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Drug Misuse, Dependence and Addiction

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ABSTRACT

Drug addiction presents a chronic relapsing disorder characterized by persistent drug-seeking and taking behaviors. Given the significant detrimental effects of this disease both socially and economically, a considerable research has been dedicated to understanding a number of issues in addiction including behavioral and neuro-pharmacological factors that contribute to the development of addiction, loss of self control and persistence of compulsive addictive behaviors. This review was designed to list out the drugs and factors which initiate and maintain dependence and how the relapse of these substances occurs in drug dependent persons.

INTRODUCTION

Drug addiction is widely considered as a pathological state that involves progression of acute drug use to the development of drug-seeking behavior, the vulnerability to relapse, and the decreased, slowed ability to respond to naturally rewarding stimuli. Abuse and addiction have been defined and redefined by several organizations over the past 35 years. The APA (American Psychiatric Association) defines substance dependence (addiction) as a cluster of symptoms indicating that the individual continues use of the substance despite significant substance related problems. (O'Brien, 2006)

Portenoy, in 1990 and 1994 defined addiction as "a psychological and behavioral syndrome characterized by evidence of psychological dependence, and evidence of compulsive drug use, and/or evidence of other aberrant drug-related behaviors" (Portenoy, 1994; Portenoy, 1990). The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) has categorized three stages of addiction: preoccupation/anticipation, binge/intoxication, and withdrawal/negative effect. These stages are characterized, respectively, by constant cravings and preoccupation with obtaining the substance; using more of the substance than necessary to experience the intoxicating effects; and experiencing tolerance, withdrawal symptoms, and decreased motivation for normal life activities (Nutt *et al.,* 2007; Koob and Kreek , 2007; American Academy of Pain Medicine, 2001).

Addiction might be confused with pseudo addiction. The later term has been used to describe patient behaviors that may occur when pain is undertreated. It is a related phenomenon and results also in "drug-seeking" behaviour (Weissman and Haddox, 1989). Pseudo addiction may occur in chronic pain patients, who are prescribed sub analgesic doses of opioids. (Lashner, 2001; Gardner, 2005)

Reasons for drug misuse, dependence and addiction

Genetic, social and environmental factors greatly contribute to the development of addictive behaviors. Addiction is culture of symptoms of some fundamental personal and/or socioeconomic problems. Such as mental illness may make someone susceptible to drug experimentation and use, but it is not a causal factor.

Similarly, poverty may increase susceptibility, but there is no automatic causal relationship with addiction. (Nedeljkovic, 2002). At present according to recent survey in Pakistan, about 3.5 million drug addicts of different kinds growing on an annual rate of 7 percent. An examination of social and demographic factors revealed that 71.5 % of the drug abusers were less than 35 years of age with the highest proportion in the 20-30 years age group (ANF, 2000-2003).

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Another survey distinguished the factor that teenagers susceptible to drug abuse can often be identified by "risk factors" such as emotional problems like depression or anxiety, these factors in turn create low self-esteem and a desire to escape feelings like self-doubt, powerlessness, and hopelessness leading to abridged coping skills (Byrne- Spring, 2000; Wexler, 1991). Studies have revealed that living in a stressful home environment with low parental support, monitoring, and communication have been significantly related to frequency of drug abuse and drinking. Poor parenting may also increase the risk of drug abuse for adolescents (Brook *et al.,* 2001; Ali *et al.,* 2011; Farrel *et al.,* 1992). Another study reports to certain psychosocial risk factors (Niaz *et al.,* in 2005).

Sex differences in drug abuse

Rate of drug addiction in men is 2-3 times higher than women is different in all the phases of drug abuse inclusing initiation followed by escalation of use and the progression to addiction with subsequent withdrawal and relapse. But this difference reflects differences in opportunity, rather than vulnerability to drug use (Caroll *et al.,* 2004 ; Lynch *et al.,* 2002, Etten and Anthony, 2001; Etten *et al.,* 1999).

If one looks at rate of escalation of drug use, however, women tend to increase their rate of consumption of alcohol, marijuana, opioids, and cocaine more rapidly than do men (Brady and Randall, 1999; Hernandez-Avila *et al.,* 2004 ; Mann *et al.,* 2005 ; Randall *et al.,* 1999). Furthermore, once addicted to a drug, women can find it more difficult to quit than men do. This is true for nicotine, as well as many other drugs of abuse (Back *et al.,* 2005 ;Breese *et al.,* 2005 ;Carpenter *et al.,* 2006). Abstinent women report higher levels of craving following exposure to cocaine-related cues than do men and women have longer periods of use after abstinence than do men (Gallop *et al.,* 2007; Robbins et al.,1999). Studies of the response to cocaine in gonadectomized male and female rats provide the strongest data regarding the neural evidence for sex differences in drug abuse. Women become addicted to alcohol more rapidly than do men and brain atrophy develops more rapidly in women than in men (other negative medical consequences involve the heart, muscle and liver which are also compromised more rapidly in women than in men (Beckerand, 2008; Zilberman *et al.,* 2003).

Women also begin using cocaine or amphetamine (AMPH) and enter treatment at earlier ages than men (Griffin *et al.,* 1989; Mendelson *et al.,* 1991; Kosten *et al.,* 1993). Thus, the progression to dependence may differ between men and women, with women progressing through the landmark stages from initial use to dependence at a faster rate (Kosten *et al.,* 1985).

The biological basis of drug addiction

Researchers have conducted numerous investigations using animal models and functional brain imaging on humans in order to define the mechanisms underlying drug addiction in the brain. This intriguing topic incorporates several areas of the brain and synaptic changes, or neuroplasticity, which occurs in these areas. It has been found that addiction is a brain disease (Wise, 2000; Lashner, 2001) and current neurophysiologic evidence suggests that the development of addiction is to some extent due to neurochemical stimulation of the brain reward center (Gardner, 2005). Acute (or recreational) drug use causes the release and prolonged action of dopamine and serotonin within the reward circuit. Different types of drug produce these effects by different methods. DA appears to harbor the largest effect and its action is characterized. DA binds to the D1 receptor, triggering a signaling cascade within the cell. (Kalivas and Volkow , 2005; Jones and Bonci ,2005; Kourrich *et al.,* 2007; Floresco and Ghods,2007).

Neurogenesis and Neuroplasticity

Drug addiction also raises the issue of potential harmful effects on neurogenesis. The Eisch and Harburg presented three new concepts they had extrapolated from the numerous recent studies on drug addiction. First, neurogenesis decreases as a result of repeated exposure to addictive drugs as with chronic use of opiates, psychostimulants, nicotine, and alcohol. Second, this apparent decrease in neurogenesis seems to be independent of hypothalamic-pituitary-adrenal (HPA) axis activation. Last, addictive drugs appear to only affect proliferation in the subgranular zone (SGZ), rather than other areas associated with neurogenesis. The studies of drug use and neurogenesis may have implications on stem cell biology (Eisch and Harburg , 2006).

Neuroplasticity is the putative mechanism behind learning and memory. It involves physical changes in the synapses between two communicating neurons, characterized by increased gene expression, altered cell signaling, and the formation of new synapses between the communicating neurons. When addictive drugs are present in the system, they appear to hijack this mechanism in the reward system so that motivation is geared towards procuring the drug rather than natural rewards (Jones and Bonci , 2005; Kourrich *et al.,* 2007; Bahi and Dreyer , 2005).

Physical-Psychological dependence and tolerance:

Tolerance, psychological and physical dependence are three separate but related processes which contribute to overall drug dependence process. Physical dependence is an expected consequence of prolonged use of drugs (Portenoy, 1996), but physical dependence may develop after the use of a dependency-producing drug for only 48 hours (Glatt, 1974 ; Morgan, 1985). Physical dependence may occur following the use of drugs producing reward as opioids and benzodiazepines. It may also occur following the use of drugs with little or no reward potential, such as beta-blockers, alpha-2-adrenergic agents (e.g. clonidine), corticosteroids and tricyclic antidepressants (Savage *et al.,* 2003).

Tolerance is characterized by reduced drug effect on repeated use, and represents cellular adaptation of central neurons where the same behavioral effect is induced by progressive increase in drug intake. (Bhattacharya *et al.,* 2003).Tolerance to the analgesic effects of opiates is a common physiologic finding that results from neuroadaptation by the body during chronic use (Savage, 1999).

Drugs which are misused, develop dependence and cause addiction

World Health Organization has recommended that drug dependence can be specified in different types as shown in table 1 (Bennet and Brown, 2003). However there are different prescription and non prescription drugs which cause addiction. In forth coming part of this text we have tried to sum up about the most commonly used dependence creating drugs.

Amphetamine is also used illegally as a recreational club drug and a performance enhancer. Tolerance is developed rapidly in amphetamine abuse, which increases the amount of drug required to satisfy the addiction. Repeated amphetamine use can produce "reverse tolerance", or sensitization to some psychological effects (Boileau *et al.,* 2006; Sax and Strakowski, 2001; Leith and Kuczenski , 1981; Chaudhry *et al.,* 1988).

Methamphetamine causes addiction especially when injected or smoked. Methamphetamine addicts may lose their teeth abnormally quickly, a condition known as "meth mouth". In the US methamphetamine use is common with varying rate of consumption (Winslow *et al.,* 2007). Other symptoms of addiction are drug craving, weight loss, withdrawal-related depression, anhedonia, rapid tooth decay, brain damage/ Meningitis (Neurotoxicity), formication (sensation of flesh crawling with bugs, with possible associated compulsive picking and infecting sores),paranoia, delusions, hallucinations (Cohen *et al.,* 2007; Grabowski *et al.,* 2004).

Khat is a plant material widely chewed in East Africa and Yemen for its stimulant properties. When the leaves of the plant are chewed, cathine and cathinone (amphetamine-like stimulant) are released and cause the body to recycle epinephrine and nor-epinephrine neurotransmitters more slowly and causes are excitement and euphoria (Nutt *et al.,* 2007; Ahmed and el-Qirbi, 1993).

Caffeine- a mild stimulant is most widely used psychoactive drug in the world. In large amounts, and especially over extended periods of time, caffeine can lead to a condition known as *caffeinism (*Mackay and Rollins, 1989; James and Stirling, 1983). Caffeinism usually combines caffeine dependency with a wide range of unpleasant physical and mental conditions including nervousness, irritability, anxiety, tremulousness, muscle twitching (hyperreflexia), insomnia, headaches, respiratory alkalosis and heart palpitations. Furthermore, because caffeine increases the production of stomach peptic ulcers, erosive esophagitis, and gastroesophageal reflux disease. Caffeine is an ergogenic: that is it increases the capacity for mental or physical labor. Several studies have showed a 7% increase in distance cycled over a period of two hours in subjects who consumed caffeine compared to control tests (Ivy *et al.,* 1979; Graham and Spriet, 1991; Trice and Haymes, 1995)

Cocaine users often report a strong response on seeing cocaine before it is administered, consisting of physiological arousal and increased drug craving with concomitant activation of limbic structures (Childress *et al.,* 1999). Sensitization in human beings has been linked to paranoid, psychotic manifestations of cocaine use based on the observation that cocaine-induced hallucinations and paranoia are seen typically after long-term exposure (mean 35 months) in vulnerable users (Satel *et al.,* 1991). ***Nicotine*** is extremely durable, as exemplified by the high failure rate among smokers who try to quit. Although more than 80% of smokers express a desire to quit, only 35% try to stop each year, and fewer than 5 % are successful in unaided attempts to quit nicotine smoking (O'Brien, 2006). Nicotine acts on brain nicotinic cholinergic receptors to facilitate neurotransmitter release (dopamine and others), producing pleasure, stimulation, and mood modulation (Benowitz, 2008).The absorbed nicotine is rapidly and extensively metabolized to inactive cotinine by CYP2A6 in human livers, which has a major impact on nicotine clearance (Nakajima, 2007). Since a smoker absorbs, on average, approximately 1 mg of nicotine per cigarette. Plasma cotinine level of 300 ng/mL corresponds to a daily intake of approximately 24 cigarettes. (Benowitz, 1994; Benowitz, 1984). **Tobacco** is used primarily in the form of cigarette. Exposure to tobacco smoke pollution has caused the premature deaths of more than 14 million Americans since 1964 (Giovino, 2007**).** It is widely recognized that polycyclic aromatic hydrocarbons (PAHs) are responsible for most drug interactions with smoking. PAHs, (products of incomplete combustion of tobacco) are found appreciably large quantities in tobacco smoke and are potent inducers of several hepatic cytochrome P450 microsomal enzymes (CYP1A1, CYP1A2, and possibly CYP2E1) (Schein, 1999). Oral forms of tobacco (snuff, chewing tobacco) are associated with cancers of the mouth, throat, pharynx, larynx, and esophagus, as well as periodontal damage and oral leukoplakia (Hatsukami *et al.,* 1999).Smoking cessation also can lead to a significant reduction in the cumulative risk of death from lung cancer for both men and women.

Sedatives and Hypnotics

Alcohol's physical dependence is demonstrated by the elicitation of a withdrawal syndrome when alcohol consumption is terminated. The symptoms of alcohol dependence include Anxiety or jumpiness, shakiness or trembling, sweating, nausea and vomiting, insomnia, depression, irritability, fatigue, loss of appetite and headache. The severity of dependence is determined by the amount and duration of alcohol consumption and includes sleep disruption, tremors, and in severe cases seizure (Fleming *et al.,* 2006). **Barbiturates** are drugs that act as central nervous system depressants, Barbiturates are abused, and some individual develop dependence on them. They have euphoriant effects. Signs of drug dependence include relying on a drug regularly for a desired effect. The person depends greatly on barbiturate to sleep, relax, or just get through the day. Continued use of barbiturates leads to physical dependence like other CNS depressant drugs (Charney *et al.,* 2006).Benzodiazepines, particularly alprazolam, clonazepam, temazepam, and nimetazepam Long-term benzodiazepine usage, in general, leads to some form of tolerance and/or dependence with the appearance of a benzodiazepine withdrawal syndrome when the benzodiazepines are stopped or the dose is reduced (O'Brien , 2005).

Table. 1: Types of drug dependence.

Type of Drug	Comments
Morphine-type	-Psychological dependence severe -Physical dependence severe; develops quickly -Tolerance marked -Cross-tolerance with related drugs -Naloxone induces abstinence syndrome
Barbiturate-type	- Psychological dependence severe -Physical dependence very severe; develops slowly at high doses -Tolerance less marked than with morphine -Cross-tolerance with alcohol, chloral, meprobamate, glutethimide, chlordiazepoxide, diazepam, etc.
Amfetamine-type	-Psychological dependence severe -Physical dependence slight: psychoses occur during use -Tolerance occurs
Cannabis-type	-Psychological dependence -Physical dependence dubious (no characteristic abstinence syndrome) -Tolerance occurs
Cocaine-type	-Psychological dependence severe -Physical dependence slight -Tolerance slight (to some actions).
Alcohol-type	-Psychological dependence severe -Physical dependence with prolonged heavy use -Cross-tolerance with other sedatives
Tobacco-type	-Psychological dependence -Physical dependence
Drug mixtures*	-Psychological dependence strong -Physical dependence occurs -Tolerance occurs

**Barbiturate-amfetamine* mixtures induce a characteristic alteration of mood that does not occur with either drug alone.

The development of tolerance and physical dependence of Opiate and Opioid analgesics with repeated use is the characteristic feature of all opioid drugs. Among these drugs Morphine is a highly addictive substance, both psychologically and physically, with an addiction potential comparable to that of heroin. Comparing with opium, dependence caused by Morphine or heroin dependence is more disabling physically and socially (Bennett and Brown, 2003; Martin and Fraser , 1961). Codeine can be used as a recreational drug, however it has lesser abuse potential than some other opiates or opioids such as oxycodone and hydrocodone. A heroin addict may use codeine to ward off the effects of a withdrawal. It is less potent and has a correspondingly lower dependence liability than morphine.73 (Vree et al, 2000)

Semi-synthetic opiates, such as Heroin (Diacetylmorphine) are the most important opiates that are used for addiction. It has unique analgesic properties for the treatment of severe pain. The level of physical dependence among heroin addicts is relatively high and those users who interrupt regular dosing develop more severe withdrawal symptoms. (O'Brien, 2006). **Cannabis** is the most widely used illicit substance in the United States, and rates of cannabis use disorders in some Native American samples have been reported to be higher than in the general U.S. population (Gilder *et al.*, 2007).

Dependence associated with treatments

Pain cannot be adequately managed when complicated by addictive disease and may even be worsen in this context (Savage, 1996; Mao *et al.*, 1995; Compton, 1994). it is well known that opioid treatment may initially be a part of the solution In chronic pain, but later it turns into a substantial part of the problem (Eriksen, 2001). Long-term treatment with opioids may be complicated by development of tolerance, dependence, addiction, abnormal pain sensitivity, cognitive dysfunction, hormonal changes and immune modulation (Savage, 1996; Bendtsen *et al.*, 1999, Sjøgren *et al.*, 2000; Breivik, 2001; Ballantyne and Mao, 2003) The use of sedation and analgesia in critically ill children is necessary for clinical management but can result in undesirable side effects such as physical dependence, tolerance and withdrawal symptoms. Weaning from sedation aims to prevent such unpleasant effects. (Collyer and Meredith , 2008) Abuse and dependence are probably the major drawback to the clinical use of benzodiazepines (Uhlenhuth EH *et al.*, 1999). Diazepam, alprazolam, and lorazepam are reported to be more likely abused than are oxazepam and chlordiazepoxide. Misuse and abuse of benzodiazepines is limited primarily to those with current history of abusing other substances, including alcohol (Posternak and Muller, 2001) There is some evidence that use of shorter half-life benzodiazepine can result in physiologic dependence earlier (days to week) and may be associated with withdrawal problems (Wagner *et al.*, 1998; Bunney *et al.*, 1999). The XR alprazolam formulation is reported to have a lower abuse potential than immediate-release alprazolam because of its slower onset of effects and lower maximum plasma concentrations (Klein, 2002) Dependence can occur after continued use of benzodiazepine over 2 to 4 months. Three types of benzodiazepine discontinuation syndromes are evident; relapse, rebound and withdrawal (Rickals *et al.*, 1999; Salzmann, 1991).

Drug Withdrawal reactions

Withdrawal is marked by "mood offset" characterized by depression lasting up to several weeks (katzung *et al.*, 2009). A part from drugs that are usually recognized as producing dependence, sudden interruption of therapy with certain other drugs also results in adverse consequences, commonly worsening

of clinical condition for which the drug was used. For example acute adrenal insufficiency may be precipitated by abrupt cessation of corticosteroid therapy, severe hypertension and sympathetic over activity may occur shortly after discontinuing clonidine (Tripathi, 2003). Opiate withdrawal symptoms can be precipitated by an opiate antagonist after short-term infusion or even a single dose of an opiate both in humans and in animals. This phenomenon has been referred to as acute dependence (Ishida *et al.,* 2008). Chronic morphine-induced withdrawal syndrome after morphine cessation remains as severe obstacle in the clinical treatment using morphine (Mori *et al.,* 2007). Alcohol and Caffeine withdrawal consists of feelings of fatigue and sedation. With higher doses, headaches and nausea have been reported during withdrawal; vomiting is rare. Although a withdrawal syndrome can be demonstrated, few caffeine users reported significant difficulty in reducing caffeine consumption, if desired (Rehm and Greenfield., 1999).

Consequences of Drug abuse

Early-onset or frequent substance use during adolescence increases the risk of developing mental health problems, as well as a range of other adverse outcomes during late adolescence and early adulthood such as alcohol or drug dependence, educational underachievement, health problems, social difficulties, lung cancer, COPD, and cardiovascular diseases, immuno suppression (by opioids) (Lubman *et al.,* 2007, Action on Smoking and Health, 2005; Ezzati and Lopez, 2003, Zhu *et al*., 2000, Sharad *et al.*, 2007). There is a high risk of cervical osteomyelitis in intravenous drug abusers due to the use of jugular veins for administration of drugs. Arum *et al.,* in 2007 described a case of rapid vertebral body destruction at two levels leading to a progressive kyphotic deformity followed by auto-fusion, secondary to cervical osteomyelitis in a I/V drug abuser . IV heroin use is associated with several well-described complications, including noncardiogenic pulmonary edema, aspiration pneumonitis, ARDS, pneumonia, lung abscess, septic pulmonary emboli, and atelectasis (Arun et al., 2007)

Management of Drug Use and dependence

A range of strategies is used to address and prevent or limiting the problems associated with drug use and dependence. These are categorized as **Primary Prevention** which is concerned with preventing initiation of drug use by warning about drug abuse consequences. **Secondary prevention** is aimed at people who use drugs by discouraging further use.

If adolescents and youth can be motivated to stay away even from the "gateway drugs" by targeting common initiation factors, it may lead to delay or possibly avoidance of development of dependence (Brigham *et al.,* 2007). **Drug education** is given to people who are dependent on drugs as they may not be fully informed on the drugs they use. **Social support** includes practical advice and use of psychological tools (effectively used by psychologists and counselors) such as motivational and counseling sessions with the patients dependent on drugs. **Detoxification** is aimed for a person to become abstinent from the drug on which they are dependent. **Rehabilitation** may include a detoxification process followed by a period of social support and intensive psychotherapy to facilitate sustained change. **Harm reduction** is a generic term to reduce the adverse consequences of drug dependence experienced by both individual drug user and society (Scott, 2004). **Pharmacogenetic approach** can be utilized for treatment of nicotine dependence (Lerman *et al.,* 2007).

CONCLUSION

There are many substances that are responsible for drug dependence and addiction. Drug dependence may cause by numerous medicines like barbiturates, opioids analgesics etc. The drug addiction is however more pronounced in males than females. Drug abuse is increasing day by day especially in under developing countries due to lack of awareness. We suggest that campaigns and educational sessions should be conducted to reduce the risk of addiction.

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