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Hallucinogens, Entactogens, and Dissociative Drugs: A Review of Amphetamine Derivatives, Phencyclidine, and Lysergic Acid Diethylamide

Introduction

Substance abuse occurs in as much as 50 to 75% of individuals with a primary psychiatric diagnosis. Most epidemiological studies have found cannabis and cocaine to be among the most commonly abused substances. Several theories have been proposed to explain the high rates of substance use in mentally ill individuals. These individuals, in particular patients with schizophrenia, receive dopamine-blocking agents (antipsychotics) to treat their condition. By blocking dopamingeric neurotransmission within the mesolimbic dopamine system, these medications disrupt the brain's reward system.

Of course many other factors interplay to account for the high incidence of substance abuse among this population. Some researchers believe that the high incidence of smoking among schizophrenic patients is the result of individuals attempting to alleviate medication-induced effects such as akathisia. Similarly, mentally ill patients use illicit substances perhaps to counteract side-effects of medications. Many substances of abuse have transient tranquilizing effects and it may be that these drugs are used in an attempt to self-medicate symptoms such as dysphoria, anxiety, and depression. Excessive illicit drug use often leads to a state of intoxication. This state of intoxication provides an escape from the emotional distress that sometimes accompanies mental illness.

Though less prevalent, abuse of other illicit drugs, in particular entactogens, dissociative drugs, and hallucinogens, is no less clinically important. This newsletter will discuss these substances of abuse in more detail.

- Entactogens are drugs that generate a sense of "the touch within" or an increased sense of awareness of oneself. These drugs usually do not produce major changes in perception or thought.
- Dissociative drugs are those that cause dissociation, a state in which certain mental functions are "separated" from others. These drugs commonly cause dissociation of sensory input and emotion from consciousness and memory.
- Hallucinogens are substances that can simulate realistic sensory experiences of things that do not exist outside the body.

Amphetamine Derivatives

Methamphetamine ("speed", "ice")

Methamphetamine is an addictive CNS stimulant. Similar to cocaine, amphetamines can increase alertness, decrease appetite, and decrease fatigue. Users who smoke or inject methamphetamine can experience a brief, but intense sensation (a "rush") that is described as being extremely pleasurable. In contrast, oral ingestion or snorting produces a longer lasting, but blunted effect (a "high").

These effects are believed to result from activation of the mesolimbic and mesocortical dopaminergic pathways that are involved in the brain's "reward system". In addition to the dopaminergic effects, methamphetamine also blocks the reuptake of norepinephrine and at high doses, serotonin.

Unlike cocaine, which is quickly removed and almost completely metabolized in the body, methamphetamine has a much longer duration of action and a larger percentage remains unchanged in

the body. This results in methamphetamine being in the brain longer, with prolonged stimulant effects lasting up to 6 to 8 hours. Amphetamines also tend to be less addictive than cocaine. From the initial rush or high there follows a typical state of agitation or anxiety. Heavy users can show progressive social and occupational deterioration. Long-term effects include drug dependence, cardiovascular dysregulation, and various psychiatric symptoms, including hallucinations.

3,4-methylenedioxymethamphetamine (MDMA, "ecstasy")

MDMA is a synthetic analogue of amphetamine. Like other amphetamine derivatives, this compound stimulates the effects of the sympathetic nervous system. In addition, MDMA has entactogenic and empathogenic effects. Users of this drug experience a state of euphoria, increased self-awareness, and a feeling of emotional closeness with people around them. Other users may experience psychedelic effects in which there is sensory enhancement or distortion as well as illusions sometimes superimposed with hallucinations. Recreational use of MDMA began in the early to mid 1980s and its use in this regard has since gained prominence particularly among college students and young adults.

Pharmacologically, MDMA is a selective serotonergic neurotoxin. Serotonin is involved in the regulation of mood, impulsivity, cognition, and sleep. In animal studies, MDMA stimulates serotonin release into the synaptic cleft while inhibiting serotonergic reuptake. Entactogens are also thought to have antagonistic effects at the alpha-$_2$ heteroreceptor, further producing serotonin release. This initial surge in serotonergic tone is followed by a gradual degradation of the serotonergic neurons. The net result from long-term use is a decrease in serotonin activity in the CNS. MDMA also affects the dopaminergic pathway, but to a lesser extent.

MDMA can be fatal when used in improper situations or to excess. Recreational use of MDMA typically involves oral ingestion of 75-150mg. The onset of effects occurs in 30 to 45 minutes, with peak effects occurring in about 90 minutes after ingestion. The duration of effect is approximately 4 to 6 hours, but a noticeable decrease in effect occurs within 2 to 3 hours. Some users opt to take a further "booster" dose several hours later, usually inducing more marked adverse effects, but not necessarily an elevation in mood. Regular use of MDMA has been associated with tolerance to desirable effects and an increase in adverse effects. Its use over a prolonged period of time has been associated with various detrimental effects such as depression.

As MDMA stimulates the sympathetic nervous system, potential toxic effects include cardiac arrhythmia, hypothermia, and dehydration leading to fluid/electrolyte depletion. Common physical symptoms include fatigue, jaw clenching, and muscle tension. Muscle tissue breakdown can result in kidney and/or cardiovascular system failure. Acute psychiatric symptoms include dysphoria, confusion, and anxiety. Currently, most MDMA use occurs during night-long dances or parties known as raves. Use of MDMA in a hot, crowded environment with poor ventilation coupled with excessive physical exertion and dehydration add to the health risks. The illicit nature of its production gives rise to impurities and toxic by-products creating a further health risk.

Phencyclidine
(PCP, "angel dust", "crystal")

As a dissociative drug, PCP distorts perceptions. This drug's effects are trance-like, with users experiencing a feeling of being "out of body" and detachment from their environment or self. PCP is commonly smoked, but can be snorted, or even eaten. PCP is sometimes applied to a leafy material such as marijuana, or consumed with alcoholic beverages. Abuse of this drug peaked in the late 1970s, but markedly declined throughout the 1980s and 1990s. The behavioral effects from PCP are largely due to disruption of the NMDA (N-methyl-D-aspartate) excitatory receptor complexes, which are sites for glutamate. Glutamate receptors are involved in the perception of pain, cognition, and emotion. PCP also blocks the reuptake of serotonin, dopamine, and norepinephrine.

Typically, PCP's effects are felt within minutes after administration and last for several hours. However, the effects are unpredictable. One dose may produce feelings of detachment from reality while another may give rise to hallucinations, panic and fear. Feelings of invulnerability, exaggerated strength,

disorientation, and violence have also been reported among PCP users. Doses of 5mg or less produce physiological effects that include shallow, rapid breathing, increased blood pressure, and elevated temperature. Doses of 10mg or more cause dangerous changes in cardiovascular and respiratory function, often accompanied by nausea, blurred vision, dizziness, and decreased awareness of pain.

People who use PCP for long periods report memory loss, difficulties with speech and thinking, depression, as well as weight loss.

In addition, repeated use often results in addiction. Users often complain of dysphoric effects long after chronic use has stopped. This effect is likely attributable to the fact that PCP is highly fat-soluble compound that is stored in body fat for long periods.

Lysergic Acid Diethylamide
(LSD, "acid", "trip")

LSD can be classified as a hallucinogen and as such, has the potential to cause profound distortions in the perception of reality. Under the influence of hallucinogens, people see images, hear sounds, and feel sensations that seem real, but do not exist. In addition, sensory perception may be highly intensified.

Structurally related to serotonin, LSD binds to several serotonin receptors, with the $5HT_2$ site being of significant importance. While the precise mechanism by which LSD alters perceptions is still unclear, it may involve interactions with serotonin receptors within the cerebral cortex and locus ceruleus.

LSD is one of the most potent mood-altering drugs known. From an oral doses as small as 30mcg, the effects typically begin within 30 to 90 minutes and may last as long as 12 hours. Users refer to the desirable (hallucinogenic) experiences as "trips" and to the acute adverse experiences as "bad trips". Similar to PCP, this drug's effects are unpredictable which can be influenced by the amount ingested, the user's personality, mood, and surroundings. On some trips, users experience enjoyable, mentally stimulating sensations that can create a sense of heightened understanding. Bad trips, however, can lead to terrifying thoughts in which there are feelings of anxiety and despair. LSD use has been associated with hallucinogen persisting perception disorder (HPPD), more commonly referred to as "flashbacks".

Physiological effects include increased blood pressure, tachycardia, loss of appetite, tremors, muscular weakness, and ataxia. The drug's major effects, however, are on the emotions and senses. Emotions may fluctuate rapidly from fear to euphoria, with transitions so rapid that users may appear to experience several emotions simultaneously. Some users of LSD experience devastating psychological effects that persist after the trip has ended, producing a long-lasting psychotic-like state.

Treatment

Acutely intoxicated states as a result of any of these four illicit drugs warrant close monitoring of respiratory and cardiovascular function. Assessment of hematology, liver function, renal function, temperature, and electrolytes should be considered. Treatment for abusers usually consists of cognitive and behavioral interventions designed to help modify thinking, expectations, and coping skills. While there is no specific pharmacological treatment, conservative use of antidepressants, benzodiazepines, and antipsychotics can be considered in those needing symptomatic treatment.

Concluding Remarks

Illicit drug use in mentally ill individuals is associated with a variety of negative outcomes, including relapses, homelessness, violence, and higher use of services. In addition, manifestations of substance use and withdrawal can simulate psychiatric symptoms. Clearly, these dually diagnosed individuals represent a challenge to the treatment team.

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