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A CASE STUDY OF CODEINE CONSUMPTION AND ITS PHYSICOCHEMICAL IMPLICATIONS

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ABSTRACT
The rate at which the addictive drug is now consumed possesses a serious challenge not only for researchers and public health agencies but also for policy makers. Drug misuse and abuse continues to be a significant problem affecting the population worldwide. These has necessitated the urgent need to review the available literature on drugs commonly abused, notably the hallucinogens, narcotics, sedatives, tranquilizers etc. This paper review codeine an opium alkaloid available in tablets, capsules and in syrup formulations. Codeine is an inexpensive over-the-counter (OTC) drug commonly abused and misused by Nigerian youths for the purposes other than its medical application. The paper also looked at the scope of the drug abuse viz-a-viz the enlightenments approach on the ways by which youths abuse drugs alongside the effort and intervention of the law enforcement agencies in combating this menace. The paper also critically reviews the biochemistry, physicochemical implications and common symptoms of codeine abuse and misuse notably among youths from Northern Nigeria where 3 million bottles of codeine cough syrups are reported to be consumed daily.
Keywords: Codeine, Codeine chemistry, Drug abuse, Causes, Physicochemical Implications

INTRODUCTION

Information around the world shows that codeine-containing drugs or medicines are being abused in a proportion that disturbed the composure in the health of the general public (PCN, 2017). Codeine is one of the over-the-counter (OTC) medications that are dispensed to the public without doctor's prescription. Hout *et al.,* (2015) reported that, codeine or 3-methylmorphine widely and frequently consumed in many nations was found to be a public health challenge. The International Narcotic Control Board in (INCB, 2010) reported that South Africa is one of a handful of countries in Africa which allows codeine and codeine containing substance to be purchased as an OTC drug while Parry *et al.,* (2016) noted that the problem does not only lies with its sale as some OTC products, but also with its inappropriate prescription. A recent publication by the UK's Medicines and Healthcare Products Regulatory Authority (MHRA), the Royal Pharmaceutical Society of Great Britain (RPSGB), the Therapeutic Goods Administration (TGA) in Australia, and Pharmacy Regulatory Authority (PRA) in Canada highlighted the ongoing concerns of the indiscriminate consumption of codeine-containing medications (PSI, 2010). From the illicit cultivation and production of opioid based medicines (including codeine) and their use, the world is faced with boundless collection of social, economic and environmental problems.

Across several major Nigerian cities, many young adults are known to be addicted to several illicit drugs but, in recent years, opioid-based cough syrups in particular have become a thoughtful nuisance. The thousands of young Nigerians already addicted are at risk of suffering from effects of sustained opioid abuse ranging from schizophrenia to organ failure (Kazeem 2018). The National Epidemiological Network on Drug Use (2015) cited in Eweniyi, (2018) reported that, in Nigeria between January and December (2015), 1,044 patients were admitted for treatment in 11 treatment centers. 28.3% of the patients had opiate addiction, 78% had tramadol addiction, 15.1% had codeine addiction, and 9.9% had pentazocine addiction, while heroin and morphine represented only 3.3% of the opiate declared. Eweniyi in 2018 reported that, since 2015, codeine has nearly overtaken tramadol as the most abused opiate in Nigeria since thousands of young people in Nigeria are addicted to codeine cough syrup- a medicine that is become a street drug.

The problem of codeine abuse, addiction or dependence is more acute in the northern part of Nigeria prior to the time alcohol consumption was regulated in the region, young adults and teenagers often turn to cheap opioid-based drugs, especially codeine cough syrup as an alternative.

The pharmacist council of Nigeria (PCN, 2017) has noticed a rapid increase in the demand and use of codeine containing preparations, especially cough syrups by a wide spectrum of individuals from different backgrounds and social status. The issue is such that it has attracted a reaction from the senate of the Federal Republic of Nigeria and they recently expressed deep concerns over the harm inherent in the growing abuse of codeine containing preparations. However, this may not be unconnected with the report published by Vanguard in December, 2017 in which they reported that 3 million bottles of codeine are consumed every day in Kano and Jigawa States, Nigeria. A survey of the usage and users of codeine containing cough syrups in Kaduna state, Nigeria indicated that (95.2%) of the users are male in their twenties and majority of them were students (39.0%) or self-employed (23.3%) (Uthman *et al.,* 2017). Madaki and Muhammed (2017) added that, the issues of substance use, abuse and addiction by youths in Nigeria most especially opiate-based preparations became a matter of public concern in occasions like political campaigns, rallies and during elections. These are the reasons this paper is developed to highlight scope of drug abuse in Nigeria. Meanwhile, the chemistry, causes, effects and symptoms of codeine were discussed.

Scope of Drug and Its Abuse in Nigeria

Drug abuse has over the time threatens the peaceful development and smooth functioning of many societies. It is a great challenge that a nation like Nigeria with more than (60%) of youth are being unnaturally negated from the potential of some youths who massively involve in to drug abuse and as a result, lead to sustain psychological distortion, diminishing intelligence, quotient, dropping out of school or university, death as a result of chronic diseases caused by these heavy drugs (International Narcotics Control Board, INCB, 2013, Olalekan *et al.,* 2014). Drug abuse is a major public health problem all over the world. The use and abuse of drugs by adolescent have become one of the most disturbing health related phenomena in Nigeria and other parts of the world. Several school going adolescents experience mental health problems, either temporary or for a long period of time and some even become insane, maladjusted to school situation and eventually drop out of school (Olalekan *et al.,* 2014).

There are over 190 million drug users around the world and the problem has been increasing at alarming rates, especially among young adults under the age of 30 (Mandal, 2019). An estimated 33 million people use codeine each year and roughly 4.7 million American reported non-medical uses of prescription pain relievers including codeine (American Addiction Center AAC review report, 2019). Cannabis was the most widely used substance in the past in Nigeria, followed by pharmaceutical opioids (mainly tramadol, and to a lesser extent codeine or morphine) and cough syrups containing codeine or dextromethorphan. The information presented in the table on the extent of use of prescription drugs such as pharmaceutical opioid, tranquilizers/sedatives and amphetamine refers to their use without the advice of a doctor and for reasons other than medical. High-risk drug users were estimated to account for 0.4 per cent of the population (approximately 376,000 people) - nearly 90 per cent of these are opioid users (Mandal, 2019, UNODC report, 2018). The extent to which drugs are consumed in Nigeria is very alarming. Considering the UNODC (2018) report on the usage of drugs in Nigeria; there are 10.6 million people uses cannabis, 4.6 million takes opioids such codeine, Morphine etc, 2.4 million and 481 thousand people uses tranquelizers/sedative respectively in Nigeria. The breakdown of other drugs is shown Figure 1.

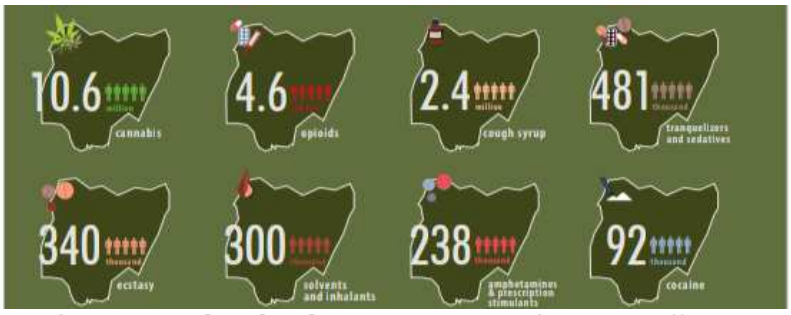

Figure1: Extent of Drug use in Nigeria, **Sources**: United Nations Office on Drugs and Crime UNODC, (2018).

A generation of research has defined three major links between drug abuse and crime. The first, drugs/crime nexus relates to the violence that can be associated with the use of drugs themselves: *psychopharmacological crime*: crime committed under the influence of drugs. The second drugs/crime link is *economic- compulsive crime*: is the result of drug users engaging in crime to support their drug consumption and addiction. In the United States, for example, 17 per cent of state prisoners and 18 per cent of federal inmates said they had committed the offence for which they were currently serving a sentence to obtain money for drugs (INCB report, 2013). The third link is *systemic crime*: the violence that occurs, for example, as a result of disputes over "drug turf" or ‚fighting among users and sellers over deals gone awry. This has been seen, starkly, in Latin America over the past 10 years, especially in countries such as Guatemala and Mexico, but it is also seen in the streets of every continent throughout the world (INCB report, 2013). However, these drug implications are costly enough to deplete the economic and social status of any nation talk less of developing country like Nigeria where law enforcement agencies were corrupt.

In a recent public observation, new current menace of drug abuse by youth in the northern and some part of southern Nigeria was discovered by some online and printed medias in (2018) and to date that quoted …*that due to the effort and intervention of the law enforcement agency (LEA) to minimize the epidemic of drug abuse, the normal drugs being addicted to by these youths are now very scarce. As a result of this development, the youth have resorted to taking Tom Tom, dissolving it in to Lacassera drink. This mixture has higher effect of intoxication than real hard drugs or alcohol. In the same development, observations have also it that these youths put magi glutamate in juices, this produce the same effect as hard drugs*. The worst thing is that it cannot be detected by the drug screening tests or urine toxicological devices (Media Watch, 2018).

Drug has been defined in myriad ways, Okeye, (2001) define drug as a substance that could bring about a change in the biological functions through its chemical actions. It is also considered as a chemical that modifies of the living tissues that could bring about psychological and behavioral changes (Olalekan *et al.,* 2014). Moreover, drug is defined as a substance that modifies perceptions, cognition mood, behavior and general body function (Balogun, 2006).

Most of the drugs are helpful to the body in term of health conditions, but unfortunately, these substances are now misuse and abuse for the purpose other than medication. The terms "drug abuse" or "substance abuse" is defined as the use of chemical substances that lead to an increased risk of problems and an inability to control the use of the substance (*https://www.healthinaging.org/aging-and-health-a-to.../topic:drug-and-substance-abuse/*).

Drug abuse or substance abuse refers to the use of certain chemicals for the purpose of creating pleasurable effects on the brain (Mandal, 2019). World Health Organization (WHO, 2019) review the definition of drug abuse or substance abuse to refers to as the harmful or hazardous use of psychoactive substances, including alcohol, opioid (codeine, morphine, and heroin) and illicit drugs.

Drugs abused are usually psychoactive drugs that are used by people for various reasons which may include according to Mandal (2019):

- Curiosity and peer pressure, especially among school children and young adults
- The use of prescription drugs that were originally intended to target pain relief may have turned into recreational use and become addictive
- Chemicals may be used as part of religious practices or rituals
- Recreational purposes
- As a means of obtaining creative inspiration

In Nigeria the following categories of drugs are commonly abused by its youth:

a. **Narcotics:** The term narcotic originally referred medically to any psychoactive compound with sleep-inducing properties (*https://www.drugbank.ca/categories/narcotics*). These drugs relieve pains, induce sleeping and they are addictive usually found in heroin, codeine, opium etc (NAFDAC cited in Haladu, 2003).

b. Sedatives: These drugs are the most widely used and misused due to the belief that they relieve stress and anxiety and similarly some of them induce sleep, ease tension, cause relaxation or help users to forget their problems**.** These drugs are sourced from valium, alcohol, promethazine, chloroform (NAFDAC cited in Haladu, 2003).

c. Tranquilizers: These drugs are believed to produce calmness without bringing drowsiness; they are chiefly derived from Librium, valium etc (NAFDAC cited in Haladu, 2003).

d. Miscellaneous: This is a group of volatile solvents or inhalants that provide euphoria, emotional inhibition and perpetual distortion of thought to the user. The chief sources of these drugs are glues, spot removers, tube

repair chemicals, perfumes, chemicals etc (NAFDAC cited in Haladu, 2003).

e. Hallucinogens: These are drugs that alter the Sensory Processing Unit (SPU) in the brain. Therefore, producing distorted perception, feeling of anxiety and euphoria, sadness and inner joy, they normally come from marijuana. Moreover, a study conducted by Mandal (2019) revealed that, these groups of drugs cause hallucinations and an "*out of this world*" feeling of dissociation from oneself. Hallucinogens may cause distorted sensory perception, delusion, paranoia and even depression. Hallucinogenic drugs include psilocybin (found in magic mushrooms), lysergic acid diethylamide (LSD), peyote, and dimethyltryptamine (DMT) (NAFDAC cited in Haladu, 2003; Zaffiri cited in Abdullahi, *et al.,* 2018).

f. Stimulants: These are substances that directly act on the Central Nervous System CNS. The users at the initial stage experience pleasant effect such as energy increase. The major source of these comes from caffeine substance (NAFDAC cited in Haladu, 2003). Caffeine is a chemical found in coffee, tea, cola, guarana, mate, and other products (1,3,7-trimethylxanthine, Anhydrous Caffeine, Caffeine Sodium Benzoate, Caffeine Citrate, Caffeinum, Methylxanthine). Caffeine is most commonly used to improve mental alertness, but it has many other uses. Caffeine is used by mouth or rectally in combination with painkillers (such as aspirin and acetaminophen) and a chemical called ergotamine for treating migraine headaches. It is also used with painkillers for simple headaches and preventing and treating headaches after epidural anesthesia (www.webmd.com|caffeine). Stimulant cause stimulation of the brain, giving rise to alertness and increased bursts of activity. Mandal (2019) note the rapid heart rate, dilated pupils, raise in blood pressure, nausea or vomiting and behavioural changes such as agitation, and impaired judgment were associated with stimulants. However, in severe cases, there may be delusional psychosis which can occur with the use of cocaine and amphetamines.

Codeine Abuse

The name codeine was derived from the Greek word *Kodeia* from poppy head and form naturally in the poppy plant *Papaver samniferum* (Hout *et al.,* 2015). Codeine with chemical formula $C_{18}H_{21}NO_3$ was named by International Union of Pure and Applied Chemistry (IUPAC) as [(5α, 6α)-7, 8-didehydro-4, 5-epoxy-3-methoxy-17-methylmorphinan-6-ol]. Codeine has many chemical names such as methylmorphine, morphine 3-methylether, morphine monomethylether, codeine anhydrous, codicept, L-codeine, e.t.c (PubChem modified July, 2018). Codeine is usually a white crystalline solid that is freely soluble in water, its formulated in a number of ways for use in various conditions and by different routes of administration (Hout *et al.,* 2015). Codeine is explored as an infallible cure for pain and cough. It is a substance derived from alkaloid and extracted from opium poppy, however, this substance has pharmacological and toxicological activity (Feizbakhsh *et al.,* 2016, Yu *et al.,* 2016). Morphine is usually used for the preparation of codeine by methylation (Yu *et al.,* 2016). Codeine is an opioid drug similar to morphine, hitherto formulated as tablets (codeine sulfate, codeine phosphate) and syrups (codeine cough syrup), available as Over-The-Counter (OTC) medicine has been reclassified in 2013 as a controlled medicine. Codeine belongs to the same opium family as morphine and heroin use for the treatment of moderated pain. Although codeine induces less euphoria and sedative than morphine and heroin, it can also produce addiction which makes the study of codeine a significant program in the area of toxicology (UNODC, 2013, Yu *et al.,* 2016 Feizbakhsh *et al.,* 2016).

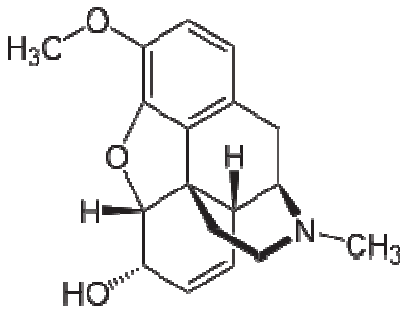

Figure2: Codeine Structure

Codeine is commercially available as water soluble hydrochloride, sulfate or phosphate and is administered orally in the form of linctuses for the relief of cough and as tablets for the relief of pain. The analgesic properties of codeine are associated with its conversion to morphine (PubChem modified 2018). Codeine is metabolized mainly in the liver where it undergoes demethylation to form morphine by the enzyme cytochrome P450 2D6, N-demethylation to form norcodeine via Cyctochrome P2D6 and by glucuronidation to form codeine-6-glucuronide via UGT2B7. A number of medication can alter the metabolism of codeine by interfering with the enzymes either by increasing or decreasing the extent of conversion and hence alter its analgesic effect (Gilman *et al.,* 1985; Straube *et al.,* 2014).

Causes of Codeine Misuse and Dependence

While the causes for codeine addiction are not well-understood, addiction is thought to be as result of the combinations of a number of factors namely:

- ***Environmental factor:*** Individuals who are raised in a home environment in which addiction runs rampant may be at higher risk for developing addiction disorders. Moreover, individuals who begin to abuse drugs at an early age may be prone to develop an addiction later in life (Oluremi, 2003)
- ***Availability of the codeine:*** In many countries, codeine is being purchased as an over the counter drugs without doctor's prescription. This has made codeine very cheap, affordable and slippery slope to drug addiction. Cough syrups containing codeine are sold over the counter in Nigeria at around N250 for a 100ml bottle (Daily Trust, 2018).
- ***Lack of parental supervision:*** The affairs of young children nowadays must be adequately and properly supervised. In a situation where parents have no or low interaction with their young adults, there is every possibility that their children may be a victim to codeine and other drugs abuse (Haladu, 2003).
- ***Peer group influence:*** peer pressure plays a major role in influencing many adolescents in to codeine and other heavy drugs abuse. This is because peer pressure is a fact of teenage and youth life, as they try to depend less on parents, they show more dependence on their friends. However, one many not enjoy the company of others unless he conforms to their norms (Haladu, 2003).
- ***Emotional and psychological stress:*** This includes state such as anxiety, frustration, unemployment and economic breakdown. People always take drugs (codeine inclusive) on order to forget their problems when they are provoked (Yusuf *et al.,* 2014).
- The need to prevent the occurrence of withdrawal symptoms. If the drug is stopped, the user usually experience what is termed as withdrawal symptom. Plain anxiety, excessive sweating and shaking characterize such as symptoms. The inability of drug users to tolerate the symptoms motivates them to continue (Oluremi, 2012).

Symptoms of Codeine Misuse and Abuse

The symptoms of codeine misuse and abuse are varied among the addicted depending largely upon the length of time abuses, the amount used and the frequency of usage. Some of the common symptoms of codeine are:

Mild symptoms

- Depression
- Anxiety
- Emotional numbing
- Euphoria
- Sense of well-being and calmness (MRC, 2018)

Behavioral symptoms

- Withdrawing socially from loved one.
- Social isolation.
- Stealing or borrowing codeine from friends and loved ones.
- Financial problems.
- Legal problems.
- Faking illnesses to obtain more codeine.
- Interpersonal relationship problems.
- Poor school performance (MRC, 2018).

Physical Symptoms

- Dizziness
- Dry mouth
- Fainting and seizures
- Low blood pressure, rashes, decreased sex drive, respiratory depression and urinary retention (MRC, 2018).

Psychological symptoms

- Hallucinations, delusions and psychosis.
- Worsening of mental health.
- Decreased memory and lack of emotions (MRC, 2018).

Physicochemical Implications

Codeine change the way the brain and nervous system respond to pain and coughing. Codeine can exist in many forms and as part of many medications, each of which when abused will affect the normal functions of human organs. Such effects are:

- Serious chronic health consequences, particularly in case of excessive or long term use of codeine in combinations with ibuprofen, aspirin and paracetamol include gastric ulcers, gastrointestinal bleeding, and hepatotoxicity among others (Barreto *et al.,* 2011, Straube *et al.,* 2014).
- Codeine administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume (Barreto *et al.,* 2011, MRC, 2018).
- Codeine may also be an iatrogenic cause of psychiatric disturbances (Manchia *et al.,* 2013).
- In ability to proceed with educational pursuit to tertiary institutions among youths, could be a factor that favors codeine containing cough syrups usage (Uthman *et al.,* 2017).
- Codeine with alcohol cause severe injury, leading to death (Medadi *et al.,* 2007).
- The side effects include confusion, agitation, hallucinations or unusual thoughts or behaviors, slow heart rate, weak pulse, fainting or shallow breathing, urination problems, seizures, nausea, vomiting or stomach pain, constipation, feeling dizzy or drowsy (Barreto *et al,* 2011).
- Pregnant women with rarer CY2PD6 genotype rapidly metabolize codeine in to morphine, resulting in high breast milk and plasma level in neonates can potentially cause infant death due to opioid toxicity (Madadi *et al.,* 2007).

RECOMMENDATIONS

This paper recommended the following:

- The Nigeria Federal ministry of health should mandate the state ministries of health and other health sectors to orient and enlighten the populace about the health effects of codeine abuse and misuse.
- There should be full implementation for the following National Drug Distribution Guidelines (NDDGs). According to the Federal Ministry of Health (2012), the:

I. Manufacturers/importers shall be registered with Pharmacists Council of Nigeria PCN and NAFDAC.
II. State Drug Distribution Centers SDDCs shall be owned by the state government and registered with PCN.
III. Mega Drug Distribution Centers MDDCs shall be private sector initiative and established in the state or at least one in each geo-political zone.
IV. Wholesalers shall be corporate body registered by PCN and involved in the distribution of pharmaceutical products.
V. Retailing outfit/community Pharmacists shall be registered by PCN and involve in selling drugs to consumers.
VI. Public Health Care Facilities Tertiary/Secondary, shall be Pharmacy Department that registered by the PCN.
VII. Patent and Proprietary Medicines Vendors (PPMV) shops registered with PCN.

- Radio stations and other media forum should constantly bring to fore the dangers inherent in the consumption of illicit drugs.
- Addicted individuals should be properly counseled on how to overcome codeine addiction as well as codeine's symptoms withdrawal.
- Parents at home and school administrators should emphasize and monitor young adults as well as their peer influence.

CONCLUSION

The menace of drug misuse or abuse among the youth is now a general world problem as it affects the educational performance of students, the quality and value of the future generation of youth cannot be predicted. This paper reviews the use, abuse, misuse and dependence of codeine among young adults in Nigeria. The availability of codeine as over-the-counter drug, peer group influence and lack of parental supervision are the major causes of codeine abuse by young people in Nigeria.

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