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The Risk of Amphetamine-Related Stimulants to Users and the General Population in Nigeria

Philip A. Adeniyi[1], Azeez O. Ishola[1], Ayodeji A. Olabiyi[2], Babawale P. Olatunji[3], Akele Y. Richard[4], Joseph O. Sanya[5]

[1]Cell Biology and Neurotoxicity Unit, Department of Anatomy, Afe Babalola University, Ado-Ekiti, Nigeria
[2]Department of Biochemistry, Afe Babalola University, Ado-Ekiti, Nigeria
[3]Biological Sciences, Afe Babalola University, Ado-Ekiti, Nigeria
[4]Department of Medical Laboratory Science, Afe Babalola University, Ado-Ekiti, Nigeria
[5]Department of Physiology, Afe Babalola University Ado-Ekiti, Nigeria

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ABSTRACT

In different communities across the globe, we see more of divergence from normal and/or expected behaviour; some psychotic in nature while others are neurodegenerative diseases of unknown origin. However, the use or exposure to some psycho stimulants at any stage of an individual's development may not be unconnected with these developments. The aim of this review is to enlighten policy makers across the globe to safe guard the rest of the populace from the psycho-social effects of the proliferation in the unlawful production and use of Amphetamine (AMPH) and its derivatives in our society. A number of amphetamine derivatives, such as AMPH and methylamphetamine (METH), are considered dopaminergic neurotoxicants; they usually resulted in long-term depletions of striatal dopamine that is accompanied by neuroinflammation and by changes indicative of neuronal terminals degeneration.

Keywords: *Amphetamine, Methylamphetamine, Neuroinflammation, Psychostimulants*

INTRODUCTION

In different communities across the globe, we see more of divergence from normal and/or expected behavior; some psychotic in nature while others are neurodegenerative diseases of unknown origin. However, the use or exposure to some psychostimulants at any stage of an individual's development may be connected with these developments.

The aim of this review is to enlighten the policy makers across the globe to safe guard the rest of the populace from the psycho-social effects of the proliferation in the unlawful production and use of AMPH and its derivatives in our society.

A number of amphetamine derivatives, such as AMPH and methylamphetamine (METH), are considered dopaminergic neurotoxicants; they usually resulted in long-term depletions of striatal dopamine that is accompanied by neuroinflammation and by changes indicative of neuronal terminals degeneration (Capela et al. 2007; Miller and O'Callaghan 2008; Khairnar et al. 2010; Granado et al. 2011; Mohamed et al. 2011; Frau et al. 2013). The term amphetamine-type stimulants (ATS) refer to a group of psychostimulant drugs that are related to the parent compound amphetamine (Hart et al. 2008). ATS include amphetamine, methylamphetamine and phenethylamines such as 3,4-methylenedioxy-methamphetamine (MDMA), METH, 3, 4 –

Correspondence: Philip A. Adeniyi, M.Sc., Department of Anatomy, Afe Babalola University, P.M.B. 5454, Ado-Ekiti, Nigeria. Email: ade.adeniyi@abuad.edu.com; +2348032922323

methylenedioxyamphetamine (MDA) and other similar substances.

AMPH and METH are central nervous system stimulants that accelerate the body's metabolism and produce euphoria, increased alertness and give a sense of increased energy (Abadinsky 2008). Other short-term effects may include hypertension and tachycardia. Long-term use can result in deficits in memory, decision-making and verbal reasoning, with some symptoms resembling those of paranoid schizophrenia (EMCDDA 2010).

The basic molecule of amphetamine can be modified to emphasize specific actions, such as appetite suppressant, CNS stimulant, and cardiovascular actions, for certain medications, including diethylproprion, fenfluramine, methylphenidate, and phenmetrazine. Both methylphenidate and amphetamine have been in Schedule II of the Controlled Substances Act since 1971 (Wise 1996; Green et al. 2003; CESAR 2013). In medical use, there is controversy over whether the benefits of AMPHs prescribed for Attention Deficit Hyperactivity Disorder (ADHD) and weight loss outweigh the drug's harmful side effects. There is agreement, however, that prescription amphetamines are successful in treating narcolepsy (Wise 1996). The structurally and/ or chemically similar drugs, which imitate the psychostimulant effects of amphetamines, and contain substances legally available over-the-counter, including caffeine, ephedrine, and phenylpropanolamine are sold on the street as "speed" and "uppers".

The stimulant effects of AMPH were not noticed when it was first synthesized in 1887 by the German chemist L. Edeleano. In the early 1930s, when amphetamine's CNS stimulant properties and use as a respiratory stimulant were discovered it was marketed as an inhaler for nasal congestion. At this time, medical professionals recommended AMPH as a cure for a range of ailments—alcohol hangover, narcolepsy, depression, weight reduction, hyperactivity in children, and vomiting associated with pregnancy. The use of AMPH grew rapidly because it was inexpensive, readily available, had long lasting effects, and because professionals purported that AMPH did not pose an addiction risk. Oral and intravenous preparations of AMPH derivatives, including METH, were developed and became available for therapeutic purposes. During World War II, the military in the United States, Great Britain, Germany and Japan used amphetamines to increase alertness and endurance and to improve mood (Capela et al. 2007). Abuse began rising during the 1960s and 1970s with the discovery that the intravenous injection of

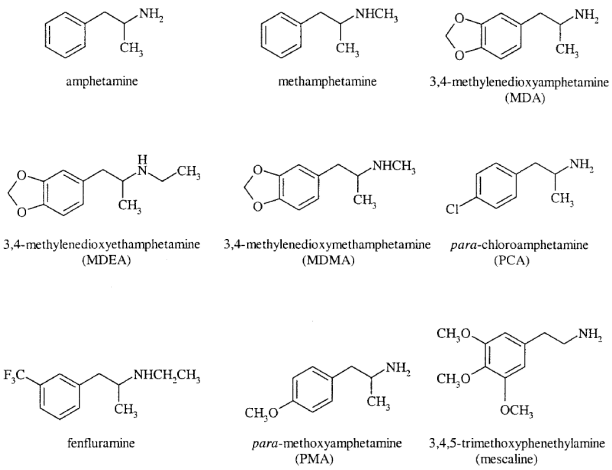

Fig. 1: Showing structure of AMPH and some of its derivatives (Green et al. 2003).

Fig. 2: Various form of ATS; A – Capsules of various colours, B – Coloured powder, and C and D – Ice comes in sheet like crystals/ crystalline powder (CEIDA 2016).

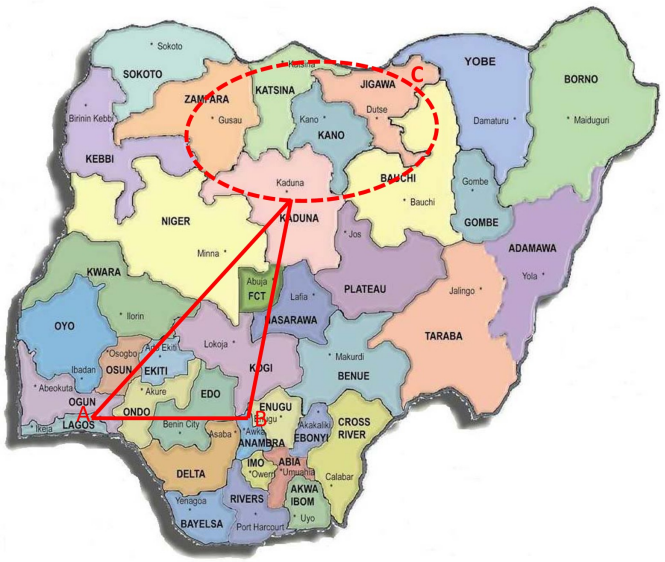

Fig. 3: Showing the 'triangle' of identified sites of illegal production of AMTH in Nigeria. The sites of production in the SW (A), SS (B) and the dotted cycle (C) is the likely location of the suspected third angle of the AMTH production and distribution channels in Nigeria.

amphetamines (particularly METH) produced enhanced euphoric effects with a more rapid onset than oral administration. Although structurally similar to AMPH, METH and MDA have more pronounced effects on the CNS (Moszcoynska et al. 2004). Between 1986 and 1989, law enforcement and treatment admission professionals in Hawaii reported that abuse of a concentrated form of METH (known as “ice,” “glass,” and “crystal”) was increasing (Wise 1996).

METH is AMPH derivative widely used psychostimulant which stimulates neural release of neurotransmitter dopamine in the brain of human and non – human subjects, and action related to the euphoric effects of the drug (Simola et al. 2006; UNODC 2011).

MDMA (ecstasy) is another AMPH derivative that belongs to the most used illicit drugs worldwide as per the United Nations Office on Drugs and Crime. These synthetic substances are categorized as amphetamine-type stimulants (ATS) (Hahn, 2011). Due to their stimulant and euphorigenic effects, ATS are often used excessively with high cumulative doses on dance-parties. In animals there is a large body of evidence indicating long-lasting neurotoxic effects after administration of MDMA and amphetamine (Amato et al. 2007; Khairnar et al. 2010; Frau et al. 2013).

The report of Moszcynska et al. (2004) compared the brain of methamphetamine users and the Parkinson disease (PD) patients and find out that there was marked degeneration in the dopaminergic neurons in the caudate and small degeneration in the putamen parts of the brain of the amphetamine users, which were very similar to degeneration observed in the PD patients’ brain. Though, they argue that the MPH users will not end up having the disease condition due to the fact that not all putamen dopamine neurons were degenerated but not statistical parameters can really sum up or equate what will happen to the AMPH users, because most of them are multiple drug users. The effects of co-administration of MPH and other drugs such as tobacco, caffeine, cocaine, marijuana, etc. may aggravate these effects (Escobedo et al. 2001; Amato et al. 2007; Khairnar et al. 2010) which may be observable in chronic users.

Amphetamine (AMPH)

AMPH is 1-phenylpropan-2-amine or C9H13N. It is a psychostimulant drug of the phenethylamine class that produces increased wakefulness and focus in association with decreased fatigue and appetite. When amphetamines are used, the neurotransmitters dopamine and norepinephrine are released from nerve endings in the brain and their reuptake is reverted (Domino 1998). This influx causes the upsurge of neurotransmitters at synapses in the brain. When nerve cells in the brain and spinal cord are activated by amphetamine, the mental focus, the ability to stay awake, and the ability to concentrate is improved, which is helpful for those with hyperactivity disorders or narcolepsy. Although the physiological experience of using amphetamines and cocaine is very similar, the effects of amphetamines can last several hours whereas the effects of cocaine generally last less than one hour (Wise 1996). When mixed with alcohol or other drugs, the stimulant effects of prescription amphetamines are enhanced. The onset of the effects from injecting methamphetamines occurs immediately. When this drug is snorted, effects occur within 3 to 5 minutes; when ingested orally, effects occur within 15 to 20 minutes (Moszcoynska et al. 2004); that is, the effects are dose and route dependent.

Methamphetamine (METH)

METH is an addictive stimulant that is closely related to amphetamine. It is long lasting and toxic to dopamine nerve terminals in the central nervous system. It is a white, odourless, bitter tasting powder taken orally or by snorting or injecting, or a rock "crystal" that is heated and smoked. METH increases wakefulness and physical activity, produces rapid

Fig. 4: Methamphetamine flows as perceived by recipient countries between 2011 and 2013 (WDR 2015).

heart rate, irregular heartbeat, and increased blood pressure and body temperature. Long-term use can lead to mood disturbances, violent behaviour, anxiety, confusion, insomnia, and severe mental problems. All users have their immune system depressed, but particularly those who inject the drug are at risk of infectious diseases such as HIV/AIDS and hepatitis due to the facts that they share common tools such as syringes, blades and other instruments.

3, 4-methylenedioxymethamphetamine (MDMA)

3, 4-methylenedioxymethamphetamine (MDMA), also known as ecstasy, XTC, Adam, E, X, clarity, Stacy, love drug, is an amphetamine derivative that has gained significant popularity in recent years and has become the recreational drug of choice for many adolescents and adults (Domino 1998; Khairnar et al. 2010; Mohamed et al. 2011). Though, the impacts of MDMA on the central nervous system (CNS) is still central to debate, MDMA has been reported to affect the brain by increasing the activity of at least three neurotransmitters: serotonin, dopamine, and norepinephrine. Studies have shown that some heavy MDMA users experience long lasting confusion, depression, and selective impairment of working memory and attention processes. Such memory impairments have been associated with a disruption of serotonin transmission and markers of serotonin function (Taffe et al. 2001; McGregor et al. 2003). MDMA has been reported to affect the region that has to do with recognition, emotion and motor function. The specific damage to 5 – hydroxytryptamine (5 – TH, serotonin) and dopaminergic nerve endings lasting for some months and years have been reported in rodents and primates respectively to demonstrated both biochemical and histological changes in their brains (Johnson et al. 1991; Taffe et al. 2001; Green et al. 2003; Sprague et al. 2003; Granado et al. 2011; Mohamed et al. 2011; Yubero-Lahoz et al. 2012; Frau et al. 2013). It also be been reported that MDMA inhibit dopamine transporter (DAT), norepinephrine (NE) transporter (NET), and serotonin (5-HT) transporter (5-HTT) (CESAR 2013; Cressey 2009). Moreover MDMA has been shown to induce neurotoxic and neuroinflammatory processes (Khairnar et al. 2010; Granado et al. 2011). On the other hand, MDMA's supporters claim that the drug is a potentially valuable therapeutic aid with little risk of causing lasting brain damage. MDMA binds to and reverses the dopamine or serotonin transporters, to produce impulse-independent/ carrier-mediated efflux of dopamine or 5-HT, respectively (Johnson et al. 1991; Taffe et al., 2001). They argue that studies showing that MDMA leads to cognitive deficiencies are procedurally flawed, and that there is no proof that a few doses of the drug will cause harm (Rothman et al. 2001; Nutt 2009), although, Moszynska et al. (2004) reported marked reduction in the dopamine level in the postmodern study of MDMA precursor, METH, users. The evidence of the occurrence of MDMA – induced neurotoxicity in human users are not easily substantiated and remain ambiguous since many of the users often take other substances simultaneously, intentionally or due to impurity in the MDMA from the producers or in the 'market'.

3, 4 – methylenedioxyamphetamine (MDA)

MDA is a metabolite of MDMA and like MDMA is known to cause the release of 5-HT, dopamine and norepinephrine from neurons by acting as substrates for monoamine transporter proteins (Johnson et al. 1991; Rudnick and Wall 1992). Like other transporter substrates, MDMA and MDA bind to plasma membrane transporters and are translocated into the cytoplasm where they promote non-exocytotic transmitter release (Verrico et al. 2007; Robertson et al. 2009). The precise mechanism underlying transporter-mediated release is not completely understood but probably involves drug-induced phosphorylation of cytoplasmic domains on the transporter, which triggers reversal of normal transporter flux (i.e., reverse transport) (Sitte and Freissmuth 2010; Davis et al. 1987). MDA has also been reported to cause hyperthermia and death in canines (NDLEA 2013). It is noteworthy that few studies have examined the molecular mechanism of the various hydroxylated metabolites of MDMA (Johnson et al. 1991; McGregor et al. 2003).

DISCUSSION

The physical effects of AMTH include, enhanced sympathetic functions and hyperactivity and a reduced parasympathetic function. The following are symptoms observable in such individuals clinically; reduced salivation or dry mouth, dilation of pupils, hypertension, headache, constipation. Although, the primary function of these chemicals and neurotoxin remain unknown, receptor interaction remains a primary suspect in the bioactivation of these agents; the possible hypothesis includes AMTH's ability to mimic epinephrine, nor-epinephrine and dopamine (catecholamine) by binding to adrenergic receptors or dopaminergic receptors in the brain and viscera (blood vessels, glands and nerve endings) or perhaps it inhibits parasympathetic system by binding associated receptors and nerve endings. It is also possible that AMTH inhibits enzymes required for clearance catecholamines such as monoamine oxidase (MAO) and catechol-o-methyltransferase, thus prolonging the activity of these substances at the synapse.

The illegal factories that are responsible for the production of these substances are not only affecting their customers but the innocent people living around the factories and who are to cope with the negative

psycho – social behavioural changes around them that lead to one form of violence or the other, in short methamphetamine production endangers the public health. The use of ATS is usually known to be western countries' lifestyle but it has gradually crept into our community in Nigeria and African continent at large, especially the West Africa sub-region (see figure 4). Between the year 2011 and 2013, about three (3) illegal factories for production of METH were discovered in Nigeria so far by the Nigeria Drug Law Enforcement Agency (NDLEA), two of which are located in Lagos state and these factories were strategically placed in 'triangle' part (West, East and Northern parts) of Nigeria for easy transportation across the nation (NDLEA 2013).

The first factory was discovered in the year 2011 in Majek area of Ijebu Lekki Local government of Lagos State, South-West (SW) of Nigeria while another one was situated in Nanka village of Anambra State in South East (SE) Nigeria (figure 3). While the third factory is yet to be sighted by the NDLEA officers, which is likely to be located in the Northern part (see figure 3) of the nation to complete the 'national marketing triangle strategy' of the drug, we have experienced a lot of report of drug traffickers arrested with about 40 kg of methamphetamine. Harmful effects of exposure to METH are very high even after several years of abandonment such effects includes; dysregulation of neurotransmission and enzyme in the molecular pathway of the cellular system involved in maintenance of neuronal-glia relationships. The different systems affected include both the cellular system involved in energy metabolism and the multicellular array that constitutes the social context of the cells. Chemical and gaseous discharges during these productions are highly injurious to public health, especially people living close to the production area. The individuals living close to the production sites are termed passive users. Although they are not addicts, they are exposed in excess to ampule amount of the drugs and chemicals via bio-accumulation over a period of time. Any society where such an illegal production is taking place without serious and timely legal action will experience the negative feedback effects of drugs ranging from violence to neurodegenerative diseases of unknown aetiology that may last for several years; the economic implications on such societies are huge and its use affects global opinion of such countries across the globe. Because exposure to AMPH gets people to lose auto-control; resulting in violence, dangerous driving and risky habits. It can also lead to long-term psychosis and possibly neurotoxicity.

The Nigerian government needs to wake up and fight this monster once and for all to safe guard over 170 million people within our borders and other neighbouring countries. Most of the violence across the nations was parented by drug addicts, as we all know that taking lives of others need extra efforts even at the war front.

Another aspect of the issue that is most dangerous is that most of these factories/ laboratories lack necessary personnel and/ or equipments or reagents for pure production of the drug and this usually leads to production of many amphetamine derivatives such as METH, MDMA, MDA and others with unknown effects (Green et al. 2003). Exposure to such derivatives may likely lead to different effects and or diseases with unknown aetiology that we may not know how to manage. It is noteworthy to mention that drug abuse is a societal issue that requires multi–disciplinary approach ranging from pharmacological treatments to counselling and rehabilitation.

The regulatory agencies are making effort in reducing drug flow by hacking on the peddlers, this is achieved by making random search on highways, schools and market places. Although this is showing little results as the fight has not been taking directly to the end users which still find a way of getting the drugs due to addiction.

Recommendations

Stringent rules should be formulated by the legislators for drug trafficking and usage which should be enacted to the last. Drug trafficking and usage should be seen as not a social problem only but as security risk as well. A lot of awareness and public campaign should be made on the effects of drug trafficking and abuse on individual, family, and community as a whole.

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Conflict of Interest

None declared.

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