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Introduction to Opioids: A Review

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ABSTRACT

Opioids are psychoactive chemical substances that have been known to reduce feelings of pain. They are a class of drugs that have been implicated in depressing the central nervous system and causing several physical and psychological reactions including numbness, inducing sleep, hyperactivity, drowsiness, mental confusion, nausea, euphoria as well as constipation. The commonest examples of opioids are tramadol, heroin, morphine, codeine, etc. The main reason for Opioid use is for therapeutic purposes. However, the use of Opioids has also been widely implicated in increasing energy and libido. It is also used as a coping mechanism against pressure, the impact of post-traumatic stress, poverty, crime, etc. The indiscriminate use of opioids is usually associated with overdose, addiction and withdrawal. This study focuses on the incidence of opioid use in Nigeria that has become an epidemic in all regions of the country. In addition to being an active component of cough syrups, Codeine and tramadol which are the predominant types of opioids in Nigeria, have been reported to be a leading cause of health implications and fatality amongst Nigerians, cutting across religion, gender, age, social and educational backgrounds. Due to their availability, ease of accessibility, relative affordability, and the euphoric sensation they cause, Codeine and Tramadol have been tremendously used indiscriminately. There are recorded incidents of fatal overdose and adverse interactions between opioids and other drug classes such as Indian hemp. The addictive ability and the resultant antisocial behaviour, fatality and potential health implication poses Opioid use as a threat in the society. This menace has therefore incited the government to put measures in place to enforce the reduction in Opioid use.

1. Introduction

Opioid also known as “narcotics” is derived from “the Greek word for stupor” and refers to a range of substances that reduces sensation and alleviates discomfort. They are referred to as psychoactive compounds with sleep inducing properties. They are chemical substances whose effects include reduction in pain, tension, anxiety, and aggression. It also causes drowsiness, inability to concentrate, apathy and decreases bowel movement. Opioids acts on the central nervous system by depressing it and binds with receptors in the brain and other organs thereby blocking the sensation of pain. Examples of opioids include heroin, cocaine, codeine, morphine, tramadol, oxycontin. They come in various forms and colours and can be swallowed, smoked, injected, or sniffed (ACOEM, 2011).

1.1. Opioid Receptor

Both endogenously generated opioid peptides and exogenously supplied opioid medications, such as morphine, activate the opioid receptor family of binding sites. There are four (4) major identified opioid receptors family:

a) Mu opioid receptor (mu for morphine): MOP-R has been linked to behavioural reactions including analgesia, hyperlocomotion, respiratory depression, constipation, and immunosuppression. MOP-R has been implicated in behavioural responses, which include numbness, hyperlocomotion, respiratory depression, convulsion, and reduction of the efficacy of the immune system. In experiments on animals, it could be discovered that MOP-

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Rs play a role in the neural circuitry that results in reward and its addictive behaviour.

b) Keppa opioid receptor (kappa for ketocyclazocine): Studies of KOP-R deficient mice suggest that KOP-R agonists may help reduce pain related to internal organs.
c) Delta opioid receptor has been linked to the emergence of morphine tolerance. Affective illnesses like schizophrenia, bipolar disorder, and manic depression may have new therapy options if ligands that target this receptor are discovered, according to studies.
d) Nociceptin/orphanin FQ opioid receptor (NOP-R)

Endocytosis is pivotal in the regulation and recycling of opioid receptors. Endocytosis's control over opioid receptors has a protective role in preventing the tolerance and reliance on opioids from developing (Waldhoer et al., 2004). Opioid ligands are chemical substances that elicit or activate receptors. The four precursors pro-opiomelanocortin, proenkephalin, prodynorphin, and pronociceptin/orphanin FQ serve as the main sources of the endogenous opioid peptides (Waldhoer et al., 2004).

1.2. Opioid Tolerance

Opioid tolerance refers to the increasing loss of reaction or decreasing efficacy of a drug, thus requiring increased dosage to achieve desired analgesic/therapeutic effects. Adverse effects such as analgesia, pruritus, nausea, sedation, and respiratory depression might develop (Marion Lee et al., 2011).

1.3. Opioid Induced Hyperalgesia

Opioid Induced Hyperalgesia is a state of pain sensitization brought on by opioid exposure is known as hyperalgesia. A patient receiving opioids for the treatment of pain may become more sensitive to some painful stimuli, which is a characteristic reaction of the disease. The type of pain felt could be different from the initial underlying discomfort or it might be the same as it. It sometimes explains opioid loss of efficacy. Opioid induced hyperalgesia is observed in former addicts, preoperative patient's exposure to opioids, and exposure to very low and very high dose of opioid (Marion Lee et al., 2011). High doses of opioids used over an extended period of time may lead to the development of hyperalgesia, which may be related to opioid metabolites such morphine 3-gluceronide (M3G). The apoptosis of cells brought on by opioids may also be linked to hyperalgesia. Spinal neural circuits may shift as a result of the death of GABA neurons through apoptosis (Mao et al., 2002). The development of hyperalgesia is also significantly influenced by NMDA receptor agonism and glycine, an inhibitory neurotransmitter that mediates the postsynaptic inhibition of spinal neurons (Mercadante et al., 2003). Gabapentin has been reported to mitigate opioid induced hyperalgesia in several case studies (Stoicea et al., 2015). The NMDA antagonist, ketamine stopped the fentanyl-induced hyperalgesia (Mao et al., 1995).

1.4. Opioid Addiction and Withdrawal

Opioid addiction is a long-term condition marked by obsessive, or uncontrollable, drug seeking and use despite negative effects and permanent brain alterations (NIDA 2018). The neuronal brain circuits linked to reward (positive reinforcement), stress and anxiety, learning and memory are all thought to be modulated in addiction (ACOEM 2011). Opioid addiction activates the mesolimbic dopamine system. Opioids all act on this system or specific receptors to increase dopamine synaptic levels (Gupta & Kulhara, 2007).

Withdrawal occurs when there is a cessation and drastic reduction dosage of opioid by a chronic user. It is dependent on the drug used, total daily dose, route of administration, and interval between doses. The symptoms include watery eyes, runny nose, sweating, restlessness, nausea, irritability, tremors, increased heart rate, and severe depression. Withdrawal takes its toll without intervention and many of the symptoms abate within few days or weeks (ACOEM 2011).

1.5. Opioid Overdose and Interaction

Opioid overdose (opioid poisoning) is the excessive consumption of opioid which can have fatal consequences. Symptoms are cold clammy skin, convulsion, slow breathing, and extreme drowsiness. Opioids interact with substances such antidepressants, antihistamines, analgesics, and alcohol. Naloxone is used as an antidote for opioid overdose (Pérez-Mañá et al., 2018).

1.6. Reasons for Opioid Use

Apart from the therapeutic use, many uses opioids to cope with pressure & stress, dull the impact of traumatic experience, to increased energy and sexual stamina, for enjoyment purpose due to its euphoric effect and induce insomnia. Other reasons include poverty, crime, unemployment, and family lifestyle (Odejide, 2006).

2. Pharmacology of Opioids

2.1. Opioid Mechanism of Action

Specific transmembrane neurotransmitter receptors (mu, kappa, delta) that couple G proteins are activated by opioids. The process of intracellular communication is started by molecules called G proteins. The intracellular process of signal transduction is started by G protein stimulation. Endogenous mu opioid receptor activation causes the classic opioid effects of analgesia, withdrawal, and reward. Different G proteins that drive Mu receptor activation can have secondary effects on messenger-producing enzymes (Cami & Ferre, 2003). Opioid receptor activation causes a sharp reduction in secondary messengers like cAMP. The molecular effects of chronic opioid receptor activation are the exact reverse of those of acute opioid injection. Long-term opioid usage alters gene transcription and upregulates cAMP levels.

Both the central and peripheral nerve systems have opioid receptors. The location of the receptor, the types of G proteins found in the stimulated brain tissues, the frequency, and the duration of activation will all affect the results of activation of neuronal mu receptors. Respiratory depression, analgesia, euphoria, and miosis are just a few of the reactions brought on by the activation of mu receptors in the central nervous system (Reisine & Pasternak, 1996).

2.2. Codeine

Codeine or 3-methymorphine ($C_{18}H_{21}NO_3$) is a mu opioid receptor agonist utilised as a central analgesic, anti-tussive and anti-diarrheal purpose, and it is usually combined with acetaminophen, aspirin, caffeine, and ibuprofen for effective pain relief. It is an active ingredient in cough syrups. Recommended daily adult dose is 240 mg through oral and

rectal administration. Apart from the therapeutic use of codeine, it is used for recreational purposes because of its intoxicating, dampening, sedative, and euphoric effect (Hout, 2014). There are reports of brown codeine used as a traditional abortion method (Oye-Adeniran et al., 2005).

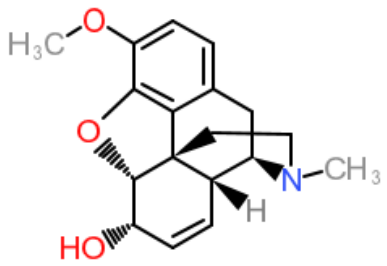

Fig. 1. Codeine structure. Source: ChEBI

2.3. Metabolism of Codeine

Metabolism of codeine is influenced by genetic factors, age, and the presences of some substances. Due to genetic variation, certain individuals metabolise codeine into morphine faster thereby rapidly increasing morphine levels in blood which can have fatal consequences even with small dosage. They are referred to as ultra-rapid codeine metabolizers. Substances such as alcohol, central nervous system depressants, and other opioids interfere with codeine metabolism. Its combination with chocolate is perceived to incur dysphoric effects.

About 70-80 percent of the dosage of codeine that is delivered is converted into codeine-6glucuronide (C6G), morphine and norcodeine, respectively, by conjugation with glucuronic acid, O-demethylation, and N-demethylation. The two main enzymes involved in the conversion of codeine to C6G are UGT-2B7 and 2B4. The main enzyme that converts codeine to morphine is cytochrome P450-2D6, and the main enzyme that converts codeine to norcodeine is cytochrome P450-3A4. Conjugation with glucuronic acid is used to further metabolise morphine and norcodeine. Morphine-3-glucuronide and morphine-6-glucuronide are the glucuronide byproducts of morphine. In humans, morphine and M6G have analgesic effects. About 10% of the total dose of codeine is unaltered codeine, and about 90% is eliminated by the kidneys. With peak plasma concentrations occurring in one hour and a half-life of three hours, it has a high oral to parenteral potency ratio (DrugBank 2019).

2.4. Adverse Effects of Codeine

The consequence of codeine includes unpleasant taste in the mouth, epistaxis, facial flushing and swelling, thin pupils, burning sensation, numbness in facial and extremities, sweating, breathlessness, severe nausea, stomachache, vomiting, diarrhoea and hallucination. It also has a dissociation effect and inhibits orgasm. Overdose symptoms include uncontrolled body spasm, loss of vision & control, difficulty breathing, paralysis and sometimes death (Hout, 2014).

Codeine and other opioids can cause seizures, but the exact mechanism by which they do so is unclear. However, the pathogenesis of these seizures is thought to involve mu, kappa, and delta opioid receptors mediating the activation of alpha adrenoceptors, antagonising the inhibitory effect of glycine in the spinal cord, inhibiting GABAergic neurons, and increasing the activity of excitatory NMDA receptors (Raji et al., 2013).

2.5. Tramadol

Tramadol, a codeine analogue, is a double acting pain reliever. It is a central nervous system reuptake inhibitor of serotonin and norepinephrine. These analogue & its metabolites act as a selective mu opioid receptor agonist with 10 fold less activity than that of codeine and has less risk of addiction. It is administered orally, rectally, sustained, and bypasses the placenta. Its presence is noticed in breast milk and implicated in Serotonin Syndrome as a single causative agent (Beakley, et al., 2015).

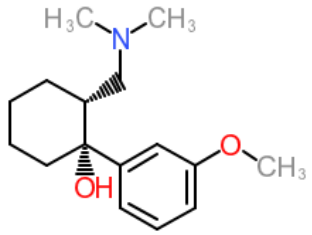

Fig. 2. Tramadol. Source: ChEBI

2.6. Metabolism of Tramadol

Tramadol metabolism is influenced by genetic factors and other substances such as alcohol, antidepressants, and other serotonergic drugs. It goes through substantial O- and N-demethylation and conjugation processes within the liver during first pass metabolism. Tramadol and its metabolites are 90% removed by the kidneys, with the remaining 10% being eliminated through faeces. The enzymes cytochrome P450 CYP2D6 and CYP3A4/CYP2B6 catalyse the demethylation process to produce the metabolites O- and N-demethylated tramadol, respectively. O-desmethyl-tramadol (metabolite M1) is the only one of the 23 discovered metabolites that has analgesic characteristics. M1, M2, and M5 are the primary metabolites. Tramadol's half-life is 5 to 6 hours, while the M1 metabolite's half-life is 8 hours (Beakley, et al., 2015).

2.7. Adverse Effects of Tramadol

Adverse effects include loss of appetite, visual and auditory hallucinations, insomnia, and hyperactivity. Overdose effects include convulsion, loss of consciousness, respiratory distress, nausea, and slurred speech. Tramadol use causes Serotonin syndrome which is potentially fatal. Serotonin syndrome is the result of excessive serotonin at the 5-HT receptor, which causes a disorder of mental, autonomic, and neuromuscular function. Tramadol influences serotonin uptake and release (Pasha et al., 2020).

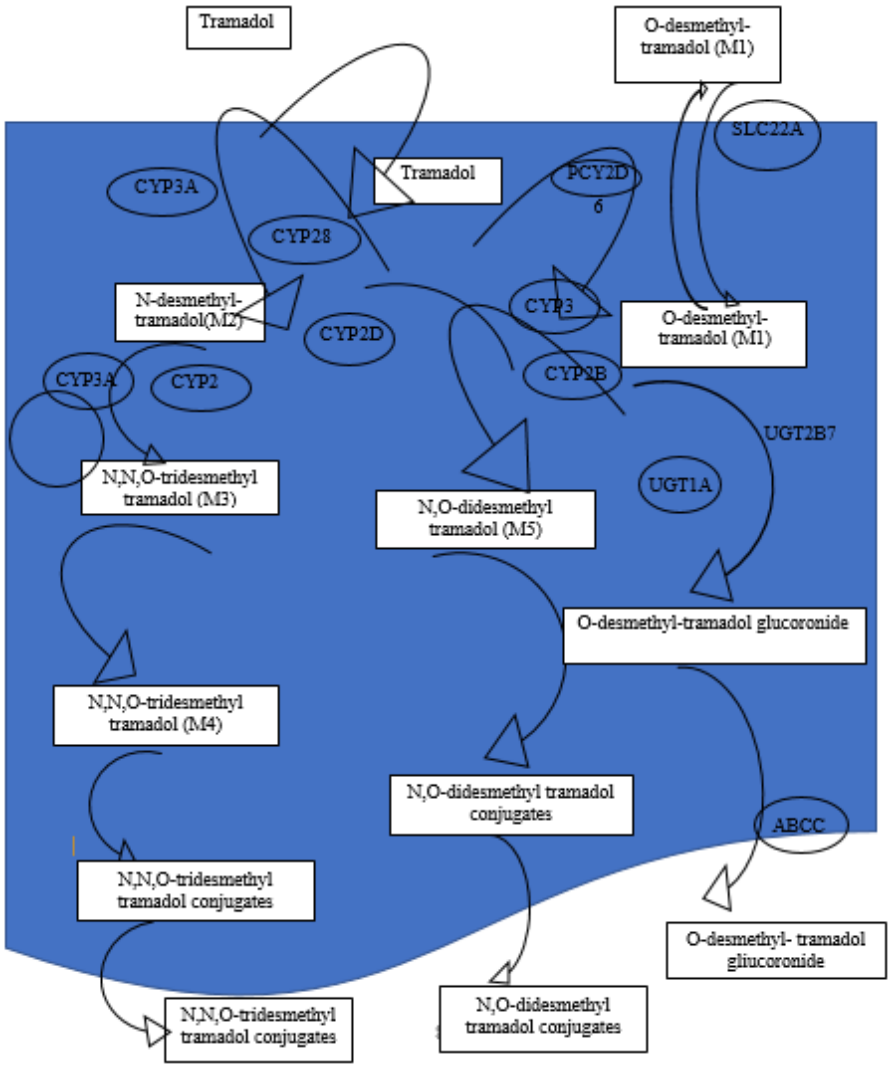

Fig. 3. Tramadol metabolism pathway Source: pharmgkb.org

Trends of indiscriminate opioid use has become a menace in Nigerian society with resultant health implications. The epidemic is reported in all part of the country and cut across both sex although it is predominant among the male counterparts. It also cut across age, religion, educational and social status (Dankani, 2012). The Federal Government declares that 14.3 million Nigerians abuse cocaine, Tramadol and others (PUNCH, 2019).

Opioids preferred by Nigerian abusers include codeine and tramadol predominantly. Cough syrup usage in Northern Nigeria has already eclipsed all other drug misuse due to the ease of access, relative affordability, and availability of the substance until a recent crackdown by the government through its laws and agencies. It serves as an alternative to alcohol because of its non-acceptance by sharia law.

According to a Daily Trust Newspaper report dated March 3rd, 2012, 11% of Northern Nigerian teenagers use drugs in some capacity. There are reports of Tramadol use and addiction in the IDP camps (Aljazeera, 2019). Physiological consequences of opioid abuse include anti-social behaviour, restlessness, insomnia, and impaired mental state.

The following are the recent policies and efforts by the Nigerian government to combat the opioid epidemic.

- On the 1st of May 2018, the Nigerian government banned the manufacturing and importation of codeine containing cough syrup (BBC News, 2018).
- Large quantities of Tramadol were intercepted at the Lagos port by NDLEA (PUNCH, 2018)
- There have been several seizures and arrests made by relevant government agencies such as the Nigeria Police, Nation Drug Law Enforcement Agency (NDLEA) and National Agency for Food and Drug Administration and Control (NAFDAC) to combat this menace.

Documented Incidences of Opioid Use

- In Imo state, two dead and a comatose student at Federal university of Technology, Owerri and Federal Polytechnic, Nekede were alleged of taking tramadol with Indian hemps for sexual purposes (Vanguard Newspaper, 2019).
- Two murder suspects Ayuba Idris (20 years) and Taisu Abubakar (23 years) confess to killing their victims after

taking Tramadol and Indian Hemps (Vanguard newspaper, 2019).

- A.O, a 23-year-old patient with a 7 year abuse history of codeine containing cough syrups with seasonal use of tramadol and alcohol. He also abuses cigarettes and cannabis. He became dependent and observed withdrawal symptoms when discontinued, and began to manifest seizure 3 years after the onset of his abuse (Raji et al., 2013).

3. Conclusion

Opioids are substances that act on the central nervous system by binding to respective receptors to block pain. Examples of opioids include heroin, cocaine, codeine, morphine, tramadol, and oxycontin. Opioid receptors are a binding site family activated by opioid peptides or opioid drugs. There are 4 types of opioids receptors which include the Mu, Kappa, Norciceptin, Delta receptors.

Opioid addiction is the uncontrollable drug seeking habit of an opioid user. Withdrawal symptoms occur when there is a drastic reduction or cessation of opioid drugs by a chronic user. Symptoms include watery eyes, runny nose, sweating, restlessness, nausea, irritability, tremors, increased heart rate, and severe depression. Withdrawal is dependent on factors like route of administration, frequency of administration and the opioid drug itself. Opioid tolerance is a situation in which increase in drug dosage is necessary to achieve desired effects.

Opioid hyperalgesia is a phenomenon of pain sensitivity to stimuli that does not elicit pain experienced by opioid users for chronic pain. Long term and high dose use have been related to hyperalgesia. It's possible that opioid-induced cell death is connected to abnormally heightened sensitivity to pain. Gabapentin mitigates the effect of opioid induced hyperalgesia. Ketamine prevents fentanyl-induced hyperalgesia.

Opioid interacts with other substances which affects its metabolism or receptor binding therefore influencing its action. Such substances include alcohol, analgesics, antidepressants, antihistamines etc. These interactions could cause opioid poisoning. Opioid overdose is the excessive intake of opioids drugs thereby becoming toxic.

Opioids work by coupling G proteins, which are molecular intermediates, to receptors in the central and peripheral nervous systems, facilitating intracellular signal transmission and communication. Secondary consequences of G protein activation include changes in the messenger-producing enzymes adenyl cyclase and phospholipase C. Opioid receptor activity generates a decline in cAMP, while constant opioid usage induces an increase in cAMP, which changes how genes are transcribed. The central nervous system's mu receptor is activated, causing reactions including analgesia, euphoria, miosis, and respiratory depression. Cough suppression is brought on by stimulating the bronchi's peripheral mu receptors.

Codeine, an active component of cough syrups, is a mu opioid receptor agonist. It is usually combined with acetaminophen for therapeutic use. Metabolism is influenced by genetics, age and other factors. The major metabolite morphine and norcodeine are catalysed by cytochrome P450 2D6 and P450 3A4 respectively which are further conjugated with glucuronic acid. Morphine and morphine-6-glucuronide (M6G) have analgesic activity in humans. Codeine is mostly excreted via the kidney. Adverse effects of codeine include nausea, vomiting, numbness, hallucinations and so on.

Tramadol is a mu receptor agonist used as an analgesic agent. It is a reuptake inhibitor of serotonin and norepinephrine. It undergoes O- and N- demethylation and conjugation reactions. Only one metabolite, odesmethy-tramadol (M1), has analgesic qualities. It is majorly excreted via the kidney. Its adverse effects include insomnia, hyperactivity, loss of appetite, serotonin syndrome.

In Nigeria, the preferred opioids included tramadol and codeine due to their ease of accessibility. Due to its addictive ability and resulting antisocial behaviour, it has been a major concern. The opioid crisis caused the government to place some sanctions and crackdown on opioids.

Competing Interests

The authors have declared that no competing interests exist.

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