THE CONCEPT OF

JODA, A. E.¹ AND ONANEYE, F. B.²

1. Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, (College of Medicine Campus), University of Lagos, IDIARABA. Dental Department, General Hospital, Ikorodu, Lagos.

KEY WORDS:

Drug Addiction, Drug Dependence, Drug Problems

SUMMARY

The article was written to serve as a basic write-up on drug addiction for use in the development of other studies by interested researchers. It started with an introduction defining relevant terms as well as elucidating the general principles involved in addiction. It then went on to highlight the social environment and impact of drug use and the populations at greatest risk of abuse as well as the common names for some drugs of abuse.

This was followed by methods of estimating drug abuse before finally itemizing the diagnostic classifications. The article concluded with the characteristics of drug dependence and the classifications based on these characteristics.

INTRODUCTION

In writing this paper, it must be pointed out that the word "addiction" has largely been superseded by the newer term "dependence". However, some authors sometimes use two words and including a third one "habituation" interchangeably. The World Health Organization in 1957 defined Drug Addiction as a state of periodic or chronic intoxication produced by the repeated consumption of a drug (natural or synthetic)1. Its characteristics include:

- An over powering desire or need (compulsion) to continue taking the drug and obtain it by any means
- A tendency to increase the dose
- A psychic (psychological) and generally a physical dependence on the effects of the drug

A detrimental effect on the individual and on society

Drug dependence according to the 1969 World Health organization definition its "A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug or a continuous on periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present. A person may be dependent on more than one drug2.

Generally, the term dependence has gained increasing acceptance.

A dependence producing drug is any drug having the capacity to interact with a living organism to produce a state of psychic or physical dependence³. Another important definition is "Drug Abuse" which is defined by WHO as "the consumption of a drug apart from medical need or in unnecessary quantities. Drug dependence is of course only one of many possible harmful consequences of drug abuse.

GENERAL PRINCIPLES

The physiological effects of drugs of dependence are markedly affected by the:

- (a) Personality of user
- (b) His expectations
- (c) The environment

The actions of these drugs and the likelihood of producing dependence vary with the dose, frequency of administration, length of time over which drug is used and route of administration. In general, the degree

of dependence increases with the amount and frequency of use, as does the degree of physical harm when such harm occurs. The rate of change and the chance of causing dependence is partly a function of route of administration and varies in order of increased rate of change as follows: oral, subcutaneous, inhalation and intravenous routes. Injection of drugs, particularly intravenously, causes the greatest physical damage because of increased toxic effects and infections.

Dependence can be psychological (a condition in which a drug produces a feeling of satisfaction and a psychic drive that requires periodic or continuous administration of the drug to produce pleasure or to avoid discomfort) or/and physical (an adaptive state that manifests itself by intense physical disturbance when the administration of the drug is suspended). These disturbances i.e. the withdrawal or abstinence syndrome, are made up of specific arrays of symptoms and signs of psychic and physical nature that are characteristic for each drug type3.

Contrary to popular belief it is psychological dependence, not physical dependence that in the long run, constitutes the main problem. Certainly, the physical abstinence symptom, which supervenes on sudden cessation or very rapid reduction of the amount of the drug, can sometimes be very distressing and even lifethreatening. But with skilled supervision, as a rule, this acute withdrawal syndrome can be handled relatively easily. What makes drug dependence so difficult to deal with in the long run and is responsible for the unfortunate fact that, essentially, states of drug dependence are relapsing disorders, is psychological dependence, the user's recurrent desire to reexperience the instantaneous relief from emotional pain, the detachment from reality and escape from it all, or the euphoric 'high' or 'buzz'. Social factors too, such as 'subcultures', peer pressure, conditioning etc. may play a big role in precipitating a relapse after the individual may have experienced a period of freedom from drug use. Incidentally, the relative importance of psychological and physical dependence can possibly be illustrated by the example of compulsive gambling. Here of course there is no physical and 'merely' psychological dependence. Nevertheless, compulsive gambling shows most of the characteristic features of compulsive drug-taking and

Social Environment and Impact

In all aspects of drug dependence not only the "agent" (the pharmaceutical nature of the drug concerned but also the psychological-biological make-up of the individual host) and social and other environmental factors have to be considered.

All too often in the past, attention was mainly directed to the nature of the drug without considering the drug user's personality and his social environment.

Thus the impact of drug problem on the social life of a people can take a sizable proportion. Alcohol is involved in 40% of all reported assaults and one third of all forcible rape and child molestation cases6. Almost 50% of inmate reported being under the influence of alcohol, with or without other drugs, when committing their offense, fewer than 10% report being under the influence of other drugs alone. When drug prices increase, property related crimes increase. When addicts were not dependent on heroin, their crime rate was 84% lower than when they were regularly using the drug

Alcohol is involved in more than half of all U.S traffic fatalities and almost 80% of fatalities from accidents occurring between 8.00pm and 4.00am. Alcohol was reportedly present in 63% of homicide victims, 49% of unintentional injury fatalities, 35% of suicide victims and 14% of

persons who died of natural causes in a rural state.

Drunk driving is less likely in those who are aware of the consequences of being arrested for drunk driving (e.g. fines, incarceration, publication of names, criminal record) and those who feel that taking a car, or calling a friend are reasonable alternatives to driving when intoxicated. Multi-media prevention messages addressing such topics should be undertaken¹⁰.

The type and setting for treatment of individual patients should be matched to specific addictions. Treatment is readily available in developed countries to those who can afford it but cannot be provided for those who cannot. Additional treatment facilities, especially for the indigent, are needed. While drug abuse prevention efforts often are singularly unsuccessful, messages, which are repeated through multiple media and demonstrate peer and social acceptance (e.g. athletes providing messages concerning drug abuse) appear to reduce use. Interruption of illegal drug movement will do little to reduce the societal burden of addiction as long as a demand exists for the drug. Prevention of initiation of drug use and assistance for those who are addicted are more likely to be effective in reducing abuse of alcohol and other drugs".

POPULATIONS AT GREATEST RISK OF ABUSE¹²

These include:

A) Fetuses and Neonates

Drug use during pregnancy results in many serious perinatal complications such as still births, premature rupture of the membranes, maternal hemorrhage and fetal distress. Asphyxia, prematurity, low birth weight, infections, cerebral infection, congenital malformation and drug withdrawal complicate neonatal care. Long term sequelae include delays in physical and mental development, sudden infant death syndrome and learning disabilities. Most abused drugs are excreted in breast milk in quantities sufficient to elicit pharmacological effects in the infant.

B) Women

Alcoholic women drink less than men-but reach the same degree of impairment. Differences in body size and composition, hormonal effects, and decreased levels of gastric alcohol dehydrogenase are contributing factors. They are more likely than men to have chemically dependent spouse, to exhibit psychiatric symptoms, especially depression, and to be suicidal.

Alcoholic women often will have histories of other drug abuse especially tranquilizers, sedatives and amphetamines by prescription but are less likely than men to abuse illicit drugs. Child care issues and pregnancy further complicate access to treatment.

C) The Elderly

The prevalence of alcoholism and other drug use may range between 14 and 44% among community based; and medical and psychiatric elderly people. The elderly require less drug to become intoxicated because of changes in body composition, metabolizing ability and neurological sensitivity.

Chronic alcohol use and, for males' age greater than 50 years, reduces the activity of gastric alcoholic dehydrogenase (which metabolizes ingested alcohol). Also misuse of prescription medication and use with alcohol is common. Increasing physical illness and psychological distress increase the likelihood of substance abuse though not all problems should be attributed to aging.

D) Ethnic and Cultural

Incidence of chemically dependent people from minority groups and developing nations are seriously under reported. Thus useful data are not available. Also treatment of identified individuals is rather inadequate. Treatment of addicted members of minority groups and in developing countries will need to accommodate language, cultural and social differences. Resources must be pooled in order to provide this service.

E) Healthcare Professionals

Alcohol is the primary abused substance among healthcare professions. Healthcare professionals over 40 years of age are more likely to abuse alcohol alone, while those below 40 tend to use other drugs alone or in combination with alcohol. Illicit drug use among healthcare professionals is less than in the general population, prescription drugs (especially opioids and benzodiazepines), alcohol and tobacco are abused most commonly.

The incidence of chemical dependency among healthcare professionals probably is similar to the general population. The drug of choice and route of administration vary among professions. Those professions, such as nursing and medicine, which use injections in the course of their usual practice more often abuse injectable drugs. Pharmacists tend to abuse multiple oral drugs and are more likely than other healthcare professionals to abuse stimulants. Specific professions tend to abuse the most readily available drugs. Nitrous oxide addiction is problematic for dentists, for instance.

F) People with Dual Diagnosis

This refers to a patient who has a psychoactive disorder requiring simultaneous treatment. Psychoactive patients as a group are at significantly increased risk for developing or having a psychoactive substance use disorder and vice versa. The prognosis in dual diagnosis is not as good as in single diagnosis cases. The dual stigma these patients experience often results in poorer social support, which is a very significant poor prognostic indicator for both disorders. These patients also have poorer compliance with treatment and are at significantly increased risk of relapse to their drug of choice. Dually diagnosed persons represent a seriously distressed and disabled population that is growing in number and whose co-existing illnesses are difficult to treat. Conflicting treatment philosophies

and fragmented service systems sometimes compound these problems. The use of the term dual diagnosis also attempts to signal to others that these clients have special needs and require specialized treatment approaches.

Common Names of Some Drugs of Abuse¹³

Heroin: Dime or Quarter bag, Persian Brown, China white, Designer drugs, Tar heroin or Mexican tar, Junk

Amphetamines: Ice, Shabu, Cross tops, Black beauties, Berries, Crank, Meth, Crystal, Speed dexies

Amphetamine look-alikes: Legal stimulants, Legal speed

Cocaine alone: Pasta, Bazooka, Buscoso, Yeo-o, 'C', Snow flake, Blow, Happy trails, Girl, Coke, Nose, Candy, The lady, Loot, Gold dust, Rock, Crack, Ready rock, Teeth, French fries, Gravel, Cloud, Dove, Love, Roxanne, Cookies

Cocaine combinations:

Cocaine + heroin: Speed ball

Cocaine + PCP: Speed base

LSD: Illusion

Cannabis: Grass, pot, weed, smoke, boo, Mary Jane, Hash, temple balls, Marijuana

ESTIMATING DRUG ABUSE

Methods Of Estimating Drug Abuse Include:

A) Direct Methods

- Personal interviews in natural household surveys
- National surveys done by tracking high school seniors throughout college and young adulthood

B) Indirect Methods

- Use of death rates from cirrhosis of the liver
- Incidence of hepatitis to predict total numbers of alcoholics or intravenous drug abusers

- Seizure of drugs by law enforcement agents though this rarely gives accurate estimates
- Data from hospital emergency room and other acute drug treatment facilities, crisis centers, medical examiners and coroners
- On-going prescription audits of physicians and pharmacies

Diagnostic Classification

The Diagnostic and Statistical Manual of mental disorders (DSM) published by the American Psychiatric Association (APA) lists the specific criteria for differentiating psychoactive use disorders. Currently, substance related disorders are divided into two large groups.

- Psychoactive Substance Induced Disorders
- 2) Psychoactive Substance Use disorders

Characteristics of Drug Dependence

The characteristics of dependent states vary with the agent involved and this must be made clear by designating the particular type of drug dependence in each specific case, for example, drug dependence of the morphine type, the barbiturate type, the amphetamine type, etc5. This classification has practical medical importance since withdrawal treatment is desirable for drugs in Groups I, is seldom necessary for Groups II drugs and not required at all for drugs in Groups III. In addition, drugs in sub group 1A are interchangeable within the subgroup (cross tolerance and dependence) and drugs in sub group 1B are interchangeable within the sub-group. Sub group 1A drugs however, cannot be substituted for sub group 1B drugs and vice versa.

Classification of dependence producing drugs based on these characteristics include¹³:

 with psychic and physical dependence

- Opiate Type: Autonomic storm and central nervous system irritability or withdrawal
 - a. Opium and derivatives, morphine, codeine, Heroine e.t.c.
 - b. Synthetics with opiate like effects: meperidine (Pethidine); phenazocine, levodromoran; Methadone

Dependence of the Opiate type is the classic prototype of addiction and is characterized by very strong psychic dependence, strong (but not fatal) physical dependence and enormous tolerance. They produce elation, pleasurable relaxation, drowsiness, sleep and dissociation of the psychic reaction to pain from its pain. Drunkenness does not occur. The opiates depress responses mediated through two neuron arcs, and stimulate supraspinal inhibition of peripheral sensory transmission. Hyperactivity in the multineural arcs initially depressed by opiate develops accounting for tissue tolerance. Persistence of the hyperactivity after withdrawal of drugs accounts for symptoms of abstinence14. These changes may be associated in complex ways with synthesis and release of neurohormones within the central nervous system.

Withdrawal from physical dependence of the opiate type is characterized by an autonomic storm (sweating, papillary dilation, fever e.t.c.) and central nervous system irritability (twitches, muscle aches, insomnia). It is self limited and not dangerous to life. Abstinence phenomena from opiates are precipitated in acute and potentially dangerous form by the narcotic antagonists nalorphine, naloxone e.t.c.

Treatment of physical dependence of the opiate-type is a simple procedure involving mere reduction of the drug of dependence or a substitution, with methadone being most suitable¹⁵. The high degree of tolerance developed to opiates and the high degree of cross-tolerance of one member of the subgroup to all others is the bases for the methadone maintenance method of management of opiate dependence.

- ii. Alcohol barbiturate Type: convulsions and delirium on withdrawal:
 - Ethanol, Barbiturate, Chloral, paraldehyde

It is characterized by strong psychic and physical dependence and by moderate, but limited tolerance. These drugs all cause dosc dependent elation, euphoria, diminished controls of behaviour, motor in-coordination (drunkenness); sedation, sleep and coma. Ethyl alcohol has the most deleterious effect to body tissues of any member of the group. Tolerance is both bio-chemical and adaptive. These drugs all increase the electrical threshold for activation of all kinds of nerve cells at all levels of the central nervous system with the cells of the cerebral cortex (concerned with thought processes) and the reticular activating system (concerned with consciousness) being the most susceptible. Signs of abstinence include nervousness, insomnia convulsions and delirium. Physical dependence of barbiturates is associated with prolongation of after-discharge in neurons and has been hypothesized to be due to denervation hypersensitivity16. Unlike abstinence from opiates, abstinence of the alcohol barbiturate type is dangerous to life and must always be treated by gradual withdrawal of the drug of dependence or an equivalent drug.

- With psychic and mild or questionable physical dependence
- Opiate Antagonist type: Similar to opiate type but some differences, Nalorphine, Levallorphan, cyclazocine

It is not of great importance since there is no large illicit source of these drugs. It is characterized by moderate-to-low psychic dependence, moderate tolerance and low grade physical dependence somewhat similar to physical dependence of the opiate type.

- ii. Amphetamine Type: Sleep, hunger, apathy, depression on withdrawal:
 - a. Amphetamine,
 Dexamphetamine,
 Methamphetamine,
 Phenmetrazine,
 Methylphenidate, Pipradol

It is characterized by strong psychic dependence, marked tolerance and a questionable kind of physical dependence. The most damaging form physically results from intravenous injection, which produces great elation, an orgiastic sensation termed a 'rush", a feeling of great mental and physical efficiency, insomnia, nervousness and eventually a reversible paranoid psychosis. Intravenous injection is associated with sudden death and many infectious complications. Withdrawal of amphetamines is followed by sleep with increased rapid eye movement (REM) encephalograms, hunger, apathy and psychic depression. These symptoms have not yet been shown to be due to a specific disturbance in brain function and may be due only to lack of sleep and food. Amphetamines presumably act by displacing biogenic amines (norepinephrine) from storage sites within nerve cells.

Amphetamine abuse treatment in the extremely agitated, paranoid patient often requires administration of haloperidol and lorazepam or droperidol to the physically restrained patient. When patients are not extremely agitated benzodiazepines or haloperidol may be administered orally. Detoxification usually takes several days and the patient must be monitored closely.

Long term treatment approaches include intensive counseling, group sessions and desensitization. This is to help to combat craving, the most difficult withdrawal syndrome, for the drug. However the theme of therapy here is that recovery is often a lifetime process¹⁷.

With Psychic Dependence Only Cocaine, Hallucinogens of the LSD type (LSD 25 and congeners), Psilocybin, Mescaline, dimethyltryptamine; Volatile solvents ("Glue"), Cannabis (Marihuana, Hashish, Tetrahydrocannabinols; Tobacco, Coffee and tea.

i. Cocaine Type: It is characterized by very strong psychic dependence, no tolerance and no physical dependence. The clinical features are very similar to those of the amphetamines and like amphetamine, cocaine may act by increasing the level of free catecholamines in the central nervous system. Cocaine intoxication affects mood, cognition, drive states and alertness or awareness. Psychological symptoms include euphoria, perception of increased mental and physical abilities, increased self confidence, talkativeness, increased concentration, heightened alertness, increased energy, general stimulation, enhar ced libido, prolonged erection and heightened orgasm. Also reported are decreased appetite, decreased shortterm memory and slight depersonalization. Physical symptoms include mild tachycardia, increased respiratory rate, dilated pupils, and pallor. If cocaine is not used again the initial symptoms are replaced by hunger, fatigue, mild depression and the desire to sleep but being unable to.

Use of pharmacologic treatment for cocaine withdrawal depends on the severity of the abuse and patient symptoms. Most often, simple cocaine withdrawal itself is not treated.

Interventions may include use of benzodiazepines for treating severe anxiety and agitation as well as insomnia and use of dopamine agonist for craving. Also. psychological treatments are sometimes employed.

ii. Hallucinogens (LSD) Type: The hallucinogens (psychotomimetics, psychodysleptics, psychedelics) cause dose related sympathomimetic stimulation (dilated pupils, increased sweating,

fever, goose flesh) and sensory perceptual distortion ranging from greater awareness of sensory stimuli to hallucination. Hallucinogenic drugs include Lysergic Acid Diethylamide (LSD). Dependence of this type is characterized by varying psychic dependence, marked tolerance (probably but not certainly due to tissue tolerance) and no physical dependence. Drugs frequently are used in hope of having a transcendental, mystic experience. Dangers include temporary psychoses with suicide occasionally occurring and precipitation of a chronic psychosis.

Drugs are usually taken orally and not continuously because of the development of tolerance. The psychic effects seem to be best explained by impairment of the central nervous system mechanisms that enable the person to suppress unimportant sensory stimuli. The individual is then flooded with a number of sensations that he can no longer ignore. Treatment or management of this effect involves two distinct approaches. The initial approach is called talking down.or reality therapy. This process tends to reassure the person that she is in a safe physical environment and that the effect of the drug will subside in a few hours. If this does not work, the second approach used is the drug therapy approach in which drugs like oral or intravenous benzodiazepines are used for sedation to allow the patient sleep through the period of the 'bad trip'.

iii. Cannabis Type: This is characterized by low to high psychic dependence, some degree of tolerance to both physiologic and psychological effects and no physical dependence. Materials used range from cannabis leaf (marihuana) to the mechanically more concentrated form of ganja and charkas. The most active material in cannabis is the 1-?9trans tetrahydro-cannabinol (-THC) and the intensity of effects are related to the concentration of ?9 THC in the material used, which varies markedly from 0.1 to 10 percent by

weight. The drugs are nearly always smoked. Cannabis and ?9 THC cause increased pulse rate, elation, euphoria, increased sensory awareness (in sufficient dose increasing to hallucinations) sedation and sleep.

The mechanism underlying these actions are varied and complex and dangers include transient psychoses. Adverse effects of cannabis are best managed by reality therapy as well as avoidance of stimulant drugs such as coffee, tea, cola, cocaine, amphetamines or stressful stimuli. The dysphoria and anxiety generally resolve within a few hours of beginning such an approach. Oral benzodiazepines may need to be employed for severe reaction though this is rarely needed.

- iv. Tobacco, Coffee and Tea: Though these are drugs of dependence they do not cause significant behavioural toxicity and are generally accepted in most cultures.
- Volatile (Inhalants) Type: Inhalants are popular among children and adolescents (they are one of the first conscious altering substances tried by children) because of their low cost, ease of availability, convenient packaging and low threat of legal intervention. Due to their high lipophilicity and route of administration, these substances produces a more rapid onset of effect than alcohol, making them easier to abuse while in school. In addition, they produce a euphoria that is qualitatively distinct from alcohol and marijuana. Some describe it as "floaty high"18.

Since the 1950's, a variety of products have been abused by inhalation, including model airplane glue, antiperspirant, shoe polish, vegetable non-stick spray, acrylic spray paint, typewriter correction fluid and refill canister for pocket lighters.

A variety of techniques are used to abuse volatile solvents. In some cases, the user soaks a rag, handkerchief or piece of clothing with the product to be abused and inhales from the soaked cloth. This is called 'huffing'. In other instances the product is sprayed or poured into a plastic bag or rubber glove and then inhaled from the closure. This is referred to as 'bagging'. If the product is a liquid such as gasoline or typewriter correction fluid, it may be abused by inhaling directly from the container, a technique called "sniffing". There are reports of spraying the inside of a salad bowl or heating the solvent over a stove in order to enhance the "high", presumably by increasing the concentration of solvent12

Occasionally liquid solvents such as lighter fluid and fingernail polish remover are mixed into carbonated beverages and are drank or injected intravenously19.

Inhalant abuse appears to be increasing, particularly among adolescents and they often introduce it to each other in group settings.

As the child grows older he either abandons this substance group or he moves on to other drugs. About 10% of those who experiment with inhalants become habitual users. Inhalant abuse results in a significant number of adolescent fatalities each year. Volatile solvents produce clinical manifestations resembling ethanol intoxication. Patients develop euphoria, slurred speech, ataxia, diplopia, nystagmus, flushing, blurred vision and varying degrees of central nervous system depression. Unlike ethanol intoxication, however solvents often cause vivid hallucinations (visual) and disorientation to place and time. In addition the symptoms usually subside more quickly than with ethanol (usually within 30 minutes)' headaches are less frequent than with ethanol20.

The greatest immediate danger associated with volatile solvent abuse is sudden and unexpected death due to direct toxicity of the solvent. This phenomenon has been called "sudden sniffing death syndrome" in medical literature21.

The first priority for treating acute volatile solvent intoxication is to stabilize the patients' vital signs. Mechanical ventilation, supplemental oxygen, fluid therapy and positioning are other measures usually employed.

REFERENCES

- 1. WHO Expert Committee on Addiction-Producing Drugs (1957). Seventh Report WHO Technical Report Series, 116,9
- 2. WHO Expert Committee on Dependence (1969). Sixteenth Report WHO Technical Report Series, 407,6.
- WHO Expert Committee on Drug Dependence (1973). Ninteenth Report WHO Technical Report Series, 516,8
- 4. WHO Expert Committee on Addiction-Producing Drug (1964). Thirteenth Report WHO Technical Report Series, 273,9
- 5. Eddy, N. B., Halbach, H., Isbell, H., Seevers, M.H. (1965). Drug Dependence: Its Significance and Characteristics. Bull. WHO, 32, 721
- 6. DHHS Pub. 1984 Alcohol and Health: Fifth Special Report to the US Congress, Washington DC: US Government Printing Office, 1984; DHHS Pub. No. (AMD) 90:1291
- 7. Ball, J.C. 1981. Cited in Study Stresses Link between Heroin dependence and incidence of crime. New York Times. Mar 22, 1981:22
- 8. Fell, J.C., Nash, C.E. (1989). The Nature of Alcohol Problem in US Fatal Crashes. Health Educ Q. 1989; 16:335
- 9. Rutledge, R., Messich, W.J. (1992). The association of trauma death and alcohol use in a rural state. J. Trauma, 1992; 33:737
- 10. Turrisi, R., Jaccard, J. (1992). Cognitive and attitudinal factors in the analysis of alternatives to drunk driving. J. Stud Alc, 1992;53:401
- 11. Strasburger, V.C. (1989). Prevention of adolescent drug abuse: why "Just say No" wont work. J. Pediatr. 1989;

114.676

- 12. Baldwin, J.N., Benson, B. (1995) Depressant and Inhalant Abuse. In: Koda-Kimble, M., Young, L.Y. eds. Applied Therapeutics: the Clinic Use of Drugs, 6th edition, p 83-11, Applied Therapeutics Inc, Vancouver, WA
- 13. Baldwin., J.N., Cook, M.D. (1995) Issues: Psychoactive Substance Use Disoders. In: Koda-Kimble, M., Young, L.Y. eds. Applied Therapeutics: The Clinical Use of Drugs, 6th edition, pp 81-1 81-16, Applied Therapeutics Inc, Vancouver, WA
- 14. Eoff J.C III, Bates R. G. In: Herfindal, E.T eds Drug Gourley, D.R Textbook of treatapentes and Disease Management, 6th edition, pg 1203 1226, applied Therapeutics inc, Vancouvrer, WA
- 15. Isbell, H (1971) In: Beeson, P.B. and McDermotts W., eds. Cecil-Loeb Textbook of Medicine. 13th edition, pp 131-146.
- 16. Jaffe, J.H., Sharpless, S.K. (1968) In: Wikler, A. ed. The Addictive States. Vol XLVI, Research Pub. of Association for Research in Nervous and Mental Diseases., pp 226-246, Williams and Wilkins, New York. Pharmacological Denervation Hypersensitivity in the CNS; a theory of physical dependence)
- 17. Inaba, D.S. Cohen, W.E. (1993). Uppers, Downers and Allarounders. 2nd edition. Ashland, OR: CNS Publications Inc; 1993:
- 18. McHugh, M.J. (1987). The abuse of volatile substances. Pediatr Clin North Am. 1987; 34:333
- 19. Barnes, 1979. solvent Abuse: a Review. Int J Addict. 1979; 14:1
- 20. Ellenhorn, M.B. Barceloux, O.G. (1988). Medical Texicology Diagnosis and Treatment of Human Poisonings. New York: Elsevier; 1988:840
- 21. Ramsey, J. (1989). An introduction to the practice, prevalence and chemical toxicology of volatile substance abuse. Hum Toxicol. 1989;8:261