

Psychostimulants and Epilepsy

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Summary: Purpose: The aim of this article is to review the literature on the effects of psychostimulants in epileptic subjects in order to reach a consensus statement regarding the use or abuse of these substances.

Methods: Psychostimulant substances have been considered the drugs that share the ability to produce excitation of the CNS leading to convulsions. The stimulation may be at cortical, brainstem, or spinal levels. In this article, the following cortical stimulants are analyzed and discussed: cocaine, amphetamine and related agents, caffeine, cannabinoids, and psychedelic drugs. This review is based on research done using pharmacological textbooks and Medline.

Results: The use of cocaine is associated with the occurrence of seizures. The reported frequency varies from 1% to 40% of addicted subjects, based on the typology of the considered

study. Amphetamines and related drugs rarely induce epileptic seizures at therapeutic doses, but seizures may occur after the first dosing. Caffeine at high doses may induce epileptic seizures because of its adenosine receptor-antagonizing properties. Marijuana, at variance with other psychostimulants, owing to its serotonin-mediated anticonvulsant action, could have a medical use for the treatment of epilepsy. Psychedelic compounds rarely induce epileptic seizures, but the most common clinical CNS complication after ingestion of ecstasy is the occurrence of seizures.

Conclusions: The use of psychostimulants, except for marijuana, can induce single or multiple seizures in healthy subjects. **Key Words:** Psychostimulants—Seizures—Cocaine—Amphetamine—Caffeine—Cannabinoids—Psychedelic drugs.

This group contains drugs that share the ability to produce dose-related excitation of the central nervous system (CNS), leading to convulsions. The stimulation may be at cortical, brainstem, or spinal levels. The cortical stimulants here analyzed are cocaine, amphetamines and related agents, caffeine, cannabinoids, and psychedelic drugs (1).

The most common complications of stimulant use that result in visits to emergency rooms and hospital admissions are referable to psychiatric, cardiopulmonary, and neurologic symptoms. Neurologic complications most commonly include seizures and stroke, but relative to the prevalence of stimulant abuse, the incidence of stroke and seizures is small (2).

EPIDEMIOLOGY

There are few studies of the prevalence of drug-induced convulsions. An evaluation of 3,155 patients with seizures during a 10-year period in a neurology clinic showed that 45 (1.7%) of these had drug-induced

seizures. The most common drugs causing seizures in this study were isoniazid, insulin, lidocaine, and psychotropic medications (3). A retrospective survey of seizures associated with poisoning and drug intoxication in the San Francisco Bay area over a 2-year period showed that the leading causes of seizures were cyclic antidepressants in 29%, psychostimulant drugs in 29%, antihistaminics in 14%, theophylline in 5%, and isoniazid in 5% (4).

A retrospective study of recreational drug-induced seizures seen at the San Francisco General Hospital identified 49 cases in 47 patients between 1975 and 1987. The recreational drugs implicated were cocaine (32 cases), amphetamine (11), heroin (seven), and phencyclidine (four). A combination of drugs was responsible in 11 cases. Seizures occurred independent of the route of administration and in both first-time and long-term abusers (5).

A study at Harlem Hospital Center, New York City, between 1981 and 1984, on the use of heroin, marijuana, and cocaine before the onset of a first seizure showed that heroin use is a risk factor and marijuana use a protective factor for new-onset seizures. Cocaine use was not shown to be a significant risk factor either for all first seizures or for subgroups of seizures (6).

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COCAINE

The risks of cocaine use, beyond the potential for addiction, involve cardiac arrhythmias, myocardial ischemia, myocarditis, aortic dissection, cerebral vasoconstriction, and seizures (7). With the recent cocaine epidemic, the seizures related to cocaine have increased. The reported frequency of cocaine-associated seizures varies from 1% to 8% in retrospective clinically based studies, but in an autopsy study, 36% of 36 fatalities related to cocaine had seizures before death (8). A study of 500 cocaine addicts showed that ~10% of subjects had a single seizure, and 3% had status epilepticus (9).

Seizures occur frequently in first-time cocaine users; one study reported 40% seizures among 44 first-time users (10). Single generalized motor seizures are most common, but multiple seizures and status epilepticus occur immediately or in <2 h after ingestion, coinciding with peak blood levels. By virtue of brain lesions resulting from cerebrovascular events associated with cocaine use, epilepsy may occur. However, the mechanism of the association between epilepsy and cocaine has not been established.

Drug abuse in men occurs about twice as frequently as in women. However, smoked cocaine use is particularly common in young women of childbearing age, who may use cocaine in this manner as commonly as do men. Pregnant cocaine users may experience premature labor and abruptio placentae. The consequences of prenatal cocaine exposure might include increased susceptibility to seizures (11). Cocaine frequently is used in combination with other drugs, which may increase the risk of seizure onset.

Mechanism of action

Cocaine augments the effects of catecholamine neurotransmitters by blocking reuptake by the dopamine transporter, which leads to increased dopaminergic stimulation at critical brain sites (12). However, cocaine also blocks both norepinephrine (NE) and serotonin (5-HT) reuptake, associated with the “kindling” phenomenon. In brain-imaging studies, it has been shown to be associated with altered brain metabolism, especially in the temporal lobes.

AMPHETAMINE AND RELATED DRUGS

This group comprises amphetamine, dextroamphetamine, methamphetamine, and methylphenidate. These sympathomimetic agents stimulate the central and peripheral nervous systems. Amphetamine and dextroamphetamine are used chiefly for their CNS effects. Dextroamphetamine has greater CNS action and less peripheral action, and is therefore generally preferred to amphetamine; it is used to treat obesity, narcolepsy, and

attention deficit–hyperactivity disorder. Epileptic seizures are relatively rare at therapeutic doses but may occur after the first dosing. The role of amphetamines in causing seizures appears to be less strong than that of cocaine (13).

Methylphenidate is the only drug of this group presently used as a therapeutic agent for attention deficit–hyperactivity disorder and is indicated for use in narcolepsy. Methylphenidate may inhibit the metabolism of coumarin anticoagulants and anticonvulsants (phenobarbital, diphenylhydantoin, primidone), and a reduction of dosage of these drugs may be required when given concomitantly with methylphenidate (14).

There is conflicting clinical evidence that methylphenidate may lower the convulsive threshold (15). Safe concomitant use of anticonvulsants (AEDs) and methylphenidate has not been established.

Mechanism of action

At variance with cocaine, the increased dopaminergic stimulation is obtained through an increase of presynaptic release. The epileptogenic effect of these substances occurs at high dosage and is mediated by the stimulation of *N*-methyl-D-aspartate (NMDA) receptors and the inhibition of γ -aminobutyric acid (GABA)_A receptors. Dextroamphetamine is 3 to 4 times more potent than the levo isomer (16).

CAFFEINE

Caffeine, a mild stimulant, is the most widely used psychoactive drug in the world. It is present in soft drinks, coffee, tea, cocoa, chocolate, and numerous prescription and over-the-counter drugs. High doses of caffeine in humans may cause nausea, trembling, nervousness, and seizures (17). Misuse of tablets can cause convulsions. Intravenous caffeine given before electroconvulsive therapy can prolong seizure duration but does not reduce the seizure threshold (18).

Mechanism of action

It has an intrinsic convulsant activity because of its adenosine receptor–antagonizing properties. Animal studies have shown changes in the activity of norepinephrine, dopamine, and serotonin. The drug also acts directly on the cerebral arterial musculature to cause vasoconstriction and a decrease in cerebral blood flow.

CANNABINOIDS

Marijuana is the most commonly used illegal drug. The smoke from burning cannabis contains many chemicals, and 61 different cannabinoids have been identified. One of these, *D*-9-tetrahydrocannabinol (*D*-9-THC), produces most of the characteristic pharmacologic effects of smoked marijuana.

A survey on the medical use of cannabis products in Germany showed that epilepsy (3.6%) was among the most frequently mentioned indications (19).

Mechanism of action

The principal psychoactive agent, D-9-THC, affects multiple neurotransmitter systems. It accelerates synthesis, neuronal uptake, and storage of norepinephrine and dopamine; inhibits serotonin uptake in the synaptic space; enhances the coupling of β -adrenergic receptors to adenylyl cyclase; reduces firing rate of acetylcholine neurons; and at low doses, reduces γ -aminobutyric acid (GABA) turnover, but increases it at high doses. Experimental data show that D-9-THC is associated with serotonin-mediated anticonvulsant action.

PSYCHEDELIC AGENTS

The most commonly used psychedelic drugs are lysergic acid diethylamide (LSD), MDMA (methylenedioxy-methamphetamine, "ecstasy"), and phencyclidine (PCP). Presently ~15% of college students report some use of these drugs during their lifetime. An increase was most striking in younger cohorts. The effects of hallucinogenic drugs are variable, even in the same individual at different times. Because of the unpredictability of psychedelic drug effects, any use carries some risk. Dependence and addiction do not occur, but users may require medical attention because of "bad trips."

Major psychedelic compounds come from two main categories. The indoleamine hallucinogens include LSD, DMT, (*N,N*-dimethylamine), and psilocybin. LSD is the most potent hallucinogenic drug and produces significant psychedelic effects with a total dose of as little as 25–50 μ g. This drug is 3,000 times more potent than mescaline.

The phenethylamines include mescaline, ethylenedioxyamphetamine (MDA) and MDMA. Acute effects are dose dependent and include tachycardia, dry mouth, jaw clenching, and muscle aches. At higher doses, the effects include visual hallucinations, agitation, hyperthermia, seizures, and panic attacks (1). A Danish report stated that seizures are among the most common clinical complications in the CNS after the ingestion of ecstasy (20). The pathophysiology of seizures due to MDMA use seems related to severe hyponatremia (20).

PCP

PCP deserves special mention because of its widespread availability and because its pharmacologic effects are different from those of the psychedelics such as LSD (21). PCP was originally developed as an anesthetic in the 1950s and later abandoned because of a high frequency of postoperative delirium with hallucinations. Abusers taking higher doses may appear to be reacting to hallucinations and exhibit hostile or assaultive behavior. Anesthetic effects increase with dosage; stupor or coma

may occur with muscular rigidity, rhabdomyolysis, and hyperthermia. Intoxicated patients in the emergency room may progress from aggressive behavior to coma, with elevated blood pressure and enlarged nonreactive pupils. Human beings tend to use PCP intermittently, but some surveys report daily use in 7% of users queried. Signs of a PCP withdrawal syndrome were observed in monkeys after interruption of daily access to the drug. These include somnolence, tremor, seizures, diarrhea, piloerection, bruxism, and vocalizations. A review of 1,000 cases of PCP toxicity reported 26 grand mal seizures and five cases of status epilepticus (22).

Mechanism of action

MDMA produces degeneration of serotonergic nerve cells and axons in rats. Although nerve degeneration has not been demonstrated in human beings, the cerebrospinal fluid of habitual MDMA users has been found to have low levels of serotonin metabolites.

Acknowledgment: Professor Trimble and the members of The Commission for the Psychobiology of Epilepsy are very grateful to the International League Against Epilepsy for their financial support of the commission and for their help with the publication of this supplement.

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