work by acting on the receptors in the brain to relieve pain and produce other effects. Naturally available opioids are called as opiates examples being morphine and codeine. Synthetic opioids are also available. To name a few, fentanyl, heroin, methadone are the examples of synthetic opioids. Opioids are also available as prescription drugs which are commonly used to treat pain or they are also available as “street drugs”. Opioids work by binding to the opiate receptors μ [mu], κ [kappa] and δ [delta] also termed as “MOP, KOP and DOP”. These are mostly found in the central nervous system, the brain and spinal cord and also in other parts. Figure 1 explains the pain pathway that starts from a trauma and reaches the brain.¹ Opioids act at each level and help in the reduction of pain. However, there is a disadvantage that use of opioid can make the people relaxed and this may cause them to over use leading to addiction. That’s the reason they fall into the category of narcotic drugs and are not used as OTC drugs even though they act as pain killers.² Prescription opioids such as fentanyl are found to be 50-100 times more potent than the naturally occurring

opioids like morphine and codeine. Opioids also tend to cause other effects such as respiratory depression, nausea etc. Majority of opioids have similar effects and also the side effects may be same although there maybe pharmacokinetic differences may be there.

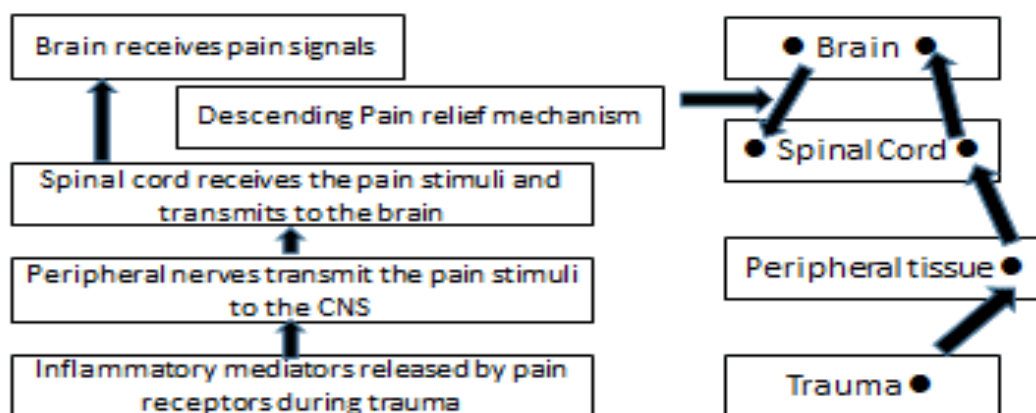


Fig. 1: Pain pathway showing the activity of opioids in reducing the pain

Though opioids are classified as natural and synthetic, there exists sub classification of opioids (Figure 2) too based on the different types of chemical structure, semisynthetic derivatives and different classes of synthetic opioids.³ The structures of the classes are depicted in Figure 3A to 3F.

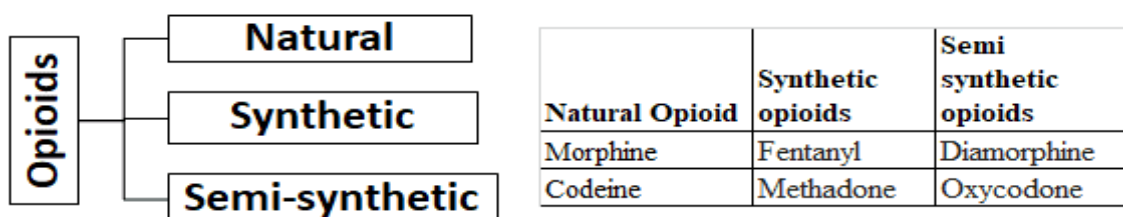


Fig. 2: Classification of opioids

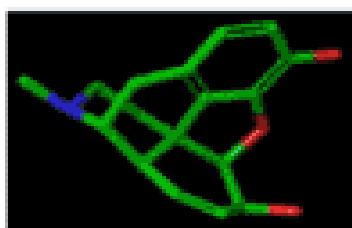


Fig 3A: 3D structure of Morphine

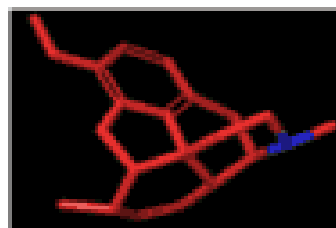


Fig 3B: 3D structure of Codeine

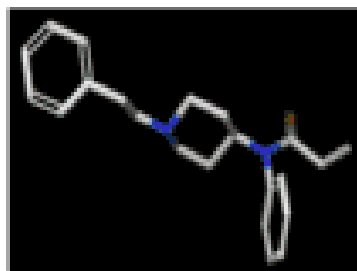


Fig 3C: 3D structure of Fentanyl

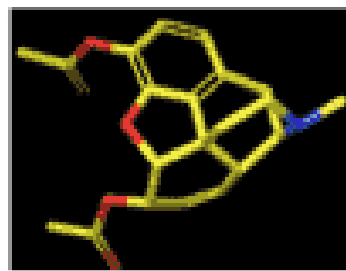


Fig 3D: 3D structure of Diamorphine

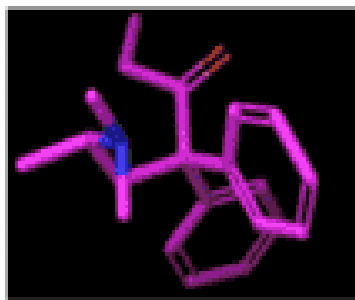


Fig 3E: 3D structure of Methadone

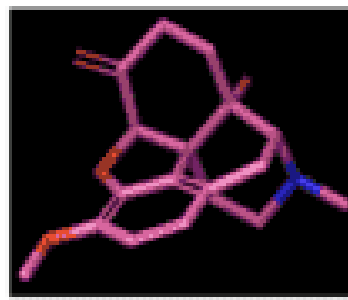


Fig 3F: 3D structure of Oxycodone

Fig. 3: Structures of Morphine (3A), Codeine (3B), Fentanyl (3C), Diamorphine (3D), Methadone (3E) and Oxycodone (3F)

2. Usage of opioids

Often pain is called as the fifth vital sign and can have a significant impact on the quality of life of people experiencing pain. Pain can have a negative impact on the mind thus making the healing process much slower. Most common symptom of chronic diseases such as cancer can be pain and pain management can be more complex and challenging.⁴ The use of these opioids dangerous as they hold a lot of risks. The recommended usage of these drugs can increase a person's resilience and reliance thus requiring more successive dosages. This may further lead to addiction. Excess dose can even lead to death when the person becomes abusive. There is always a risk of respiratory depression too especially in those patients who are consuming opioid for the first time and also using concomitant medications. Therefore, opioids should only be used when here is severe pain and no alternative pain killers are available.⁵

2.1 Risk factors of opioid overdose

Risk factors include individuals with opioid dependence and also persons who inject narcotics. Person injecting both prescription as well as heroine are also under risk of opioid overdose. Concomitant usage of opioids with other tranquilizers may cause death due to overdose. Moreover, using of opioids for the treatment of chronic diseases such as cancer, HIV can lead to subsequent increased dosing leading to overdose. There is always a confusion on gender based opioid overdose. Several studies have mentioned different results which contradict to similar studies. Opioid overdose was highest among age group of 45 to 54 years. Racial differences have gained a lot of attention in US where white patients were prescribed more of prescription opioids during emergency set up. Discontinued treatment is also an important risk factor for overdose.^{6,7}

2.2 Opioid overdose

As per the Diagnostic and Statistical Manual of Mental Disorders, Opioid Use Disorder is explained as "A problematic pattern of opioid use leading to clinically significant impairment or distress".⁸ At higher doses they depress the respiratory system acting on the medulla and may further cause death. Often overdose is identified on the basis of "opioid overdose triad" which explains three signs and symptoms namely pinpoint pupils, unconsciousness and respiratory depression. Higher respiratory depression is also found when opioids are consumed with alcohol and other sedatives which is fatal. In US around 63,632 deaths due to overdose were noted in which increased by 21% from the year 2017 and were mainly because of the prescription opioid.⁹

2.3 Emergency response to opioid overdose

Death is more commonly observed after a narcotic overdose which can be avoidable if the person who has consumed too much of opioid will get treated immediately with Naloxone

along with other supporting treatments. Naloxone is an opioid antagonist has the tendency to reverse the impact of a narcotic overdose. The most preferable route of administration for Naloxone to be successful for the opioid treatment is by intravenous (IV), intramuscular (IM), subcutaneous (SC), and intranasal routes of administration. Naloxone can be available only with medical practitioners. Several countries Naloxone is not available even in the healthcare setting including the ambulances. Italy is the only country where Naloxone is available without prescription at pharmacy outlets.¹⁰

2.4 Opioid crisis in the U.S.

The opioid crisis in US is a remarkable one as the crisis came in three waves involving huge number of deaths.¹¹ First wave started in 1991 when there were more opioid prescriptions and opioid was used as choice of combination drug for the management of pain. The increase in the number of prescription of opioids by the doctors was mostly on the assurance given by the pharmaceutical companies, that the risk of dependence on these prescribed opioids was very minimal. Even though there was no evidence of benefits over risk, these drugs were given to even those patients who were getting treated for pain other than cancer where alternative medicines were available. By 1999, year-end 86% of patients were using opioids for pain other than cancer. Patients who had easy access to opioids were the first ones to experience the drug abuse property of these narcotics. The second wave started in the year 2010 and there was rapid increase in the death rate due to heroin which is easily available and a potent illicit narcotic. This was observed in all age groups and with all socioeconomic background. Later in 2013, third wave started with an increase in death rate was observed with the manufacture of fentanyl and other synthetic opioids which continued even till 2016. This was due to the illegal manufacturing and sales of fentanyl which was substituted or adulterated with other drugs that cause abuse.

2.5 Deaths due to drug overdose fall

As per the data collected by Centres for Disease Control and Prevention (CDC) drug overdose death rate reduced by 5.1% in 2018 compared to the last year. This had happened for the first time ever since the year 1999 which had increased between 2014 to 2017. The Centres for Disease Control and Prevention showed that as much as 68,557 had died in the year 2018 which was comparatively less than people died in the year 2017 which was around 72,224. However, deaths with fentanyl increased as Fentanyl was found to be 100 times more potent than morphine and was available illegally in US market.¹²

3. Digital health

Before the start of Covid-19, opioid crisis was considered as National emergency in the USA. Digital health is the use of digital technologies in health and healthcare to enhance the efficiency of healthcare delivery, thus making medicines more customized and accurate. Digital health has been beneficial in combating this disorder by offering new ways of treatment, helping in diagnosing etc.¹³

3.1 Innovation challenge by FDA

In the year May 2018, FDA's Centre for Devices and Radiological Health (CDRH) initiated an Innovation Challenge. The main objective behind this program was to encourage the people to invent advancements in technologies in the area of medical devices/ digital

healthcare that could substitute using narcotics like opioids for the treatment of pain. This challenge was accepted by the medical device manufacturers and FDA received more than 250 applications for the same.¹⁴

Based on the above mentioned measure, eight applications were selected:

Brainsway, Ltd (Brainsway Deep Transcranial Magnetic Stimulation (DTMS) Device)

Avanos (Pain Therapy Device)

iPill Dispenser (iPill Dispenser)

Masimo Corporation (Overdose Detection Device)

ThermoTek, Inc. (NanoTherm™ and VascuTherm™ Systems)

Milliman (Opioid Prediction Service)

Algomet Rx, Inc. (Rapid Drug Screen)

CognifiScience, Inc. (Virtual Reality Neuropsychological Therapy)

3.2 Block chain technology

The severity with which the opioid crisis was rising led to the development of many new digital technologies. One such technology is the implementation of block chain technology which has tremendous potential to direct towards unique challenges that has been obstructing opioid research.¹⁵ Block chain technology helps in tracking the prescription, through which opioid overdose or over-prescription can be identified and avoided.¹⁶ Implementation and usage of block chain technology into the software system that are most commonly used by digital marketers could solve the misuse of drug marketing through online. Through this technology it is possible to fill the prescription for one time. All the online retailers would be connected to each other through a central interoperable framework which can avoid the patients from purchasing the medicines using the same prescription from different sources. Alternatively, Block chain technology can control opioid crisis also through a secure digital identity. Several companies are now working on this that can help in verifying the patient's identity online. This will help in detecting the false identities and helps in linking patient's demographics with his prescription.¹⁷

3.3 Quell wearable pain relief technology

A survey conducted by Neurometrix revealed that 90% of the patients are seeking new therapy with latest technology for treatment of chronic pain. And with this mission, Neurometrix developed the Quell 2.0 system which has many features such as compact design that is 50 % smaller than the original device, redesigned Quell App etc. Quell 2.0 a wearable pain relief technology device manufactured by Neurometrix was unveiled PAINWEEK 2018 for the treatment of chronic pain. This device is 100% drug free, prescription strength nerve stimulation technology is approved by the FDA for the treatment of severe pain. It is intended to give comfort to patients suffering from very severe pain. The new device comes along with a user friendly app (Quell Relief App), and the device is 50% smarter, and more powerful. The advanced neurotechnology helps in altering bodies pain response system by activating the sensory nerves. It is very beneficial to those patients who are deprived of sleep due to chronic pain as the device is wearable and can be used while sleeping too. The app provides treatment customization, monitoring of pain and also sleep as per the patient's necessities.¹⁸

3.4 Proclaim elite SCS system

Spinal cord stimulation is one of the most commonly used modality for the treatment of chronic pain. Manufactured by Abbott, this system delivers two types of spinal cord stimulation therapies to minimize the levels of pain felt. They are BurstDR stimulation and Tonic stimulation. BurstDR stimulation involves specially delivered packets of electrical energy along with a recharge mechanism which mimics a patients' natural neuronal activity. BurstDR stimulation converts the pain signals reaching the brain. This provides relief from pain. The Proclaim XR implantable pulse generator (IPG) is an innovative device approved by FDA and design provides low dose BurstDR stimulation. The battery used for this purpose is comes along with the guarantee period of 5 to 10 years with appropriate programming.¹⁹

3.5 St. Jude medical invisible trial system (FOR DRG)

Chronic pain is considered as one of the factor for poor Quality of Life. Keeping this in mind, in order to benefit more patients with pain, Abbott has invested lot of time and energy to deliver innovative mechanism that will be safe and effective treatment option for pain. Dorsal Root Ganglion (DRG) neurostimulator technology is an innovative product manufactured by Abbott, and it operates by changing the dorsal root ganglion which plays an important role in causing progressive pain when the cell bodies in DRG undergoes pathophysiologic changes resulting in chronic pain.²⁰

3.6 Sana pain management mask

Sana device is worn externally on the on the face and comes in contact with the skin and sends coordinated pulses of light (Audio Visual Stimulation (AVS)) through the closure of eyelids and sounds at different frequencies. AVS is a form of neurological feedback mechanism and a non-drug intervention that acts on the CNS by merging neurons to various frequencies of sounds and light which is presented to the eyes and ears of the users. Sana is first non-invasive bio-therapeutic device intended to treat patients suffering from chronic pain. It produces deep relaxation and promotes hemispheric balances in just 16 minutes which is sufficient to relieve pain. This restoration of balance in the brain induces a flow state by using a combination of visual and auditory impulses. Sana device is a simple mask and comes with headphones and a travel case so that it can be carried anywhere during travel. Sana device is coupled with "The Sana Relief App" which helps in physical and psychological well-being. The scores in the Sana app gives an insight of overall wellness like pain, sleep etc which is very important for the patients and the care givers.²¹

4. Conclusion

Opioid Use Disorder (OUD) is the most dangerous and public health crisis which is gaining a lot of attention worldwide. This is leading to personal issues too like impacting the relationship with the family and friends. With huge amount of people dying worldwide it was imperative to bring in more innovative strategies and devices which would substitute and replace use of opioids or narcotics for the management of pain. Understanding these issues, FDA came up with the challenge program for device manufacturers and were successful in bringing various new technologies into the market. FDA allowed increased interaction with these manufacturers giving them expert opinions, guidance on conducting clinical trials and expedited review. In the past few years CDRH was able to approve more than 200 devices for the management of chronic pain including the pain technologies explained in this article.

Innovation Challenge has proved how collaborative work can bring out new ideas and deliver various therapy options which are safe and effective. Digital Health Technology has an immense role in achieving this. Digital health is used by patients for managing, tracking their health and wellness related activities and thus improving Quality of Life not only by affordable treatment options but also better adherence to treatment.

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