CHAPTER 18

Do Central Nervous System Stimulants Lower Seizure Threshold?

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INTRODUCTION

Central nervous system (CNS) stimulants are a broad class of drugs that can be used to increase motivation, alertness, mood, energy, and wakefulness. Over the last decade their use has increased substantially, raising issues of adverse effects. One of the major concerns is whether stimulants decrease seizure threshold? There exists considerable controversy surrounding this issue. Many patients in need of stimulants have an underlying neurological disorder that is associated with a lower seizure threshold. Alternatively, stimulants may reduce seizure threshold in patients not otherwise predisposed to seizure. This review will examine the literature in an attempt to address this important question.

Classification of stimulants

CNS stimulants can be classified into the following broad pharmacological categories:

1. Sympathomimetics – including amphetamines (dextroamphetamine, methamphetamine), modafinil, and methylphenidate, all of which have multiple clinical indications.
2. Cocaine, cannabinoids, lysergic acid diethylamide (LSD), methylenedioxymethamphetamine (MDMA or "ecstasy"), and phencyclidine (PCP), have CNS effects that make them popular for illicit drug use.
3. Methylxanthines like caffeine and theophylline that are traditionally part of our daily consumption.

Psychiatric Controversies in Epilepsy

CNS stimulants are often described as "amphetamine like," since amphetamine is the prototypical stimulant agent. It is noteworthy that many of these drugs have a long history of efficacy and safety, whereas others are highly addictive substances associated with considerable morbidity and mortality (Table 18.1). {AQ1}

Mechanism of action

Stimulation may occur at cortical, brainstem or spinal levels and through different mechanisms. Most CNS stimulants are known to interact with monoamine neurons in the CNS. Neurons that synthesize, store, and release monoamine transmitters (norepinephrine, dopamine DA), and serotonin) are widely distributed in the mammalian CNS (Rothman and Baumann, 2003). These neurons possess specialized plasma membrane proteins that transport previously released transmitter molecules from the extracellular space back into the cytoplasm (Masson *et al.*, 1999). Psychostimulants target these monoamine transporters and increase extracellular DA (Wise, 1996; Volkow *et al.*, 2001), serotonin (5-HT), and norepinephrine (Bymaster *et al.*, 2002) by basically two mechanisms: reuptake inhibition and substrate-type release (Masson *et al.*, 1999). Other CNS stimulants like caffeine block adenosine A1 and A2A receptors (Daly and Fredholm, 1998).

DA-receptor blockage has been correlated with seizure occurrence. The discovery of multiple DA-receptor families (mainly D1 and D2, but also D3, D4, and D5), sometimes mediating opposing influences on neuronal excitability, heralded a new era of DA epilepsy research (Sultan *et al.*, 1990). In this context, there is a growing awareness that seizures might be precipitated as a consequence of treating other neurological disorders with D2 antagonists (schizophrenia) or D1 agonists (parkinsonism) (Starr, 1996). Animal studies showed that the pretreatment of rats with SCH 23390, a D1 antagonist, did not alter the incidence of seizures induced by high doses of cocaine, d-amphetamine and methamphetamine. Suggesting that the mechanism of seizure induction by these drugs is complex and dose-dependent (Derlet *et al.*, 1990).

CNS stimulants may induce seizures by the blockade of several receptors, by a hormonal mechanism, or by a kindling activity.

ATTENTION DEFICIT ASSOCIATED WITH NEUROLOGICAL DISORDERS

Epilepsy is primarily considered a disorder of paroxysmal events, but it is a broader-spectrum disease (Neville, 1999) that includes a range of disabilities such as autistic disorders (Taylor *et al.*, 1999), attention deficit–hyperactivity disorder (ADHD) (Dunn *et al.*, 2003), learning difficulties, and motor impairments (Neville and Boyd, 1995). In some patients these "comorbid" conditions may become the main clinical problem.

TABLE 18.1 Central nervous system stimulants

	Composition	Names	Mechanism of action	Indication	Epileptogenic evidence
Amphetamines	Methylphenidate hydrochloride	Ritalin Concerta Metadate	Unknown.	ADHD Narcolepsy	Uncertain. PDR recommends discontinuation in the presence of seizures. May interact with AEDs.
	D-amphetamine saccharate, D,L-amphetamine aspartate, D-amphetamine sulfate, and D,L-amphetamine sulfate	Adderal	Dopamine reuptake inhibition.	ADHD Narcolepsy	Uncertain. Case reports.
	Dextroamphetamine sulfate	Dexedrin	Dopamin reuptake inhibition.	ADHD Narcolepsy	Uncertain. It was used in the past to treat epilepsy.
Modafinil		Provigil	Unknown.	Improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder.	No evidence.
Cocaine			Monoamine transporters inhibition.	None.	Strong association with seizures (1–10%).
Cannabinoids	Delta-9-tetrahydrocannibinol (THC) and cannabidiol (CDB) –among others–.		Probable interaction with cannabinoid and NMDA receptors.	Anorexia Antiemetic	Uncertain. Case reports of cannabinoid – induced seizures. Experimental evidence of antiseizure effect.
MDMA	3,4-Methylenedioxymethamphetamine	Ectasy	Increased DA and 5-HT release.	None.	Seizures are a ommon CNS complication.
PCP	Phencyclidine		Noncompetitive antagonist of the NMDA receptor. Interacts with DA and 5-HT receptors.	None.	Evidence shows epileptogenic and antiepileptic properties.
Methylxanthines	Caffeine		Adenosine receptor blockage.		High doses decrease seizure threshold.
	Theophylline		Unknown.	Asthma	Case reports of seizures with asthma treatment.

Attention is part of the neurobehavioral spectrum of cognitive functions impaired in epilepsy patients. Attention deficits are easily recognized in children because of continuous parent supervision and its impact in learning and development. Attention, mental speed, memory, and language are affected in adults with epilepsy as well (Devinsky, 2004). Attention is also impaired in patients with Parkinson disease and Lewy body dementia (Ballard *et al.*, 2002), further studies suggest that reduction of noradrenaline impairs attention and DA depletion slows responses in Parkinson's disease (Riekkinen *et al.*, 1998). Furthermore, methylphenidate increases the motor effects of L-Dopa in Parkinson's disease (Camicioli *et al.*, 2001), probably by blocking DA's transporter. Studies using *in vivo* brain imaging techniques, such as positron emission tomography have shown that DA transporter densities are affected in Parkinson's disease (Kim *et al.*, 1997).

Treatment of other conditions like narcolepsy-related sleepiness traditionally employs amphetamine and amphetamine-like stimulant drugs, such as methylphenidate (Mitler *et al.*, 1994). Stimulants are used to treat depressive symptoms, especially apathy, in patients with depression and other disorders involving the frontal lobes (Marin *et al.*, 1995).

ADHD is a behavioral phenotype frequently seen in children with epilepsy (Lindsay *et al.,* 1979). Some children may have both epilepsy and ADHD. Others may have an underlying CNS dysfunction that causes both epilepsy and difficulty with attention. Still others may have problems with attention secondary to their epilepsy (Dunn and Kronenberger, 2005). (Noeker and Haverkamp, 2003) have suggested that children with the combined type of ADHD and epilepsy may have concurrent comorbidity in which inattention and epilepsy are both related to a common CNS disturbance.

About 65% of children will continue to have impairing ADHD symptoms into adulthood (Faraone *et al.,* 2000). CNS stimulants are an effective treatment frequently prescribed for ADHD, specially after the multimodal treatment study demonstrated long-term efficacy and superiority over other treatment modalities (The MTA Cooperative Group, 1999). Though the safety of stimulants in {AQ2} patients with well-controlled epilepsy and concurrent ADHD has been documented (Feldman *et al.,* 1989; Gross-Tsur *et al.,* 1997a, b); CNS stimulants have {AQ3} been related with decreasing seizure threshold, although there are no controlled studies that support this statement. One study addressed first time seizure onset on 234 children with ADHD (Hemmer *et al.*, 2001). Electroencephalograms (EEGs) obtained up to 8 weeks of being on CNS stimulants showed a 15.4% incidence of epileptiform activity, considerably higher than the estimated incidence (1.1%) of EEG abnormalities in normal children (Cavazzuti *et al.*, 1980).

Borgatti *et al.* (2004) evaluated children with epilepsy before starting an antiepileptic drug (AED) and after 1 year of treatment. They found problems with attention in 21% of the children at baseline and 42% one year later, suggesting that factors related to the seizure disorder or therapy had a negative effect on performance. There are numerous anecdotal reports of cognitive decline or behavioral

dysfunction in association with many of the antiepileptic drugs, although it has been difficult to demonstrate with controlled studies (Williams *et al.*, 1998). Most antiepileptic drugs do not adversely affect attention and behavior in therapeutic doses, with the exception of phenobarbital, gabapentin, and topiramate. Some antiepileptics, such as lamotrigine and carbamazepine, may even have beneficial effects (Schubert, 2005).

SEIZURE INCIDENCE AND CNS STIMULANTS

Few studies have correlated the use of CNS stimulant drugs and seizures. A retrospective survey of seizures associated with 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%, CNS stimulant drugs in 29%, antihistaminics in 14%, theophylline in 5%, and isoniazid in 5% of cases (Olson *et al.*, 1994). Another retrospective study of recreational drug-induced seizures at the San Francisco General Hospital identified 49 cases in 47 patients between 1975 and 1987. The recreational drugs implicated were cocaine, amphetamine, heroin, and PCP (Alldredge *et al.*, 1989). Epidemiological data has shown that heroin is a risk factor for first time seizures, marijuana had a protective effect and cocaine did not have any correlation (Ng *et al.*, 1990).

Amphetamines

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. This group comprises amphetamine, dextroamphetamine, methamphetamine, and methylphenidate. They have Federal Drug Administration (FDA) approval for the treatment of ADHD and narcolepsy. Amphetamines act as substrate for monoamine transporters thereby stimulating non-exocytotic transmitter release and elevating synaptic levels of DA, norepinephrine, and 5-HT throughout the neuraxis (Kuczenski *et al.*, 1995).

Epileptic seizures are relatively rare at therapeutic doses but may occur after the first dose. Amphetamine-related seizures appear to be less common than cocaine (Hanson *et al.,* 1999). Seizures as a toxic effect of amphetamine-like drugs are often accompanied by other signs of overdose like fever, hypertension, cardiac arrhythmias, delirium, or coma (Alldredge *et al.*, 1989). Methamphetamine-related seizures appear to be refractory to phenytoin pretreatment, the only AEDs that influenced seizure occurrence were diazepam and valproate (Hanson *et al.*, 1999).

Methylphenidate

Methylphenidate is used as a therapeutic agent for ADHD and narcolepsy. Methylphenidate may inhibit the metabolism of anticonvulsants (phenobarbital,

diphenylhydantoin, and primidone), and a decreased dose of these drugs may be required when given concomitantly with methylphenidate (Gross-Tsur *et al.*, 1997a, b). Though, other authors have been unable to demonstrate an effect of methylphenidate on AED levels (Mirkin and Wright, 1971; Kupferberg *et al.*, 1972).

Methylphenidate is commonly believed to lower seizure threshold. However, no control studies have proved this hypothesis, and most is anecdotal evidence. Nevertheless, the *Physician's Desk Reference* (Montvale, 1998) and many other reference books discourage the use of stimulants in children with ADHD or even epileptiform discharges in the EEG alone (Aldenkamp *et al.,* 2006). However, studies have shown that methylphenidate does not increase the risk for development of seizures in children without epilepsy or in children with epileptiform EEG abnormalities (Gross-Tsur *et al.*, 1997a, b), even some studies report beneficial effects on the EEG (Gucuyener *et al.,* 2003). A retrospective study of adults and children with traumatic brain injury and active seizure disorders, found a trend toward a lesser incidence of seizures during methylphenidate therapy (Wroblewski *et al.,* 1992).

Modafinil

It is a wakefulness-promoting agent. The precise mechanism(s) through which modafinil promotes wakefulness is unknown. Modafinil has wake-promoting actions like sympathomimetic agents including amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of sympathomimetic amines. The mechanism of action has not been fully characterized, but there is evidence that a single injection of modafinil increases DA levels in the nucleus accumbens (Murillo-Rodriguez *et al.*, 2007).

Modafinil is indicated to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. Its use in healthy people is being explored by the military to improve performance and alertness of aviators (Caldwell *et al.,* 2000). There is no evidence that modafinil induces seizures in healthy individuals or people with epilepsy.

Illegal substances

Cocaine

By contrast of amphetamine-like drugs that are substrate for monoamine transporters (Seiden *et al.*, 1993), cocaine and other chemically related drugs are nonselective, competitive inhibitors of monoamine transporters (Ritz *et al.*, 1987).

Cocaine, specially in high doses has been associated with seizures (Pascual-Leone *et al.*, 1990), though it is not clear if cocaine use can reduce seizure threshold in patients with underlying epilepsy as a direct effect or indirectly by contributing to poor compliance with antiepileptics, poor diet, or poor sleep habits

(Koppel *et al.*, 1996). The reported frequency of cocaine-associated seizures varies from 1% to 8% in retrospective clinical studies. A study of 500 cocaine addicts showed that 10% of subjects had a single seizure, and 3% had status epilepticus (Choy-Kwong and Lipton, 1989). Seizures occur frequently in first-time cocaine users; one study reported 40% seizures among 44 first-time users (Lowenstein *et al.*, 1987). Cocaine and its metabolite: benzoylecgonine, produced seizures when injected in the ventricular system of rats (Konkol *et al.*, 1992).

Cocaine-induced seizures often occur in the absence of other signs of toxicity. They can appear immediately or several hours after use, owing perhaps to pharmacologically active metabolites (Myers and Earnest, 1984; Lowenstein *et al.*, 1987). A focal signature to seizures should suggest a structural lesion such as cocaine-related intracerebral hemorrhage. Seizures are more likely to occur after smoking crack than after intranasal cocaine HCl, probably as a consequence of the much higher doses with the former mode of administration (Brust, 2006).

Cannabinoids

Marijuana is the most commonly used illegal drug in the United States. Approximately, 60 cannabinoids and 260 non-cannabinoid constituents have been identified (Turner *et al.*, 1980). The main constituents of marijuana are delta-9-tetrahydrocannibinol (THC), the primary psychoactive constituent, and cannabidiol (CBD) the primary non-psychoactive constituent. Dronabinol, the synthetic form of THC, has FDA approval for the treatment of anorexia and as antiemetic (Montvale, 1998).

Cannabinoid receptors are found in the brainstem, limbic, and neocortical areas that modulate seizure activity (Abood and Martin, 1996). The mechanism by which marijuana and the cannabinoids alter seizure threshold is not well defined. There may be a functional connection between cannabinoid and *N*-methyl-d-aspartate (NMDA) receptors because the two receptors are co-localized in many brain areas (Feigenbaum *et al.,* 1989). Cannabinoids have been shown to interact with glutamatergic transmission in the CNS through interaction with NMDA and non-NMDA receptors. The synthetic and non-psychotropic cannabinoid: dexanabinol (HU-211), blocks NMDA receptors in a stereospecific manner, blocking NMDA-induced tremor, seizures, and death in mice (Ameri, 1999). There is also electrophysiological evidence that cannabinoids are capable of inhibiting presynaptic release of glutamate in rat hippocampal cultures. By presynaptic inhibition of glutamate release cannabinoids may enhance their anticonvulsant activity (Shen *et al.*, 1996).

In the 19th century, marijuana was used to treat epilepsy (Gordon and Devinsky, 2001). However, little medical attention was subsequently given to its possible antiepileptic effects. Little is known about the extended effects of marijuana or its constituents on the brain. Short-term use of marijuana can decrease alpha amplitude {AQ4} and frequency, sleep duration, and rapid eye movement (REM) sleep. However, within an average of 10 days of continued administration, these functions returned

to normal (Jones *et al.*, 1981; Hughes, 1996). Further, there is a dose-dependent effect of cannabinoids on CNS excitability, with low doses producing activation and high doses reducing electrical activity (Pertwee, 1988).

The main problem of cannabinoids used as antiepileptic drugs concerns the separation of their psychoactive from anticonvulsant activity. However, the cannabinoid metabolite: CBD, devoid of psychotropic actions, has been reported to possess anticonvulsants effects comparable with those of phenytoin (based on similar spectra of anticonvulsant activity) in mice with electroshock convulsions (Karler and Turkanis, 1981). Moreover, clinical trials with CBD were undertaken in patients with complex partial seizures with secondary generalization. The data revealed that CBD in oral doses of 200–300 mg/day is, in fact, effective against this form of epilepsy (Cunha *et al.,* 1980; Carlini and Cunha, 1981). One epidemiologic study of illicit drug use and new-onset seizures found that marijuana use appeared to be a protective factor against first seizures in men (Ng *et al.*, 1990).

3,4-Methylenedioxymethamphetamine

MDMA is a ring-substituted amphetamine derivative that is also structurally related to the hallucinogenic compound mescaline. MDMA has both CNS stimulant and hallucinogenic properties. The mode of action for MDMA is based on its ability to bind 5-HT, DA, and norepinephrine transporters (Slikker *et al.*, 1989), resulting in the release of monoamine neurotransmitters via monoamine transporter reversal (Rudnick and Wall, 1992). However, while enhanced DA neurotransmission is thought to predominantly mediate the behavioral effects of amphetamine, a unique contribution of 5-HT has been proposed to underlie the neuropsychopharmacology of MDMA (Callaway *et al.,* 1991).

Overdose with MDMA can cause seizures, delirium, coma, and death (Kalant, 2001). A Danish study reported that seizures are among the most common CNS complications after the ingestion of ecstasy. The pathophysiology of seizures due to MDMA use seems related to severe hyponatremia (Hedetoft and Christensen, 1999).

Phencyclidine

Originally developed as an anesthetic in the 1950s, PCP was later abandoned because of a high frequency of postoperative delirium with hallucinations. PCP is a non-competitive antagonist at the NMDA receptor complex (Lodge and Anis, 1982), but it also acts on the dopaminergic (Chaudieu *et al.*, 1989) and serotoninergic systems (Hori and Kanda, 1996). PCP intoxication is characterized by stupor or coma, muscular rigidity, rhabdomyolysis, and hyperthermia. Intoxicated patients may progress from aggressive behavior to coma, with elevated blood pressure and enlarged non-reactive pupils. PCP withdrawal syndrome has been observed in monkeys after interruption of daily access to the drug. It is characterized by somnolence, tremor, seizures, diarrhea, piloerection, bruxism, and vocalizations

(Zagnoni and Albano, 2002). A review of 1,000 cases of PCP toxicity reported 26 grand mal seizures and five cases of status epilepticus (McCarron *et al.*, 1981).

The PCP analog: metaphit, induces tonic–clonic seizures in mice exposed to audio stimulation. Metaphit blocks PCP NMDA receptors, and seizures can be prevented by pretreating mice with PCP, thus in these experiments PCP showed a seizure protective role (Debler *et al.*, 1993).

Methylxanthines: caffeine and theophylline

Caffeine and theophylline are consumed worldwide to enhance wakefulness, but the cellular mechanisms are poorly understood. Caffeine blocks adenosine receptors suggesting that adenosine decreases cortical arousal (Nehlig *et al.*, 1992). Adenosine decreases the firing rate of neurons and exerts an inhibitory effect on synaptic transmission and on the release of most neurotransmitters, while caffeine increases the turnover of many neurotransmitters, including monoamines and acetylcholine (Nehlig, 1999). Theophylline's antiinflamatory mechanism has been extensively characterized, while its CNS properties are poorly understood.

Both caffeine and theophylline lower the convulsive threshold and, when administered in high doses, produce seizures (Chu, 1981; Czuczwar *et al.*, 1987). High doses of caffeine in humans may cause nausea, trembling, nervousness, and seizures (Frucht *et al.*, 2000). Intravenous caffeine given before electroconvulsive therapy can prolong seizure duration (Lurie and Coffey, 1990). Status epilepticus has been reported during asthma treatment with theophylline and aminophylline (Schwartz and Scott, 1974; Yarnell and Chu, 1975). It also has been shown that non-convulsive doses of theophylline markedly attenuated the anticonvulsant potential of topiramate (Luszczki *et al.*, 2007).

Seizures and hallucinations have been reported in patients who received both quinolones and theophylline (Raoof *et al.,* 1987). It has been postulated that quinolones have a γ-aminobutyric acid (GABA) receptor binding inhibition activity that enhances the excitatory effect of theophylline (Segev *et al.,* 1988).

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Author Queries

{AQ1}: Please confirm the cit5ation of Table 18.1 in the text.
{AQ2}: Please confirm the citation of the reference "The MTA Cooperative Group (1999)" in the text.
{AQ3}: Please confirm the insertion of the labels "a and b" for the reference citation "Gross-Tsur et al. (1997)" in the text.
{AQ4}: Note that we have changed the expansion of the acronym "REM" as "rapid eye movement". Please suggest.