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A review of the influence of the female gender on drug addiction

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Abstract: *Drug abuse and addiction is a social maladywhich is responsible for productivity losses, divorce, armed robbery and other social vices. Illicit drugs and alcohol contribute to the death of more than 100,000 Americans, while tobacco is linked to an estimated 440,000 deaths per year. The manifestations and treatment response in female drug addicts differ from those of their male counterparts. In Nigeria, the prevalence of drug addiction among male and female undergraduates was 57.2% and 42.8% respectively; most commonly abused drugs/substances being alcohol, tobacco, cannabis, kolanut, caffeine and sedatives. This review was aimed at highlighting the causes of gender differences in treatment response to drug addiction.Previous works and research findings on this subject assessed through Google Search, Pubmed, Hinari websites as well as standard textbooks on Pharmacology provided the needed information in the process of this review.Estrogens increase the response to addictive drugs by increasing the level of dopaminergic receptors in the reward regions of the brain. Progesterone, being anti-estrogen, attenuates the addictive effects of drugs. Treatment response is better in the luteal phase of the menstrual cycle when circulating plasma progesterone level is highest.*

Key words: *Drug addiction, estrogen, gender, progesterone, menstrual cycle, treatment response.*

I. Introduction

Drug addiction is a state of periodic and chronic intoxication detrimental to the individual and the society produced by the repeated consumption of a drug[1]. It is also defined as a medical condition characterized by overwhelming desire to continue taking a drug to which one has become habituated despite negative consequences. It is a chronic neurological disorder with genetic, psychological and environmental factors influencing its development and manifestations. Drug addiction is used interchangeably with drug dependence.

In addition to road traffic accidents, social vices such as armed robbery, kidnapping, prostitution, and divorce are linked to drug abuse and addiction.It contributes to the death of more than 100,000 Americans, while tobacco is linked to an estimated 440,000 deaths per year[2]. Most commonly abused drugs/substances include alcohol, cigarette, cannabis, kolanuts, caffeine and sedatives[3,4].

Prevalence of drug abuse and addiction has been on the increase in Nigeria[5].Ene and Stanleyfound the prevalence among male and female undergraduates to be 57.2% and 42.8% respectively[6].

Reasons for drug abuse include relief from stress, promotion of mental alertness, promotion of sexual performance, relief from chronic painful conditions and as a result of negative peer influence[7,4].

The female gender is particularly affected by drug addiction because of the modulating influence of the female gonadal hormones. For example, women progress faster from initially trying cocaine to becoming dependent upon the drug and also display a greater incidence of relapse[8]. While the prevalence of drug addiction is higher among men, the phases of the menstrual cycle profoundly affect the woman's response to addicted drugs[9].

The main objective of this work is to review the effect of the female gender on treatment response in drug addiction. Specific objectives include:

(a) To review the effect of estrogen/progesterone on the pathogenesis of drug addiction.
(b) To review the effect of these hormones on treatment response in the drug addicted female.

II. Risk factors for drug addiction

In addition to gender, several other factors influence the manifestations and response to treatment in drug addiction. Such factors include age, genetic makeup of the patient, route of administration and abuse potential of abused drug, co-morbid mental illness, and presence of environmental toxins. It has been found that the younger the age at which a person begins to use addictive drugs the more likely his or her chances of becoming addicted to that drug[10]. It is also reported that40-60% of vulnerability to addiction could be attributable to genetic factors[11]. It has also been established that whereas family and social factors are influential in determining whether an individual begins to use psychotropic drugs, the progression from the use to abuse of drug was due largely to genetic factors[12].

The route of administration of drugs of abuse affects the rapidity of progression from abuse to addiction. Smoked or injected drugs are more likely to produce addiction compared with orally administered

drugs because they rapidly reach the central nervous system and produce pleasurable effects which drop sharply because of sudden fall in the plasma level of the drugs. This elicits compensatory demand for more drugs thereby leading to addiction[13]. The abuse potential of drugs differ: drugs with high lipid solubility and drugs with short half-lives are more likely to produce addiction[14,15].

Co-morbid mental illnesses increase vulnerability of an individual to drug addiction because the limbic system which controls reward and emotion is also involved in some mental disorders. For instance, in schizophrenia and depression there is abnormality in this area of the brain. Stress, known risk factor for mental illness, also predisposes to drug addiction as it has been demonstrated that dopaminergic pathways are implicated in stress-induced drug addiction[11].

Exposure to environmental toxins in early life produceschanges in the dopaminergic system that could lead to neurodegenerative disorders. Environmental pollutants such as bisphenol A and polychlorinated biphenyl behave like estrogens and stimulate dopaminergic neurons that enhance drug abuse and addiction[16].

III. Mechanisms of drug addiction

Addictive drugs have three basic mechanisms through which they activate the mesolimbic system. First, they canactivatetheinhibitory G protein-coupled receptors thereby causing the hyperpolarization of inhibitory GABA interneurons in the ventral tegmental area (VTA) of the brain. This enhancestherelease ofdopaminefrom the dopaminergic neurons. Drugs that act through this mechanism include the opioids, cannabinoids, and hallucinogens. Secondly, they can bind to inotropic receptors and ion channels to activate dopamine release from the dopaminergic neurons. Such drugs include alcohol, nicotine, and benzodiazepines. Finally, they can block biogenic amine transporters thereby blocking the reuptake, or stimulating the non-vesicular release of dopamine, serotonin, or norepinephrine in target structures. They include cocaine and amphetamine. Though the re-uptake of other monoamines (serotonin, norepinephrine)is also blocked as shown in Table 1, studies have shown that the reuptake of dopamine is the major neurotransmitter mechanism that leads to addiction[17].

All drugs of abuse activate the dopaminergic receptors in the reward pathway. This rewarding property of addictive drugs is responsible for subsequent progression to addiction. Studies have identified the mesolimbic system as the brain region where the reward sensation originates and most drugs of abuse increase extracellular levels of dopamine in this region[18]. Any drug or activity that produces a sharp increase in extracellular dopamine concentration in the brain will most likely produce a pleasurable and addictive effect. Consequently, dopamine is also released in the mesolimbic region of the brain during pleasurable activities like sex, eating, drinking, listening to music, and other recreational activities. Furthermore, enhanced expression of dopamine D_3 mRNA and receptors have been demonstrated in the rodent brain after acute, sub-acute, and chronic exposure to cocaine, nicotine, morphine, and alcohol[19]. More recently, Lucena et al.demonstrated increased number of dopamine D_3 receptors in the brain of cases of sudden death from cocaine over dosage[20].

Table 1: Some neurotransmitters involved in drug addiction, their mechanisms of action andphysiological effects.

Drug	Neurotransmitter	Mechanism	Behavioral response
Alcohol	GABA	Stimulation of GABA receptors	Reduction of anxiety, disinhibition
Cannabis	Endocannabinoids	Stimulation ofcannabinoid receptors	Disinhibition
Amphetamine	Dopamine	Blockade of dopamine reuptake	Arousal, appetite stimulation
Cocaine	Dopamine	Blockade of dopamine reuptake	Arousal, appetite stimulation
Hallucinogens	Norepinephrine	Blockade of norepinephrine reuptake	Regulation of cognition
Opioids	β-endorphins	Activation of μ-opioid receptors	Pain relief, induction of sleep
Nicotine	Acetylcholine	Stimulation of nicotinic receptors	Arousal, cognition acetylcholine
Antidepressants	Serotonin	Blockade of serotonin reuptake	Regulation of emotions

Functional brain changes in drug addiction

Prolonged drug use produces functional changes in the structure of the brain. Henry et al. measured the functional activity of the prefrontal cortex during cocaine administration using positron emission tomography (PET) imaging technique and found that increased cocaine exposure resulted in recruitment of cortical regions beyond the prefrontal cortex. This suggests that initial subjective effects in cocaine addiction are mediated by activity in the prefrontal cortex, but that with increased exposure to cocaine higher order processes such as attention, emotion, and cognition become involved[21]. Also, Volkow et al. found that metabolic activity in the

orbifrontal cortex correlated significantly with the intensity of craving for cocaine[22]. It is equally significant to note that pathological changes were observed in the orbitofrontal cortex in patients with obsessive compulsive disorders which bear functional resemblance to drug addiction.

Addictive drugs affect brain function by decreasing the expression of genes for certain structural and functional proteins in the brain. For instance, administration of amphetamine to rats for nine days resulted in decreased expression of mRNA for activity-regulated cytoskeletal protein (ARC), nerve growth factor inducible protein A (NGF I-A), and nerve growth factor inducible protein B (NGFI-B)[23]. Furthermore, EEG changes suggestive of reduced cerebral blood flow were observed in the brains of chronic marijuana abusers[24]. This reduced cerebral perfusion could also explain the widespread loss of grey matter, the intensity of which was directly related to duration of cocaine abuse[25]. This is not surprising since cocaine causes cerebral vasospasm with attendant cerebralvasculitis and infarction[26]. This vasospasm is mediated by extracellular monoamines, particularly dopamine, as dopamine-rich brain regions appear to be relatively specific targets for such cerebral ischemia[27]. This also applies to other psychotropic drugs since most of them mediate addiction via dopaminergic pathways.

IV. Treatment of drug addiction

Management of drug addiction involves pharmacological and non-pharmacological methods. Relapses are common as in many other chronic illnesses and these should not be taken as failure of treatment. In general, the following principles apply for effective management of drug addiction.

- Treatment strategy is individualized. The individual's social, economic and environmental peculiarities must be taken into consideration.
- Treatment must be adequate both in content and duration to minimize chances of relapse. A minimum period of three months duration is often required.
- Counseling, group therapies and peer support programmes are often helpful.
- Pharmacological treatment combined with counseling and psychotherapy is often beneficial.
- Continuous monitoring should be adopted to ensure compliance to drugs and psychotherapy.
- Co-morbid psychiatric conditions must be identified and managed together.
- Gender, age, and cultural peculiarities must be taken into consideration.

Pharmacological treatment: The following steps are usually followed in drug treatment of addiction.

- Withdrawal of the addictive drug and treatment of withdrawal symptoms.
- Detoxification with specific agents
- Maintenance therapy.

In drug addiction, there is compensatory decrease in dopamine receptors necessitating dose escalation of drugs to produce desired effect (tolerance). Upon drug withdrawal in the drug addict, there is compensatory increase in endogenous monoamines including dopamine, norepinephrine, and serotonin. The resulting increased sympathetic activity produces withdrawal symptoms. Alpha2-adrenergic agonist (clonidine) and b-blockers (propranolol) reduce the release and block the effect of these monoamines respectively. Together with diazepam (anxiolytic) they are useful in treatment of withdrawal symptoms of most addictive drugs.Detoxification and maintenance therapy involve the use of substitution, blockers, and aversion to reduce or completely stop intake of drugs. In addition to these conventional methods of treatment, phytotherapy and vaccines are undergoing clinical trials.

Ibogaine, a psychoactive alkaloid obtained from the West African shrub *Tabernantheiboga*, has been shown to decrease extracellular levels of dopamine and increase extracellular level of serotonin. For instance, Glick and Maisonneuvedemonstrated that at a dose of 40mg/kg it decreased self-administration of ethanol and nicotine in rats[28]. However, it produces irreversible cerebellar damage and inhibits cholinesterase thereby leading to cholinergic toxicity.An Iboga alkaloid congener 18-methoxcoronaridine (18-mc) does not have these serious adverse effects of ibogaine. Other medicinal plants with proven efficacy for the treatment of addiction in animal studies include *Hypericumperfortum, Valerianaofficialis, Ginkgo biloba,*and*Panax ginseng*[29]. Most of these herbal products are undergoing clinical trials.

Anti-drug vaccines stimulate the immune system to produce antibodies that attach to drug molecules, forming compounds that are too heavy to cross the blood-brain barrier. Thus, the higher the level of antibodies produced, the more effective the vaccine in preventing drug-related euphoria. Such vaccines include anti-nicotine, anti-cocaine, anti-metamphetamine, and ant-opium vaccines[30,31,32,33].

Even gene therapy appears promising. Researchers found that viral transfection of genetically engineered cocaine hydrolase in rats caused the plasma level of this enzyme to increase 50,000 fold resulting in rapid destruction of any injected cocaine[34,35,36].

V. Peculiarity of the female gender

The role of gender in the initiation of drug use and subsequent addition has been demonstrated. For instance, disorders associated with marijuana use in USA were significantly higher among men compared to women across all age groups[37]. Differences in the distribution of dopaminergic receptors in the brain, fluctuations in steroid hormones levels during different phases of the menstrual cycle, and differences in the intestinal absorption and hepatic metabolism of drugs are important contributory factors[9]. There is an inverse relationship between the availability of dopamine D_3 receptors and vulnerability to drug addiction[38]. To buttress this fact, Kaasinen et al., using positron emission tomography (PET), demonstrated higher binding potential for dopamine receptors in the reward region of the brain in women compared to men[39]. The reward system, composed of dopaminergic neurons in the mesencephalon, is affected by the female menstrual cycle and by extension the female gonadal hormones estrogen and progesterone. Animal studies show that the dopaminergic system is sensitive to estrogens and progesterones and that the dysfunction of these hormones can result in drug addiction and other psychiatric disorders[40]. Estradiol increase dopamine receptors in the female brain and dopamine receptor density in the reward regions of the brain is inversely related to vulnerability to drug addiction[38].Thus Franklin et al. demonstrated that women in the follicular (high estrogen) phase of the menstrual cycle had less craving for smoking compared with women in the luteal (low estrogen, high progesterone) phase or men[41]. Other studies corroborated this finding. For instance, it was observed that acute administration of progesterone in mice reduced the intensity of diazepam withdrawal symptoms[42,43].

The pharmacological effects of drugs differ in both males and females. These gender differences can be explained by differences in body fat content, volume of distribution of administered drugs, plasma proteins, regional blood flow, and most importantly, differences in hepatic drug metabolism. Excessive body fact reduces tissue blood flow thereby affecting the volume of distribution[44]. In women, the rate of cerebral blood flow is higher thereby increasing the distribution of drugs to the brain[45].Differences in drug metabolism are important determinants of gender differences on the effect of administered drugs. These reflect the expression of specific hepatic P_{450} and other drug metabolizing enzymes[9]. The metabolism of several drugs oxidized by the hepatic CYP3A4 enzyme is more efficient in women because of high plasma levels of this enzyme[46]. This is because growth hormone (whose secretion is higher in women) has positive effect on expression of hepatic drug metabolizing enzymes[47]. Growth hormone also positively affects the expression of phase II drug metabolizing enzymes such as glutathione transferase and sulfotransferase[48]. The enhanced metabolism of drugs of abuse leads to compensatory increase in demand of such drugs thereby leading to addiction.

The female sex hormones (estrogen and progesterone) affect the vulnerability and response to treatment in drug addicts. Estradiol modulates DOPA hydroxylase activity, dopamine release, metabolism, and dopamine receptor behavior in the nigrostriatal and mesolimbic pathways[49]. It causes increased release of dopamine by direct down-regulation of the inhibitory autoreceptors at dopaminergic nerve terminals[50]. Progesterone, an established estradiol antagonist, blocks the expected estradiol-induced enhancement of cocaine self-administration in preclinical studies[51]. Progesterone and progestins thus attenuate the subjective and physiological effects of cocaine in humans. Administration of drugs of abuse in humans and non-humans significantly increased plasma progesterone levels. Expectedly, progesterone, an established estradiol antagonist, blocks the expected estradiol-induced enhancement of cocaine self-administration in preclinical studies[51]. Cigarette smoking also produces high plasma levels of dehydroepiandrostrone. To further support the protective role of progesterone in drug addiction, Sofuoglu et al. demonstrated that progesterone at doses of 400mg/day for 4 days improved cognitive performance and reduced craving for cigarette smoking in female tobacco addicts but not in males[52]. Progesterone produces these effects by increasing the metabolism of estrogens and by inhibitory action on the dopaminergic and endocannabinoid systems[51]. These observations imply that progesterone is a natural homeostatic mechanism that decreases the reward response, thereby reducing drug addiction[53,54].

Expectedly, the phases of the menstrual cycles affect the response to treatment in female addicts. In the late follicular phase of the cycle when estrogen levels are high, the urge to abuse drugs are higher in female addicts. For example, female rats selected higher doses of cocaine during this phase of the cycle[55]. Also ovariectomized female rats given estrogen replacement demanded self-administered cocaine more than those without estrogen replacement[56]. On the other hand, Allen et al.demonstrated that nicotine patch had a more pronounced effect in reducing the cravings for smoking during the luteal phase of the menstrual cycle when the plasma progesterone level is relatively higher[57]. Thus the phase of the menstrual cycle is important in deciding when to initiate treatment for drug addiction in females.

Nearly 90% of drug abusing women are of child bearing age[58]. Treatment of drug addiction in pregnant women had its own challenges because of adverse effect of drugs on the fetus. Methadone was the drug of choice for treatment of opioid-dependent pregnant women. However, Methadone cause neonatal abstinence syndrome characterized by CNS hyperirritability and ANS dysfunction. Buprenorphine does not have this adverse effect and is now the preferred agent[59].

The menopause is a period of emotional challenges in the female. These challenges may precipitate drug addiction or worsen an existing one. Menopause is accompanied by physiological reduction in the level of circulating estrogens and progesterone and this affects the response to treatment for drug addiction. Allen et al. found that tobacco addicted postmenopausal women on hormone replacement therapy (estrogen/progesterone) who are treated with nicotine patch experienced less withdrawal symptoms than those who are not on hormone replacement therapy[57]. Since such replacement therapy usually consists of estrogen and progesterone combination, it is assumed that the positive effect of such therapy on treatment response is attributable to progesterone content of such combination since progesterone is known to attenuate the addictive effects of many abusive drugs as already stated above. However, Oncken et al. demonstrated that hormone replacement therapy did not moderate treatment outcome for nicotine addiction. The reason could be because the effects of the estrogen and progesterone contained in the replacement therapy cancelled out[60].

VI. Conclusion

Initiation of drug abuse and addiction is gender sensitive. These gender differences are as a result of female gonadal hormones, estrogens and progesterone. Phases of the menstrual cycle affect vulnerability to drug addiction and response to treatment, with response to treatment being optimized in the late luteal phase when circulating plasma progesterone levels are highest. Treatment programmes for female drug addicts should take these differences into consideration.

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