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Brief Overview about Opioid Use Disorder: Review Article

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ABSTRACT

Background: Recurrent opioid usage despite negative consequences is a hallmark of opioid use disorder. There are about 16 million people with an opioid use disorder worldwide, including over 2.1 million in the United States; annually, opioids cause over 120,000 deaths. When visiting Egypt several epidemiological studies on drug abuse in Egypt were conducted in the past few decades. 5.5% of high school students tested positive for cannabis use, while 0.84% tested positive for opiate use.

Objective: Review of literature about opioid use disorder.

Methods: We scoured scholarly papers and databases including PubMed, Google Scholar, and Science Direct for information on Opioid Use Disorder (OUD) between July 2013 and September 2022, however, only the latest or most comprehensive study was considered. The authors also assessed the usefulness of references taken from similar books. Documents written in languages other than English have been overlooked because of a lack of funding to translate them. Unpublished articles, oral talks, conference abstracts, and dissertations were all generally agreed upon not to constitute valid scientific investigation.

Conclusion: Addiction of opioids is characterized by compulsive opioid seeking and use, impaired self-control regarding drug intake, and the emergence of negative effective symptoms (hyperkatifeia) in the presence of drug absence. The binge/intoxication phase of substance abuse initiates an allostatic chain reaction that results in the subsequent withdrawal/negative affect phase and the preoccupation/anticipation phase. With continued drug use, each stage builds on the previous ones until addiction has set in. Medical intervention is used to treat opioid withdrawal symptoms (OWS). Opioid agonist therapy (OAT) is the gold standard for relieving OWS in individuals with moderate to severe OUD.

Keywords: Opioid use disorder, Opioid withdrawal symptoms, Opioid agonist therapy.

INTRODUCTION

OUD is characterised by recurrent opioid use despite adverse consequences. More than 120,000 deaths a year can be directly related to opioids, and over 16 million individuals globally, including more than 2.1 million in the United States, suffer from OUDs **(1).**

In the United States, the number of people who routinely use opioids is comparable to the number of people who have been diagnosed with obsessive-compulsive disorder (OCD), psoriatic arthritis, or epilepsy. OUD is defined by the DSM-5 of the American Psychiatric Association as the compulsive need for and use of opioids notwithstanding negative personal, family, or professional consequences. Opioids include drugs like heroin, morphine, codeine, fentanyl, and even oxycodone, which is a synthetic opioid. OUD is characterised by compulsive opioid seeking, tolerance, and withdrawal symptoms upon abrupt cessation of opioid usage. OUD encompasses a spectrum of disorders, the most serious of which is addiction **(2).**

EPIDEMIOLOGY

In 2018, opioids were the second most commonly used restricted substance in the world, behind only cannabis, with an estimated 58 million users between illicit (30.4 million) and prescription (28 million) opioids. About 1.2% of the global population aged 15-64 falls into this category. Deaths caused by opioids have been on the rise since the 1990s, with many countries currently reporting unprecedented highs.

North America, Australia, the Middle East, and South Asia have the highest rates of opioid abuse in the world. Heroin is more commonly used in the Middle East and South Asia than prescription opioids are in North America and Australia **(3).**

Opioid abuse and addiction occur at different rates among people of different ages and sexes. Opioid use, opioid dependence, and opioid-related fatalities are disproportionately experienced by men. Opioid analgesic prescriptions are more common among women than among men. Opioid overdose deaths are most common in people aged 40–50, reflecting the overall age distribution of people who use opioids. Heroin overdoses are more common among people in their twenties and thirties. Opioid use disorder treatment is most common in those aged 20–35 years **(4).**

When visiting Egypt several epidemiological studies on drug abuse in Egypt were conducted in the past few decades. 5.5% of high school students tested positive for cannabis use, while 0.84% tested positive for opiate use. The preponderance of research shows that men are the ones that abuse drugs; for example, 8.79% of male college students used cannabis compared to 0.09 % of female college students, and 8.36% of male college students took sedatives compared to 5.97 % of female college students. Initial drug use occurred between the ages of 17 and 28. 40% of drug misuse

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cases in Fayoum Governorate's schools and new colleges used cannabis, followed by tramadol (37%), benzodiazepines (23%), and parkinol (9%). The survey found that among drug-using students, 62% also engaged in polydrug usage [4].

RISK FACTORS

Opioid use disorder has many origins. Substance addiction and dependence result from interactions between these four factors: biology, environment, genes, and psychology. Overprescribing of opioid drugs may contribute to the rise in OUD.

According to NHANES statistics, those who are overweight are more likely to consume prescription opioids than those who are not overweight. Tolerance, craving, and withdrawal symptoms are all hallmarks of opioid addiction, and the opioid receptor system has been linked to reward circuitry in the brain.

These results point to the complexity of opioid addiction as a disease. Psychiatric disorders like schizophrenia and bipolar disorder have been studied using the polygenic risk scores approach, and the results have backed up the notion that these conditions are intricate diseases with several causes [5].

Stages of the addiction cycle:

Addiction to opioids is characterized by compulsive opioid seeking and use, impaired self-control regarding drug intake, and the emergence of negative affective symptoms (hyperkatifeia) in the presence of drug absence. Based on theoretical frameworks derived from animal model neurobiology, clinical brain imaging research, and social psychology, a suggested OUD cycle of bingeing/intoxication, withdrawal/negative effect, and preoccupation/anticipation has been put forth.

The dysfunction with incentive salience/pathological habits is represented by the binge/intoxication stage, mediated by the basal ganglia; the dysfunction with negative affective states is represented by the withdrawal/negative affect stage, mediated by the extended amygdala; and the dysfunction with executive function is represented by the preoccupation/anticipation stage, mediated by the lateral prefrontal cortex (PFC). The binge/intoxication phase of substance abuse initiates an allostatic chain reaction that results in the subsequent withdrawal/negative affect phase and the preoccupation/anticipation phase. With continued drug use, each stage builds on the previous ones until addiction has set in (figure 1) [6].

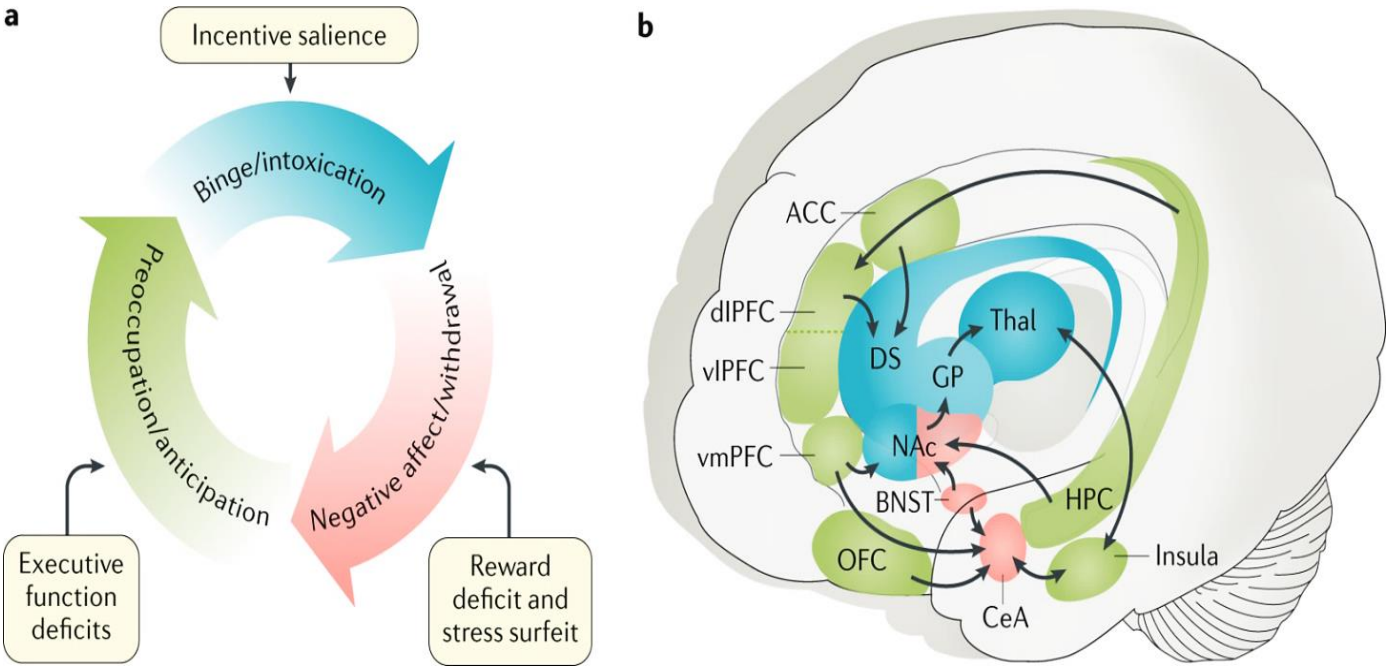

Figure (1): Brain circuits that put people at risk for addiction and how to think about them as a whole. (a) It has been hypothesized that addiction is a three-stage cycle. (b) The binge/intoxication stage [7].

During this time of withdrawal and low mood, the brain's circuits responsible for unpleasant emotions become more active. The negative emotions felt during drug withdrawal may be due to the loss of reward function in the basal ganglia during this time [8].

The preoccupation/anticipation (seeking) stage necessitates the engagement of brain circuits involved in executive function, such as processing signals and environments that elicit craving, as well as the dysregulation of the prefrontal cortex (PFC) and other cortical and allocortical regions. The default mode network, which regulates our interceptive awareness, also shows increased activity during this desire period. The top-down PFC regulation to minimize impulsivity and compulsiveness may be less developed in adolescents, which may increase their susceptibility to substance use problems at a younger age, according to one theory involving prefrontal regions [(7)].

Molecular mechanisms of opioid tolerance:

Opioid tolerance has been linked to several molecular mechanisms, including desensitisation, phosphorylation, -arrestin binding, endocytosis, re-sensitization, and recycling. However, the molecular pathways underlying in vivo opioid tolerance are still unclear. When the receptors are activated by endogenous-opioid peptide endorphin or exogenous opioid agonists like morphine, the G and G subunits dissociate and bind to potassium and calcium channels, respectively. By altering voltage activation, inwardly rectifying potassium channels, and restricting calcium conductance, this method produces cellular hyperpolarization and decreases tonic brain activity [(9)].

Proinflammatory cytokines in morphine tolerance:

Both intra- and inter-systemic adaptation may play a role in the development of drug tolerance. Tolerance to a medicine might develop within a system if it causes the body to behave in an unexpected way. Recent research has shown that chronic morphine use leads to an increase in the expression of a subset of the MOR receptors that signal via the stimulatory Gs adenylyl cyclase rather than the predominantly inhibitory Gi/Go adenylyl cyclase. In particular, MOR-1B2 and MOR-1C1 had their carboxyl-terminal regions phosphorylated due to chronic morphine usage, which increased their interaction with Gs proteins [(10)].

Inter-system adaptation involves the linking of non-primary drug-action systems to the primary drug-action system. Innate immune signaling, including TLR4- and NLRP3-mediated inflammasomes, and neuroinflammation and the production of proinflammatory cytokines are essential molecular processes for cross-system adaptability [(11)].

Neuroinflammatory processes are set into motion when glial cells in the brain are stimulated by circulating cytokines and secrete additional mediators. IL-1 is a crucial modulator of inflammatory pain and opioid analgesia and plays a vital role in host defence and inflammation [(12)].

Long-term morphine therapy was shown to activate glial TLR4, which then boosted nociceptive signals in the spinal cord and contributed to neurotoxicity [(13)].

DIAGNOSIS

Diagnostic criteria:

OUD is a new diagnosis that combines opioid abuse and dependence from the DSM-5. The number of symptoms is used to determine the severity of the disease [(14)].

According to the DSM-5, a'mild disorder' diagnosis requires meeting only two or three of the following criteria, whereas a'moderate disorder' diagnostic needs meeting four to five, and a'severe disorder' diagnosis needs meeting six or seven [(15)].

Opioid misuse without dependence is often classed as hazardous usage if patients are at danger of infection or bodily or mental injury according to the International Classification of Diseases, 10th Revision (ICD-10). This classification system is still widely used in many countries. Opioid use disorder (OUD) is characterized by continued opioid use despite increased physical, mental, social, or criminal problems caused by opioid use, and is characterized by tolerance to the opioid's effects and a shift and preoccupation with minimizing the effects of withdrawal (dysphoria) over achieving euphoria [(16)].

Evaluation:

A thorough history and physical examination is the first step for providers who suspect OUD. In the beginning, a patient might not want to share anything. Sometimes people are just obviously deceitful and manipulative. Adverse medication reactions are a real concern for these people. Heroin addicts have a higher risk of contracting an infection than non-addicts. Therefore, many individuals should have laboratory tests and, based on their symptoms, chosen imaging is performed [(17)].

MANAGEMENT

Opioid use disorder treatment focuses on alleviating OWS, stopping relapse, and reversing overdose. Symptoms of OWS range widely and may include, but are not limited to: hyperalgesia, tremor, anxiety, sadness, excessive desires, irritability, nausea, vomiting, diarrhoea, sleeplessness, lacrimation, sweating, and rhinorrhea. Regular usage of opioid medicines leads to modifications that cause these symptoms. Extreme hunger, sadness, and irritation are all symptoms of OWS that have been linked to the mesolimbic system [(18)].

Mu-opioid receptors in the gastrointestinal system have been linked to nausea, vomiting, and diarrhoea. The locus coeruleus (LC) and its projections have been linked to many of the physical dependence symptoms observed in OWS. When opioids bind to mu receptors on LC neurons, the firing rate of those neurons drops, leading to lowered respiration, muscular tone, blood pressure, and sleepiness. In the absence of opioids, OWS is caused by the adaptive response of increased baseline activity caused by continuous inhibition of LC neurons [(19)]. Managing OWS is the first stage in

treatment for both stopping opioid use and reducing dosage. The severity of an individual's OUD is taken into account when planning treatment for OWS, as per the criteria laid out in the DSM-5 (DSM-5) [18].

MANAGEMENT STRATIGIES

Improvements in patient satisfaction and MOUD adherence have been linked to OUD management in primary care. When it comes to OUD treatment, MOUD is first-rate [20]. In the United States, buprenorphine with or without naloxone and injectable naltrexone make up the MOUD offered at primary care clinics (Box 1). Buprenorphine's efficacy in reducing opioid use and increasing treatment retention has been repeatedly established, leading to better health (i.e., fewer new cases of HCV and HIV) and longer life expectancy [21].

Medications for opioid use disorder:

Several medications for opioid use disorder have been approved by the Food and Drug Administration in the United States. OUD can be treated with a variety of medications, including oral methadone, buprenorphine implants (Probuphine), buprenorphine sublingual tablets (Suboxone), buprenorphine sublingual tablets (Subutex), and injectable long-acting naltrexone (Vivitrol). Buprenorphine, methadone, and naltrexone have all been approved by the FDA for use in patients aged 16 and up, although naltrexone requires patients to be at least 18 years old [22].

Methadone:

Methadone, the medicine for which the most studies have been conducted, may also be the most effective in keeping patients in treatment for opioid use disorder. Its use is associated with a decline in illegal opioid use and a reduction in HIV risk behaviours that contribute to transmission of that virus as well as a reduction in the overall risk of death[23].

Patient Selection:

Patients with a documented opioid use problem and of legal age can enroll in most opioid treatment programs. Patients consuming more than 120 mg of methadone daily, especially those at risk for a prolonged QT interval, should undergo electrocardiography due to the increased risk of torsades de pointes. Oversedation is another risk for those with compromised liver function. Regular programme visits may either hasten or postpone stability, therefore clinicians should discuss this with patients before commencing maintenance therapy [24].

Buprenorphine:

Primary care clinics have access to two helpful medications: buprenorphine and buprenorphine/naloxone. It indicates that buprenorphine, when administered at a dose of at least 16 mg per day, is just as effective as methadone in reducing illicit opioid use and encouraging treatment adherence [25].

Patient Selection:

Most people with opioid use disorder can get buprenorphine from their primary care doctors. The increased risk of overdose from buprenorphine led the FDA to previously advise against administering it to patients who were also taking benzodiazepines or consuming alcohol. Opioid overdose warnings that previously included alcohol and benzodiazepines have recently been removed [26].

Given that naloxone's effects may be exacerbated in those with liver disease and that hepatotoxicity has been linked to buprenorphine use, those with a Child-Pugh score of 7 or above should be given buprenorphine alone at a lower dose while their liver function tests are monitored. Patients who are dependent on opioids for the management of pain may benefit from switching to buprenorphine [27].

Dosing consideration:

Patients need to be in a moderate withdrawal stage before treatment can begin. You can begin your prescription regimen at home without worry. To alleviate withdrawal symptoms and reduce cravings, the patient's dosage should be increased gradually over the next few days. Higher doses are associated with improved treatment adherence and reduced use of illicit opioids, and the typical dose ranges from 12 to 24 milligrams [27].

Naltrexone:

Naltrexone is a drug that blocks the opioid receptor. Once bound, it blocks the effects of opioids, reducing withdrawal symptoms and the need for additional pain medication [28].

Oral naltrexone (Revia) is rarely effective for persons with opioid use disorder due to low treatment compliance. Opioid use and cravings can be reduced with intramuscular naltrexone; however, the treatment's success is hindered by high attrition rates in the early phases. Patients who successfully initiate treatment with injectable naltrexone tend to achieve similar rates of opioid abstinence as buprenorphine recipients. While buprenorphine and methadone have been found to decrease mortality and overdose, naltrexone has not. Naltrexone patients are at a higher risk of overdosing on opioids because their tolerance for these drugs has been reduced [21].

Patient' selection:

In order to avoid experiencing withdrawal symptoms too early, individuals using naltrexone must abstain from opioids for seven to fourteen days beforehand. Transaminitis and injection-site reactions are quite uncommon with the intramuscular version. Patients on naltrexone will also have no reaction to typical opioid dosages. Patients in excruciating pain

may require additional interventions, including high doses of opioids, regional or general anaesthesia, or both [29].

Dosing consideration:

Every four weeks, patients receive an intramuscular injection of 380 mg of naltrexone. To make sure the patient is through with opioid withdrawal before starting naltrexone, a naloxone challenge (i.e., 0.8 mg subcutaneously) may be utilized [30].

Reducing harm:

Patients with opioid use disorder should have access to pharmacotherapy, although some won't respond to treatment and others will relapse. It is important to educate patients with a history of opioid use disorder on the many harm reduction strategies available to them [31].

Naloxone:

To reduce the negative effects of opioid use disorder, naloxone is the primary medication. Naloxone should be provided to anyone with a history of opioid use disorder, who receives a prescription for chronic opioids (particularly at doses greater than or equal to 50 mg morphine equivalents daily), or who uses illicit drugs. Because fentanyl and other synthetic opioids can be contaminated with non-medical opioids, benzodiazepines, cocaine, and methamphetamine, all drug users are at risk of an opioid overdose [32].

Naloxone should be administered to any potential witnesses to an overdose. Most states have rules protecting both prescribers and people who administer naloxone in the community from liability when they treat an overdose victim. Intranasal formulations are simple to deliver, even for those with limited experience. When prescribed naloxone, the vast majority of patients respond positively and do not engage in potentially harmful behaviour (such as increasing their dosage or mixing it with other drugs) [33].

CONCLUSION

Addiction to opioids is characterized by compulsive opioid seeking and use, impaired self-control regarding drug intake, and the emergence of negative effective symptoms (hyperkatifeia) in the presence of drug absence. The binge/intoxication phase of substance abuse initiates an allostatic chain reaction that results in the subsequent withdrawal/negative effect phase and the preoccupation/anticipation phase. With continued drug use, each stage builds on the previous ones until addiction has set in. Medical intervention is used to treat opioid withdrawal symptoms (OWS). Opioid agonist therapy (OAT) is the gold standard for relieving OWS in individuals with moderate to severe OUD.

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