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Pathophysiology of Substance Abuse: A Review

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Abstract: ***Substance abuse is one of the types of substance use disorders. According to American Psychiatric Association (APA), substance abuse can be defined as faulty adaptation of using substances as evidenced by recurrent and adverse effects associated with frequent use of the substance. Opioid analgesics and heroin are the most commonly abused drugs. Opioid's abuse is more common in men compared towomen. The substances of abuse can be categorised as depressants or stimulants of the central nervous system. These substances interfere with the release and reuptake of the neurotransmitters as well as their accessibility to the receptor binding sites. They also affect the reward pathway by stimulating neurons to release neurotransmitters leading to subjective feeling of wellbeing. Substance abusers are prone to many problems like addiction, tolerance, dependence, accidents, behavioural and health related problems, suicidal attempt, morbidity and mortality. Quite number of reference literature were accessible using various search engines and internet for this research. Out of which 21 were selected based on their relevance to the tittle and contents of the research. The 21 articles and related information were reviewed critically, to assess the aetiological risk factors, pathophysiology, consequences and possible pharmaco-therapeutic options of substance abuse disorder, excluding alcohol and tobacco.Diagnosis is mainly clinical. Some of the treatment options are methadone, buprenorphine and naloxone. However, prevention is better than cure. Young adults are discouraged from taking any substance or drugs not specifically prescribed by a doctor or qualified health personnel.***

Keywords: Substance, abuse, neurotransmitter, opioids, withdrawal symptoms

1. Introduction

Substance abuse is one of the types of substance use disorders. According to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-4) of American Psychiatric Association (APA), substance abuse: can be defined as faulty adaptation of using substances as evidenced by recurrent and unfavourable results associated with frequent usage of substances.Alternatively, substance abuse is also an insistent and repetitive application of the substance, despite solemn health related problems.Substance dependence is associated with augmented tolerance for that particular substance, making an individual to look for much higher dose or quantity of the substance to attain the desired effect. Drug addiction: simply means the obsessive looking for and using a substance (drug) in spite of unfavourable outcomes (Nestler and Landsman, 2001).The two words Addiction and dependence of a substance are often used interchangeably. In view of the confusions arising in making diagnosis, the current fifth edition of DSM-5 modified the definitions and amalgamated them into a single disorder known as "substance use disorder" with a rangeof severity starting from mild, moderate to severe, in view of the confusions arising in making diagnosis (American Psychiatric Association, (2013). According toWorld Health Organisation (WHO): it is characterised by; disappointment in taking major responsibilities at work, school or home, frequent substance associated legal issues and insistent inter personnel issues aggravated by unfavourable effect of the substance (World Health Organization, 2004).Opioidand opiate analgesics including heroin are most commonly abused drugs, ever since 1990s. Virtually, Americans used up 80% of the world's opioid supply (Preda, 2015).Opioid abuse is more common in males than females. Male to female ratio is about 3:1 for heroin and 1.5:1 for Opioid analgesics.Substance use disorder is a global problem not only affecting a country or few countries of the world. It was estimated in 2010 that, the Global burden of substance use disorder and Prevalent Cases were as follows: Opioid dependence (64.1%), Cocainedependence (37.6%), Amphetaminedependence (35.3%)andCannabis dependence, 32.9% (Whiteford et al., 2015). According to one study conducted in Nigeria, the most common substances of abuse are as follows in Table 1 below.

Table 1: some of the commonly used drug of abuse in Nigeria

Substance of abuse	NO (%)
Tramadol	52(50)
Flunitrazepam (Rhohypnol)	18(17.3)
Diazepam	17(16.3)
Codeine	11(10.6)
Pentazocine	5(4.8)
Heroin	4(3.8)
Solution	1(1.0)

Source: Onyencho *et al*., (2016).

2. Aim and Objectives

Main aim

The main aim of this research is to describe the medical consequences of substances of abuse in the central nervous system, to suggest possible pharmaco-therapeutic options for condition.

Specific objectives

The specific objectives are:

- To recognise the various types of substances of abuse
- To elucidate some of the likely risk factors/ causes of the disease.
- To understand the derangement of body functions in an individual following exposure to substance of abuse (pathophysiology).
- To describe the cellular, biochemical as well as genetic aspect of the disease.

- To describe the development of addiction, tolerance and dependence due to substance abuse particularly in opioid and opiates analgesics (pathogenesis).
- To recognise the complications associated with the disease.
- To know the basic treatment options for particularly opiate abuse and preventions.

3. Methodology

Quite number of reference literature were accessible using various search engines and internet for this research. Out of which 21 were selected based on their relevance to the tittle and contents of the research. The 21 articles and related information were reviewed critically, to assess the aetiological risk factors, pathophysiology, consequences and possible pharmaco-therapeutic options of substance abuse disorder, excluding alcohol and tobacco.

3.1 Classification

Substances/illicit drugs can be categorised as follows:

Depressants of Central Nervous System: Benzodiazepines (e.g. Diazepam), barbiturate (e.g. phenobarbital), Rohypnol (Flunitrazepam) aka "the date rape drug" and Ketamine. General Effects; Slow down nervous system activity, decrease anxiety, drowsiness and sedation.Modes of usage; orally, Injectably, Smoking and Snorting.Withdrawal Symptoms; Seizure, hallucinations, tremors, irritability and anxiety (World Health Organization, 2004; Williams and McElhiney, 2011).

Stimulants of Central Nervous System: These substances together with opiates and opioids strongly stimulate the brain's rewardsystem and decrease the rewarding effect of normal behaviour. Examples; Cocaine (crack), amphetamines, methamphetamines, nicotine and even caffeine (in very high dose).General Effects; elevate nervous system activity, raise heart rate and blood pressure, swinging mood, but poor of appetite.Modes of usage; Snorting, Smoking, Injectable, orally, rubbing into gums, rectal insertion.Withdrawal Symptoms; Depression, Severe hunger, Exhaustion (Williams and McElhiney, 2011).

Opiate and Opioid (narcotic) analgesics: Natural opioids: six opium alkaloids: morphine, narcotine, codeine, thebaine, papaverine and narceine. Endogenous neural polypeptides like endorphin and enkephalin are also natural opioids.Semi-synthetic opioids: heroin, oxycodone, oxymorphone, and hydrocodone.Synthetic opioids: buprenorphine, methadone, fentanyl, alfentanil, levorphanol, meperidine (Preda, 2015).Modes of usage; orally, snorting, smoked and injection. Effects; Drowsiness, sedation and analgesia.Prolonged Use/Abuse, physical and psychological dependence, etc.Withdrawal Symptoms;generally, start within 24 hours after the last usage and end up to 10 days. They include, yawning and uneasiness (Williams and McElhiney, 2011).

Hallucinogens (Psychedelics): They causechange in state of observation and misrepresentation of reality LSD (lysergic acid diethylamide) MDMA (3,4methylenedioxyamphetamine, ecstasy), PCP (phencyclidine), and Salvinia divinorum (herb) commonly found in Mexico and South America.General Effects; visual and auditory hallucination, fast emotional swings, delusions, sexual dysfunction, development of chronic mental disorders subsequent long-term use.Modes of usage; Injected, Ingestion, swallowing, Smoking and Sniffing.Withdrawal Symptoms;although psychological dependence is possible; no withdrawal symptoms happen when use is stopped. (World Health Organization, 2004; Williams and McElhiney, 2011).

Inhalants: reduce body function based on the quantity used. They affect both CNS and PNS. Their chemical contents are absorbed into myelin sheath that lastly lead to polyneuropathy. **Aerosols**- (Spray paint and lighter fluid). Nitrous oxide - Nitrous oxide combined with oxygen to deliver effective analgesia. Nitrites - Amyl nitrite (used in treatment of angina).General Effect; loss of appetite, dizziness, slurred Speech, Halitosis, eye irritation, Chronic damage to nervous system as well as damage to brain, liver and kidney, blood and bone marrow. Peri-oral signs; chemical burns and sores around nose and mouth. Modes of usage; Inhalation, bagging and huffing. Withdrawal Symptoms,even though psychological dependence is possible; withdrawal Symptoms do not happen when usage is stopped (Williams and McElhiney, 2011).

Cannabis (Marijuana):
It is a derivative of cannabis sativa plant. The active ingredient is delta-9-tetrahydrocannabinol (THC). It contains more benzopyrene (carcinogen) than tobacco. General Effect; damage to immune system, misperception, abnormal coordination, high risk of lung cancer, chronic bronchitis, reduced memory (temporary and permanent). Modes of usage; Smoking and oral consumption. Withdrawal Symptoms; irritability, sleeplessness, anxiety and aggressiveness (World Health Organization, 2004; Williams and McElhiney, 2011).

3.2 Risk Factors/Causes

- **Pharmacological risk factors**; it is due to their pharmacological action and the effects they produce. E.g., opioids are powerfully strengthening drugs due to their special euphoric, analgesic effects and the likelihood to decrease anxiety. They are particularly associated with increase abuse. (Preda, 2015).
- **Social risk factors**: the poor parental function and high rate of redundancy and cultural belief play important role in tilting majority of individuals to substance abuse. (Williams and McElhiney, 2011; Preda, 2015).
- **Environmental risk factors**; most of these substances are readily available, accessible and cheap throughmedia and within our geographical settings (Williams and McElhiney, 2011).
- **Psychological risk factors**;ego defects constitute the foundation of drug use. Opioids were hypothesized to aid the ego in handling problems of anxiety, anger and agitation.
- **Behavioural theory** assumes that basic reward mechanisms prolong addictive behaviour. Similarly, pre-

existing mental health disorder is correlated with substance abuse (Preda, 2015).

- **Genetic aspect/risk factor**; epidemiological genetic investigations proposed a high grade of heritable susceptibility for substance dependence. Gene polymorphisms for various neurotransmitters and or their transporters or their receptors and Catechol-O-methyltransferase (COMT) altogether linked with susceptibility to substance (opioid) dependence (Preda, 2015).

Genome Wide Association Studies (GWAS) showed that the disease is highly polygenic; the genes involve in specific endophenotypes and populaces. (Hall et al., 2013).

- **Family and adoption studies**; indicates that substance dependence is a familial trait attributed to either shared environment or shared genes.
- **Twin studies** consistently show higher monozygotic (identical twins) than dizygotic (non-identical twins) coincidence,indicating a genetic effect (World Health Organisation, 2004). The heritability summary of some substances of abuse (See Table 2).

Table 2: Heritability summary for some of the selected substances of abuse

Substance of abuse	*Estimated heritability (%)*	*Linkage*	*Candidate genes*
Opioids	70	------	CYP2D6
Nicotine	60-80	Chromosome 5q close to D1 receptor loci	CYP 2A6 Dopamine D4 and β-hydroxylase
General combine risk for substance dependence	50-60	Loci on chromosome 15, 19q12-13	Dopamine D1, D2, and D4 receptors. Monoamine oxidase A.

Source: World Health Organization, (2004).

3.2.1 Pathophysiology

Understanding the basis in studying the deranged function of organs/body systems in an individual following exposure to substance of abuse is of paramount important. However, there are three important components in the pathophysiology of the disease: The nerve cell, neurotransmitters and receptors.Cellular communications within the brain take place between neurons. Abused/illicit drugs modify several parts of this communication between the neurons to exert their effects. Neurons are specific cells existing in different forms and sizes. (World Health Organisation, 2004). They consist of four fundamental portions; the cell body, dendrites axon (nerve fibre) and axon terminals as seen in figure 1, (Williams and McElhiney, 2011).

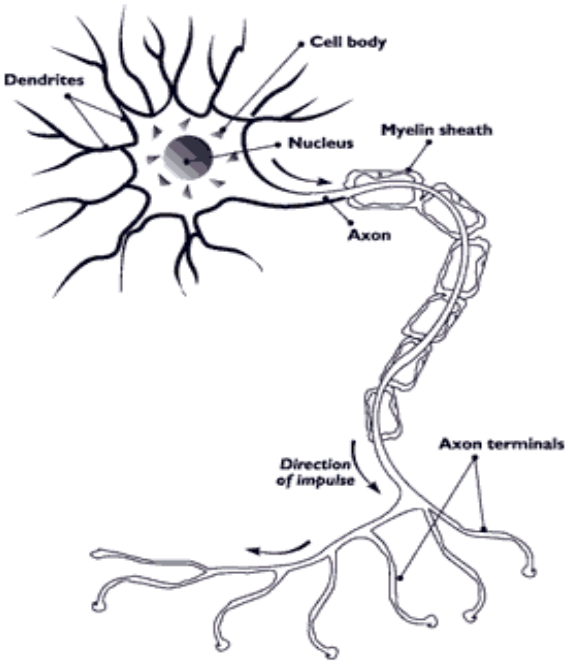

Figure 1: The structure of a functioning and normal neuron. Source: Williams and McElhiney, (2011)

The transfer of the messages from the axon of one nerve cell to the dendrites of the next nerve cell is known as neurotransmission (Figure 2). Neurotransmittersare then released upon arrival of nerve impulses/action potential to the axon terminal. Neurotransmitters spread across the synaptic cleft to bind with specific receptors on the dendrite of the impulse receiving neuron that depicts the effect of the neurotransmitter. The neurotransmitter either stimulates or inhibits an electrical reaction in the receiving neuron. Approximately forty neurotransmitters are in the central nervous system. Substances of abuse /illicit drugs interfere with the release and reuptake of the neurotransmitters as well as their accessibility to the receptor binding sites. (Williams and McElhiney, 2011; Liechti, 2015)

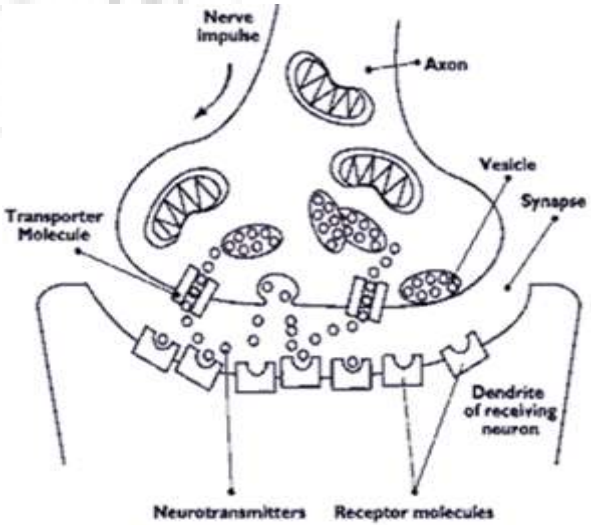

Figure 2: Mechanism of neurotransmission between one neuron to another. Source:Williams and McElhiney, (2011).

Figure 2 above shows the mechanism of neurotransmitter release, how it is transported to interact with its specific receptor at postsynaptic membrane of the postsynaptic cell.

Neurotransmitters are chemical substances released in to the synaptic cleft by one neuron and affect the function of another neuron in a particular fashion. E.g. dopamine, serotonin, Gamma amino butyric acid (GABA), Norepinephrine, epinephrine, Acetylcholine, endogenous peptides like enkephalin etc. they are widely distributed within the Central Nervous System in the hypothalamus, midbrain, hippocampus, amygdala and ventral tegmental area etc. (World Health Organization, 2004; Williams and McElhiney, 2011).A neurotransmitter should have the following qualities: must be formed in the neuron, should be existing in the presynaptic neuron, should be discharged in an adequate amount to produce a postsynaptic effect and exert the same effect when release by natural means i.e. either endogenously or exogenously when used as a drug (World Health Organization, 2004).

Receptors are complex proteins on to which neurotransmitters bind to initiate communication of signal between neurons. G-protein couple receptors (GPCRs) are the main category of drug targets. They are located on the plasma membrane and intensify signal transduction pathways. GPCRs are the major receptor family and can be specific in some tissues.GPCRs associated with substance abuse are; opioid receptors, dopaminergic, serotonergic,cannabinoid, nicotinic, cholinergic and GABA receptors (See Figure 3, 4, 5 and 6).Figure 3 below describes the formation of dopamine in the dopaminergic neuron from tyrosine to L-Dopa by the action of the enzyme tyrosine hydroxylase then, finally converted to dopamine and stored in the vesicles. After release, it reaches synaptic cleft, from where it gets access to and interacts with its receptor on the postsynaptic membrane of the postsynaptic cell. However, in noradrenergic neuron, the formation of noradrenalin is from dopamine while in serotonergic neuron from tryptophan.

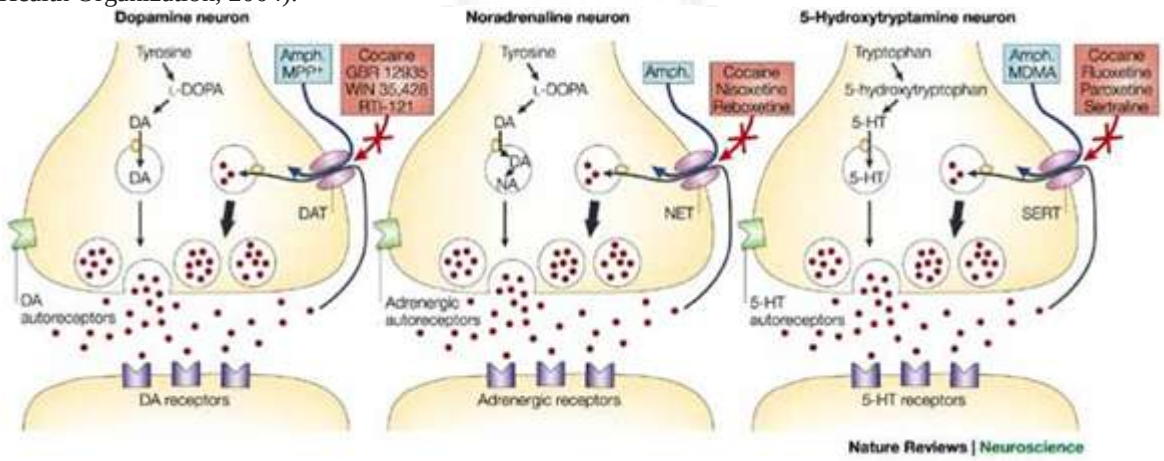

Figure 3: Various receptor types. Source: Williams et al., (2013)

Dopamine receptors: D1 and D2

From the figure 4 below for example, Cocaine and Amphetamine are central nervous system stimulants and thus can increase the amount of dopamine in the synaptic cleft by inhibiting the dopamine transporter. This will subsequently lead to reduction of inhibitory effect on D2 receptors.

From figure 5 below, the GABA (Gamma amino butyric acid) receptors are of 2- types, GABA-A and GABA-B receptors. For example, Benzodiazepines and barbiturates interact with GABA-A receptors while GABA-B receptors are G-protein couple of receptors.

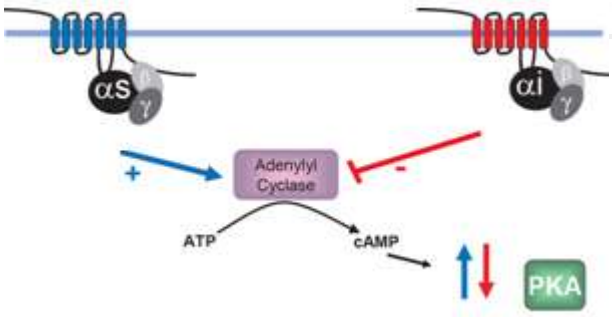

Figure 4: The two types of dopamine receptors with opposing action on cAMP. Source: Williams *et al.,* (2013)

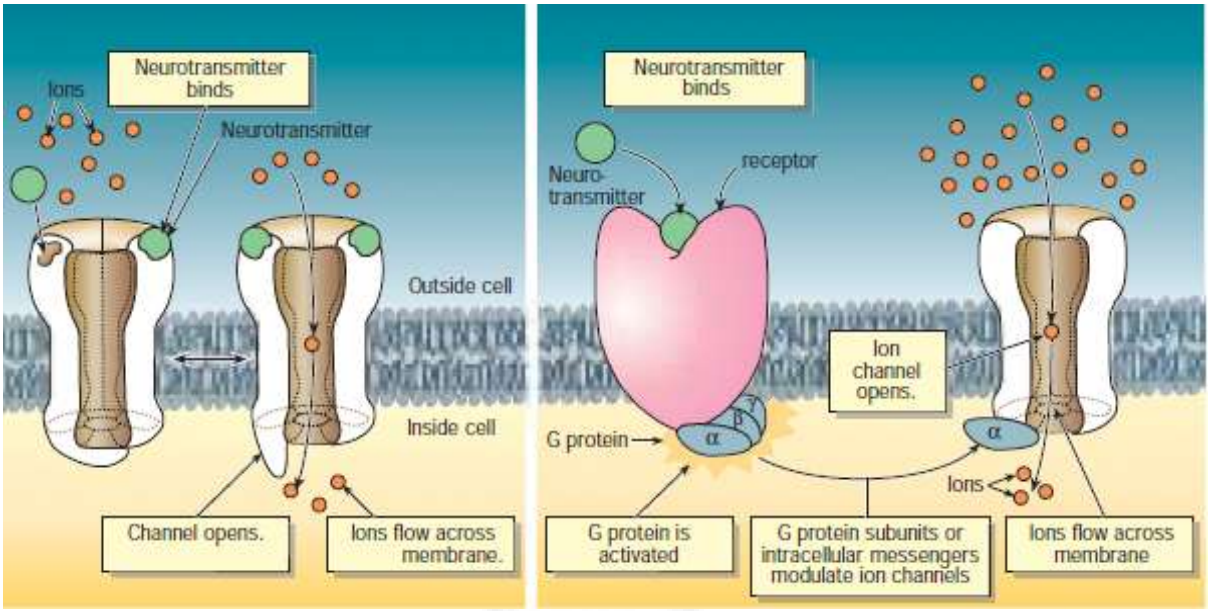

Figure 5: GABA receptors GABA-A receptor on the right and GABA-B receptor on the left. Source: World Health Organization, (2004)

Opioid receptors:Four major types of opioid receptors have were identified: mu, kappa, delta, and the more recently identified OFQ/N. (Preda, 2015)). Altogether coupled to Gi alpha subunit of GPCR. Upon stimulation, they decrease the excitability of the neurons. The resultant effects are analgesia, euphoria and sedation (Williams et al., 2013). See figure 6 the various locations of the receptors in the CNS including the opioid receptors. From figure 6 below, it is clearly observed that opioid receptors are commonly located in the central nervous system within the following structures such substantia nigra, amygdala and nucleus accumbence.

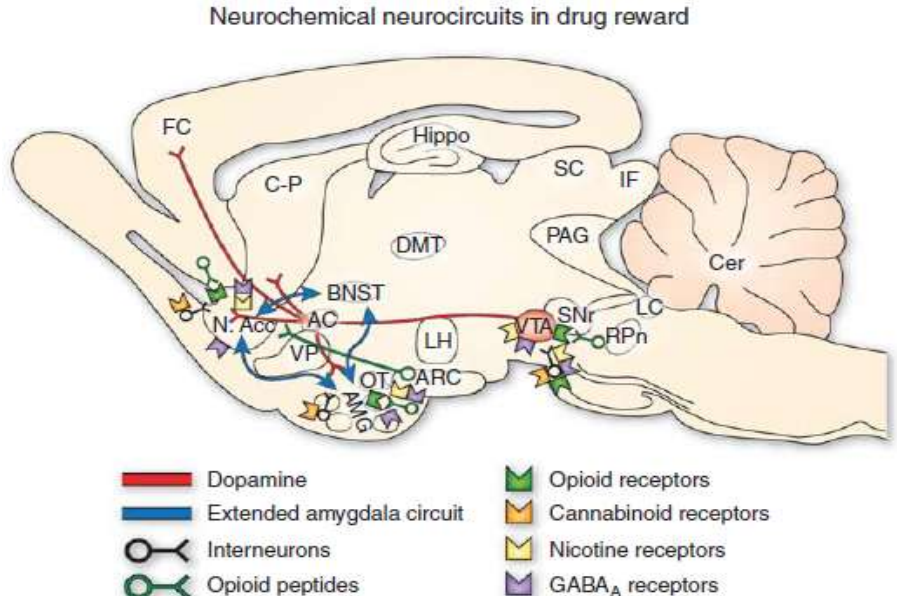

Figure 6: Neurochemical and receptor circuit of brain reward pathway. Source: Nestler & Landsman, (2001).

Mechanism of Opioid Action, Addiction and Dependence
Figure 7 below shows how opioid act at their receptors and mechanism of opioid addiction which occurs as a result of decrease activity of adenylyl-cyclase (AC) as well as increase activity of phospholipase C (PLC) and MAPK. Increase efflux of K ion and decrease influx of Ca ion, the resultant effect is decrease cAMP level and hyperpolarisation of the nerve cell and decrease pain sensation.

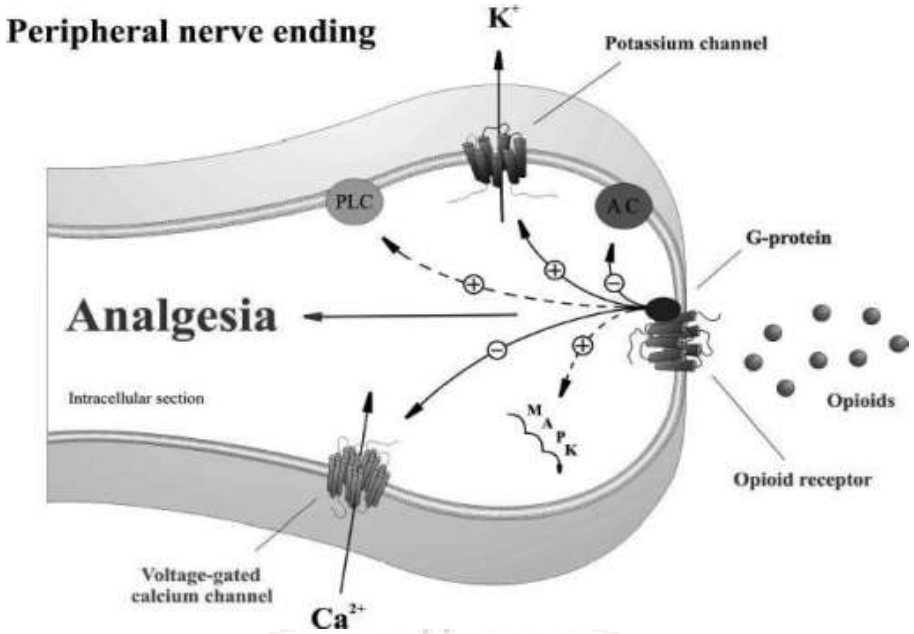

Figure 7: Mechanism of opioid action and addiction. Source: Williams, (2013).

In figure 8 below, the analgesic and euphoric effect obtained because of interaction between morphine (opioid) and mu receptor tilt substance abusers to have an increased desire and dose of the substance for them to attain the desired effect they need. Consequently, dependent on that particular substance ensues.

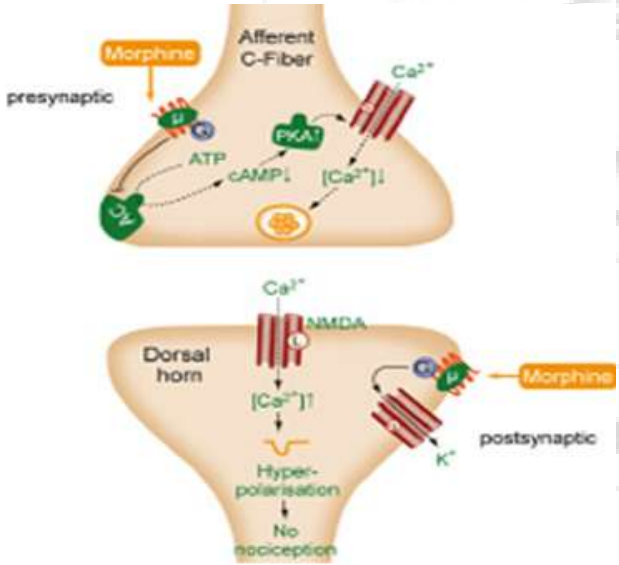

Figure 8: Development of tolerance and dependence. Source: Williams *et al*., (2013).

Reward Pathway

Reward pathway is a reinforcement pathway in the human brain within the limbic system. Substances of abuse stimulate it, which potentially lead to addiction and consequently intoxication.It is composed of both CNS structures and endogenous neurotransmitters communicating between these structures (Lowinson, 2005; Niesink et al., 1998; Koob & Moal, 2002; Little et al., 1999). It promotes the activities that are essential to human race and other animals. Substances of abuse affect the pathway by stimulating neurons to release neurotransmitters leading to subjective feeling of wellbeing (Lowinson, 2005; Niesink et al., 1998). It comprises ofnucleus accumbence(NA), an important structure in the pathway becausemost of abused drugs target it (Lowinson, 2005; Niesink et al., 1998; Koob & Moal, 2002; Dager et al., 1999; Little et al., 1999). Ventral tegmental area (VTA), Ventromedial and ventrolateral nuclei of hypothalamus and amygdala, all connected together by median fore brain bundleas seen in figure 9 (Bunch, 2007).

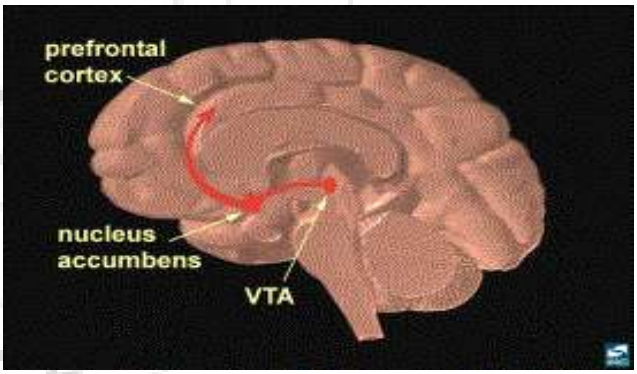

Figure 9: Core structures of brain reward pathway. Source: Bunch, (2007).

4. Diagnosis

The diagnosis of substance abuse/intoxication is mainly clinical; this includes history taking and examination.According to DSM-5, any individual who manifest with at least two of the following features occurring within 12-month period is likely to be a substance abuser.

- Taking higher dose/substance over a longer period
- Attractive in unsuccessful efforts to cut down the substance use.
- Wasting a great deal of time necessary to obtain/recover from the effects of the drug.
- Craving (strong desire or urge to use the substance).
- Failure to fulfill major role obligations at work, school, or home due to the effect of the drug.

- Ongoing use of the drugs despite experiencing recurrent social or interpersonal problems.
- Decrease in important social, occupational, or recreational activities.
- Ongoing use of the substance in circumstances in which it is bodily harmful.
- Ongoing use of opioids in spite of knowledge of having recurrent bodily or psychological problems aggravated by the substance.
- Tolerance
- Withdrawal symptom

Diagnostic criteria of the severity in substance abuse;Substance abuse is a single disorder with a range of severity from Mild = 2-3, Moderate = 4-5 and Severe ≥ 6 symptoms (American Psychiatric Association, 2013).

Differential Diagnosis
Some of the differential diagnosis of substance abuse are Depressive disorder, Manic disorder, Bipolar affective disorder (BAD), Schizophrenia, Anxiety disorder, Personality disorder (Center for Substance Abuse Treatment, 2005).

Investigations
Investigations like magnetic resonance imaging (MRI) and electro-encephalogram (EEG) may be useful to differentiate substance use disorder from the related conditions above, especially when the diagnosis is confusing. Other relevant investigations include; full blood count (FBC), urine drug screening, gas-liquid chromatography/thin layer chromatography, enzyme immunoassay and radioimmunoassay, liver function test and blood screening for HIV and hepatitis. Radiological investigation as Chest-X-ray (CXR) is not necessary however, in chronic intravenous drug abusers CXR findings may show evidence of lung fibrosis if the substance of abuse comprises of microcrystalline talc (Preda, 2015).

Complications
Suicidal attempt, accidents, abnormal behaviours such as rape, steeling, robbery etc., transmission of infections like HIV and hepatitis especially among intravenous drug abusers, sudden sniffing death syndrome particularly in inhalant abusers, increased risk of cancers, legal problems, poor parental, interpersonal and community relationship, increased morbidity and mortality. (World Health Organization, 2004;Williams and McElhiney, 2011; Preda, 2015).

5. Treatment

Methadone belongs to class of narcotic opiate analgesics. It is a partial agonist at the μ-receptor. It is useful in prevention of withdrawal symptoms in individuals or patients addicted to opiate drugs. After development of tolerance, the impact of methadone on mood and judgment is not significant.Thus, not the drug of choice for maintenance therapy. **Buprenorphine** is another partial agonist at theμ-receptor (it can only partially activate the receptor). Therefore, the intensity of mood alteration induced by buprenorphine highlands, and users do not experience high and deepfeeling when using other opioids,this has been termed as "ceiling effect". Buprenorphine is adequate to avoiddesire of the drug and withdrawal symptoms. **Naloxone** on the other hand, is an opioid antagonist that inhibits the activities of all the opioids receptors. This can lead to withdrawal symptoms. It is useful in cases of several opiate drug abuse (EMCDDA, 2015; Preda, 2015). Similarly, a combination of naloxone and buprenorphine is used in long-term follow up where available.

Challenges
The mechanism of action of most drug therapiesinvolves interconnections of many neurotransmitters and receptors making target difficult. Most of treatment options for opiates are also opiates thus, inadequate desired effect of treatment.Tolerance and dependence make abusers difficult to stop. Development of withdrawal symptoms and risk of developing chronic and irreversible complications are other problems.

Prevention
Primary prevention; involves health education. Secondary prevention; early diagnosis and treatment of the disease. Tertiary prevention; family, personnel, interpersonal, social, moral and governmental support.

6. Conclusion

Substance abuse/use disorder is a pandemic problem that is associated with many complications such as disabilities, morbidity and mortality, sufficient health education will help to curtail the spread of the disease, youth and other abusers are strongly advised to stop it, so as to improve their quality of lives. Moreover, families, communities and government should be actively involved in solving this health related ailment or problem.

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