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**Medicine**

**IS ADDICTION A BRAIN DISORDER?**

**KEY WORDS:**

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**ABSTRACT**

World Health Organisation defines Drug Abuse as the harmful or hazardous use of psychoactive substances, including alcohol and illicit drugs. **Enough is enough. Let us try to stop the drug abuse and addiction by improving the mental health conditions. Tempting situations and impulsive decisions will ruin the personality. Drug addiction is a complex but treatable brain disease.** Listening to the children and youth is the first step to help them to grow healthy and safe. **Clinical depression can be a killer. Researchers say more than 18,000 people who take their lives each year in the United States suffer from severe depression.** **When a loved one dies, a marriage ends, a job promotion doesn't come through, or a tear-jerker movie wrenches at your heartstrings. Suffering from clinical depression- a medical disorder (just like heart disease, diabetes or high blood pressure) that can affect both your behavior and physical health. Left untreated, depression can wreak havoc on your life. In fact, only heart disease results in more days spent confined to bed, and only arthritis is blamed for more chronic pain. Women who suffer from depression twice as often as men are most likely to try snacking, shopping and having a heart-to-heart talk with a friend. Men, on the other hand, more frequently seek distracting, pleasurable activities-like sex- to zap depression. And males are far more likely than women to turn to potentially dangerous behaviors to alter their moods, including abusing drugs and alcohol. The problem is, recreational drugs and alcohol not only don't work, but researchers have concluded they can actually cause- as well as worsen- depression. (1)** Drug abuse is defined as the manipulative drug-seeking behavior or the compulsive use of drugs for non-medical purposes, despite harmful side-effects. Some people suffer from emotional problems like anxiety, tension, fear, loneliness, etc., leading to neuroses. The drugs which primarily affect mental processes to improve moods are called psychoactive drugs and, hence, are classified under CNS stimulants. Neurosis and psychosis are mental illnesses which are associated with psychological disorders involving the brain. A prolonged CNS stimulation always results in depression.

**INTRODUCTION**

Drug addiction is a complex but treatable brain disease. It is characterized by compulsive drug craving, seeking, and use that persist even in the face of severe adverse consequences. For many people, drug addiction becomes chronic, with relapses possible even after long periods of abstinence. In fact, relapse to drug abuse occurs at rates similar to those for other well-characterized, chronic medical illnesses such as diabetes, hypertension, and asthma. As a chronic, recurring illness, addiction may require repeated treatments to increase the interval

The metabolism of opioids closely relates to their chemical structure. Opioids are subject to O-dealkylation, N-dealkylation, ketoreduction, or deacetylation leading to phase-I metabolites. By glucuronidation or sulfation, phase-II metabolites are formed. Some metabolites of opioids have an activity themselves and contribute to the effects of the parent compound. This can go as far as that the main clinical activity is exerted through active metabolites while the parent compounds are the only weak agonist at m-opioid receptors, as in the case of codeine and tilidine. The clinical effects of tramadol also involve an important contribution of its active metabolite. With morphine, the active metabolite morphine-6-glucuronide exerts important clinical opioid effects when it accumulates in the plasma of patients with renal failure.(3)

between relapses and diminish their intensity, until abstinence is achieved. Through treatment tailored to individual needs, people with drug addiction can recover and lead productive lives. (2)

Use of opioids can present a challenge because adequate pain control is necessary while balancing the risk of overdose due to altered drug clearance and accumulation of the opioid parent drug and/or metabolites in the presence of renal dysfunction. (4)

Recent scientific advances have led to a greater understanding of the neurobiological processes that underlie drug abuse and addiction. These suggest that multiple neurotransmitter systems may play a key role in the development and expression of drug dependence. These advances in our knowledge promise not only to help us identify the underlying cause of drug abuse and dependence but also to aid the development of effective treatment strategies. The chemicals that humans abuse are structurally diverse and produce different behavioral effects in the user. Nevertheless, all share the common feature that they can modulate the brain reward system that is fundamental to initiating and maintaining behaviors important for survival (e.g., eating, sexual activity). (5)

Heroin reinforcement resulted in impaired energy production via different pathways, including glycolysis, the TCA cycle, keto body metabolism, etc. A disturbance in the substrate supply in the circulatory system may partly explain heroin toxicity in the central nervous system. These findings provide new insight into the mechanism underlying the relapse to heroin use. (6)

After i.v. heroin injection, 6-MAM was the predominant opioid present shortly after injection and during the first 30 min, not only in the blood but also in rat brain ECF. 6-MAM might, therefore, mediate most of the effects observed shortly after heroin intake, and this finding questions the general assumption that morphine is the main and most important metabolite of heroin. (7)

Toxicity resulting from excessive intra-synaptic serotonin historically referred to as serotonin syndrome is now understood to be an intra-synaptic serotonin concentration-related phenomenon. Recent research more clearly delineates serotonin toxicity as a discrete toxidrome characterized by clonus, hyperreflexia, hyperthermia, and agitation. Serotonergic side-effects occur with serotonergic drugs, and overdoses of serotonin reuptake inhibitors (SRIs) frequently produce marked serotonergic side-effects, and in 15% of cases, moderate serotonergic toxicity. (8)

Exposure of cortical neurons to street heroin-induced a slight decrease in metabolic viability, without loss of neuronal integrity. Early activation of caspases involved in the mitochondrial apoptotic pathway. Drug addiction seriously affects public health worldwide. Amongst the most abused illicit drugs, opioids, such as heroin cause some of the most severe effects. (9)

Cocaine and heroin are frequently co-abused by humans, in a combination known as the speedball. Recently, chemical interactions between heroin (Her) or its metabolite morphine (Mor) and cocaine (Coc) were described, resulting in the formation of strong adducts. (10)

Cocaine is a psychostimulant drug with sympathomimetic properties that is widely abused. In the central nervous system, cocaine interacts with monoaminergic systems, which mediate many of the drug's effects. However, the interaction with the dopaminergic system is the main cause of cocaine's addictive effects. Cocaine shares chemical similarities with dopamine and binds to the dopamine transporter at the plasma membrane of dopaminergic terminals, blocking dopamine re-uptake, resulting in increased synaptic dopamine. Excess dopamine levels may induce oxidative stress through dopamine auto-oxidation, generating reactive oxygen species. Cocaine has also been shown to impair mitochondrial function in several models. (11)

Methamphetamine intoxication causes long-lasting damage to dopamine nerve endings in the striatum. The mechanisms underlying this neurotoxicity are not known but oxidative stress has been implicated. Microglia are the major antigen-presenting cells in the brain and when activated, they secrete an array of factors that cause neuronal damage. (12)

The rapidly escalating abuse of methamphetamine (METH) places a sense of urgency on understanding its effects on the human brain and its medical consequences. METH is a particularly problematic drug in that not only is it highly addictive but its administration to laboratory animals results in damage to dopamine (DA) terminals (13) Studies in humans have also documented a significant loss of DA transporters (DAT), which have been used as markers of DA terminals, in the brains of METH abusers (14)

The abuse of methamphetamine is a serious public health problem due to its ease of synthesis and because of the ability of high-dose methamphetamine administration to cause long-term damage to striatal dopamine (DA)-containing neurons. (15)

A patient using opioids can develop opioid-induced neurotoxicity secondary to dehydration, infection, or drug interactions. Opioids are indicated for dyspnea with advanced disease of any cause. • Opioid-induced neurotoxicity can be common in frail older adults and those with renal failure. Opioids with few or no active metabolites are generally better tolerated. Opioid-induced neurotoxicity is managed by rotating the opioid and by rehydration. Opioids should not be discontinued if they are needed for pain or dyspnea. (16)

Opioid-induced neurotoxicity is a multifactorial syndrome that causes a spectrum of symptoms, from mild confusion or drowsiness to hallucinations, delirium, and seizures. (17)

Heroin is rapidly metabolized in humans to 6-acetylmorphine (6-AM), which is further metabolized to morphine and morphine conjugates. Urinary 6-AM is the best diagnostic indicator of heroin abuse. This metabolite, however, is usually present in urine at less than 3% of the concentration of urinary total morphine (MOR). (18)

Chronic marijuana intake was known to induce morphological changes to the brain impairing memory and learning ability. However, several studies demonstrated the protective effect of marijuana post-brain traumas. (19)

**HISTORY**

The term "narcotic" is believed to have been coined by the Greek physician Galen to refer to agents that numb or deaden, causing loss of feeling or paralysis. It is based on the Greek word *ναρκωσις* (narcosis), the term used by Hippocrates for the process of numbing or the numbed state. Galen listed mandrake root, (eclata) (20) seeds, and poppy juice (opium) as the chief examples. (21,22) It originally referred to any substance that relieved pain, dulled the senses, or induced sleep. (23) Now, the term is used in a number of ways. Some people define narcotics as substances that bind to opioid receptors (cellular membrane proteins activated by substances like heroin or morphine) while others refer to any illicit substance as a narcotic. From a U.S. legal perspective, narcotics refer to opium, opium derivatives, and their semi-synthetic substitutes, (24) though in U.S. law, due to its numbing properties, cocaine is also considered a narcotic.

The sense of "any illegal drug" first recorded 1926, Amer. Eng. The adj. is first attested c.1600. (25) There are many different types of narcotics. The two most common forms of narcotic drugs are morphine and codeine. Both are synthesized from opium for medicinal use. The most commonly used drug for recreational purposes created from opium is heroin. Synthesized drugs created with an opium base for use in pain management are fentanyl, oxycodone, tramadol, Demerol, hydrocodone, methadone, and hydromorphone. New forms of pain medication are being created regularly. The newest drug to come out in 2014 is zohydro, an intense dosage of hydrocodone medication, the strongest yet created for pain management. (26)

In 1932, the American Psychiatric Association created a definition that used legality, social acceptability, and cultural familiarity as qualifying factors: as a general rule, we reserve the term drug abuse to apply to the illegal, nonmedical use of a limited number of substances, most of the drugs, which have properties of altering

the mental state in ways that are considered by social norms and defined by statute to be inappropriate, undesirable, harmful, threatening, or, at minimum, culture-alien. (27)

In 1966, the American Medical Association's Committee on Alcoholism and Addiction defined abuse of stimulants (amphetamines, primarily) in terms of 'medical supervision 'use' refers to the proper place of stimulants in medical practice; 'misuse' applies to the physician's role in initiating a potentially dangerous course of therapy; and 'abuse' refers to the self-administration of these drugs without medical supervision and particularly in large doses that may lead to psychological dependency, tolerance and abnormal behavior.

In 1973, the National Commission on Marijuana and Drug Abuse stated drug abuse may refer to any type of drug or chemical without regard to its pharmacologic actions. It is an eclectic concept having only one uniform connotation: societal disapproval. ... The Commission believes that the term drug abuse must be deleted from official pronouncements and public policy dialogue. The term has no functional utility and has become no more than an arbitrary codeword for that drug use which is presently considered wrong (28)

The first edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (published in 1952) grouped alcohol and drug abuse under Sociopathic Personality Disturbances, which were thought to be symptoms of deeper psychological disorders or moral weakness. (29)The third edition, published in 1980, was the first to recognize substance abuse (including drug abuse) and substance dependence as conditions separate from substance abuse alone, bringing in social and cultural factors. The definition of dependence emphasised tolerance to drugs, and withdrawal from them as key components to diagnosis, whereas abuse was defined as "problematic use with social or occupational impairment" but without withdrawal or tolerance.

NIDA's roots can be traced back to 1935, when a research facility (named the Addiction Research Center in 1948) was established in Lexington, Kentucky as part of a USPHS hospital. The Drug Abuse Warning Network (DAWN) and National Household Survey on Drug Abuse (NHSDA) were created in 1972. In 1974 NIDA was established as part of the Alcohol, Drug Abuse, and Mental Health Administration and given authority over the DAWN and NHSDA programs. The Monitoring the Future Survey, which surveys high school seniors, was initiated in 1975; in 1991, it was expanded to include 8th and 10th graders.(30)

In October 1992, NIDA became part of the National Institutes of Health, United States Department of Health and Human Services. At that time, responsibility for the DAWN and NHSDA programs were transferred to the Substance Abuse and Mental Health Services Administration (SAMHSA). NIDA is organized into divisions and offices, each of which is involved with programs of drug abuse research. As of 2012, Nora Volkow, MD, is the director of NIDA (31)

**SIGNIFICANT GAP IN RESEARCH**

The increasing legalization of marijuana for medical and recreational use renewed the interest in its potential effect on health and therapeutic applications. Marijuana, THC, and other cannabinoid agonists all have a common problem of a narrow therapeutic window between clinical benefits and the unwanted psychic side-effects.(32)

Cocaine addiction may be described as a neurological disorder, because cocaine abusers present several neurological impairments. The interaction with the dopaminergic system is the main cause of cocaine's addictive effects, leading to excess synaptic dopamine levels that may induce oxidative stress through dopamine auto-oxidation, generating reactive oxygen species. Cocaine also affects glutamate levels and the expression of glutamate receptors, which may mediate excitotoxic cell damage and long-term neuroadaptive effects. Interaction with these neurotransmission systems may underlie cocaine neurotoxicity.

Cocaine abuse shares some common aspects with neurodegenerative disorders, which also involves a dysfunction in the dopamine system. (33)

Some metabolites of opioids have an activity themselves and contribute to the effects of the parent compound. This can go so far that the main clinical activity is exerted through active metabolites, whereas the parent compounds are only weak agonists at  $\mu$ -opioid receptors. The role of the metabolite of morphine with agonist opioid activity, morphine-6-glucuronide, is most pronounced in patients with renal failure, in whom the metabolite accumulates.(34)

**WHERE THE RESEARCH GO NEXT?**

More data are needed on the adverse effects of cannabinoids in animals, especially on controversial issues such as their effects on the brain and immune system. However, one should be very careful when interpreting the results and apply them to humans. The best approach to human toxicology rests on the study of human data. (35)

Opioids should be used cautiously in this patient population due to possible accumulation of the parent drug and/or metabolites. Usual or adjusted doses may be appropriate for certain opioids (e.g. morphine, hydromorphone, hydrocodone). Oxycodone should not be used in dialysis patients, and others should be avoided at all times (e.g. codeine, meperidine, and propoxyphene). Methadone and fentanyl are generally not first-line therapies, although they can be carefully used in patients with renal dysfunction or on dialysis, and methadone is not advised in severe liver failure. For most patients with renal or hepatic dysfunction, either morphine or hydromorphone could be a good starting therapy if an opioid agent is used.(36) Historically, opioid analgesics have been called "narcotic analgesics". Narcotic analgesic literally means that these agents cause sleep or loss of consciousness, in addition to their pain-relieving effect. The juice (Opium in Greek) or gum from the unripe seed-pods of the poppy, *Papaver Somniferum*, is among the oldest medications recorded. The pharmacist, Surturnev, first isolated an alkaloid from opium in the year 1803. Codeine, thebaine, and papaverine and other medically important alkaloids that were later isolated from opium gum. Opioid analgesics are used for moderate to severe pain that cannot be relieved with other agents. Increasing tolerance and dependency are normal consequences of opioid therapy. This should not be confused with addiction. While addiction is a psychological dependency, generally referred to as 'drug abuse', the opioid drugs may be a physiological necessity. Patients with chronic, severe pain must not consider themselves addicts just because they are being treated with opioids. (Patients and their family members must be educated regarding the difference between tolerance, physical dependence, and addiction).

Some people suffer from emotional problems like anxiety, tension, fear, loneliness, etc., leading to neuroses. The drugs which primarily affect mental processes to improve moods are called psychoactive drugs and, hence, are classified under CNS stimulants. Neurosis and psychosis are mental illnesses which are associated with psychological disorders involving the brain. A prolonged CNS stimulation always results in depression.

**MAJOR ADVANCES AND DISCOVERIES**

Analeptics are a class of CNS stimulants which excite the medullary centers when they are in a depressed state and improve the metabolic activity of the brain. Analeptics are used for certain respiratory diseases, post-anesthetic respiratory problems, circulatory failure causing low blood pressure, and to counter an overdose of barbiturates, narcotics, analgesics, and general anesthetics. Caffeine, a xanthine derivative, stimulates the cardiac muscles, enhances diuresis, bronchi, and coronary arteries. Anxiolytics include tranquilizers, relaxants, and anti neurotic agents, and are mood stabilizers which act on the brain. They include i) chlordiazepoxide (Librium), ii) diazepam (Valium), and iii) prazepam (veteran; central).

Psychotomimetic drugs are used for mental illness. The effects of these drugs include disturbed perception, hallucinations, the feeling of weightlessness, vision of patterns of color and memory.

These drugs are habit-forming and used repeatedly. These drugs only are used under a doctor's supervision.

Cocaine is unique among local anesthetics in having the ability to block the sodium-chloride (Na<sup>+</sup>-Cl<sup>-</sup>)-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in individuals taking cocaine. In addition, the duration of epinephrine and norepinephrine is increased. Like amphetamines, it can increase blood pressure by α1-antagonist actions and β-stimulatory effects

Opioids, because of their analgesic property, opioids are commonly combined with other anesthetics. The choice of opioid is based primarily on the duration of action needed. The most commonly used opioids are fentanyl and its congeners, sufentanil and remifentanil because they induce analgesia more rapidly than morphine. They may be administered intravenously, epidurally, or intrathecally (into the cerebrospinal fluid). Opioids are not good amnesics, and they can all cause hypotension, respiratory depression, and muscle rigidity, as well as, postanaesthetic nausea and vomiting. Opioid effects can be antagonized by naloxone.

Morphine and other opioids exert their major effects by interacting stereospecifically with opioid receptors on the membranes of certain cells in the CNS and other anatomic structures, such as the gastrointestinal (GI) tract and the urinary bladder. Morphine also acts at k-receptors in lamina I and II of the dorsal horn of the spinal cord. It decreases the release of substance P, which modulates pain perception in the spinal cord. Morphine also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli. Morphine and other opioids cause analgesia (relief of pain without the loss of consciousness) and relieve pain both by raising the pain threshold at the spinal cord level and, more importantly, by altering the brain's perception of pain. Morphine produces a powerful sense of contentment and well-being. Morphine causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide.(37)

**RECENT RESEARCH**

Recent scientific advances have led to a greater understanding of the neurobiological processes that underlie drug abuse and addiction. These suggest that multiple neurotransmitter systems may play a key role in the development and expression of drug dependence. These advances in our knowledge promise not only to help us identify the underlying cause of drug abuse and dependence but also to aid the development of effective treatment strategies. The chemicals that humans abuse are structurally diverse and produce different behavioral effects in the user. Nevertheless, all share the common feature that they can modulate the brain reward system that is fundamental to initiating and maintaining behaviors important for survival (e.g., eating, sexual activity).

**CURRENT DEBATE**

Drug abuse, in addition to being an area of scientific research, is also a major subject of public policy debate. Accordingly, elected officials have sometimes attempted to shape the debate by introducing legislation in reference to NIDA research. In 2004, Congressman Mark Souder introduced the Safe and Effective Drug Act, calling for a "meta-analysis of existing medical marijuana data." It was criticized for being limited to smoked cannabis (rather than vaporizers and other methods of ingestion) and not requiring any new research. (38) In some cases, NIDA has held its ground when its more moderate stances were questioned by legislators favoring a hard-line approach. On April 27, 2004, Souder sent NIH Director Elias A. Zerhouni a letter criticizing needle exchange programs for causing increases in infection rates. (39)

**CONCLUSION**

In 2017, two countries hit a milestone. In Mexico, there were

29,168 murders, the highest number on record. Across the border in the United States, nearly 70,000 people died from drug overdoses, over three times as many as were dying annually less than two decades ago. More Americans now die every year from overdoses than died in the entire Vietnam, Afghanistan, and Iraq wars (40) Listening the children and youth is the first step to help them to grow healthy and safe. The theme seeks to increase support for prevention of drug use that is based on science and thus an effective investment in the well-being of children and youth and their families and their communities.(41)

World Health Organisation defines Drug Abuse as the harmful or hazardous use of psychoactive substances, including alcohol and illicit drugs. Addiction is an advanced stage of substance abuse where the addict develops a compulsion to take the drug, persists in its use despite harmful consequences and exhibits a determination to obtain the drug by almost any means. Psychoactive substance use can lead to dependence syndrome - a cluster of behavioural, cognitive, and physiological phenomena, which are marked by social withdrawal. Symptoms of addiction include loss of appetite and weight, loss of interest in day to day work, sweating, reddening of eyes, nausea or vomiting and body pain, drowsiness or sleeplessness and passivity, acute anxiety, depression, mood swings among others.(42)

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