29 Central Nervous System Stimulants

David A. Taylor

DRUG LIST

Central nervous system (CNS) stimulation is the primary action of a diverse group of pharmacological agents and an adverse effect associated with the administration of an even larger group of drugs. CNS stimulation consists of a range of behaviors including mild elevation in alertness, increased nervousness and anxiety, and convulsions.

In general, any hyperexcitability associated with drug administration (as either a desired or an undesired effect) results from an alteration in the fine balance normally maintained in the CNS between excitatory and inhibitory influences. Thus, the bases for CNS stimulation by this class of drugs reside in adjusting the integration of excitatory and inhibitory influences at the level of the individual neuron. An agent that induces CNS stimulation appears to act by one or more of the following mechanisms: (1) potentiation or enhancement of excitatory neurotransmission, (2) depression or antagonism of inhibitory neurotransmission, and (3) altered presynaptic control of neurotransmitter release.

Although the use of CNS stimulants (also known as *analeptics* or *convulsants*) has declined, certain compounds within this category do possess some clinical utility. Historically, general CNS stimulants were used primarily as respiratory stimulants in the treatment of acute overdosage with CNS depressants (e.g., barbiturates). Several factors have contributed to the almost complete lack of use of CNS stimulants in this clinical situation. First, since the stimulants were not *specific* antagonists of the depressant agents, they frequently were not effective in reversing severe pharmacologically induced CNS depression. Second, the duration of action of the CNS stimulant was generally shorter than that of the depressant. Third, the dose of most CNS stimulants required to reverse severe CNS depression was quite close to the dose that produced convulsions and cardiac arrhythmias. In such cases, the CNS stimulant often exacerbated the clinical picture by producing severe life-threatening complications. Another factor contributing to the decline in CNS stimulant use for drug-induced CNS depression has been the development of generally safer procedures for patient management. Supportive measures (e.g., maintenance of a patent airway, elevation of low blood pressure) often provide greater bene-

T A B L E **29.1**	Classification of CNS Stimulants	
Analeptic Stimulants	Psychomotor Stimulants	Methylxanthines
Doxapram	Amphetamine	Caffeine
Nikethamide	Methamphetamine	Theophylline
Pentylenetetrazol	Methylphenidate	Theobromine
Strychnine	Pemoline	
Picrotoxin	Ephedrine	
Bicuculline	Phentermine	
	Fenfluramine	
	Phenylpropanolamine	

fit to the patient than does the use of analeptic drugs. Tolerance and abuse potential are additional problems associated with the use of such psychomotor stimulants as amphetamine and many of its congeners.

Compounds that possess as their primary action the stimulation of the CNS can be divided into three major categories (Table 29.1) based on either their proposed mechanism of action or their chemical structure. Each class of compounds is discussed in general terms, and individual drugs are mentioned only as appropriate.

ANALEPTIC STIMULANTS

Chemistry and Pharmacokinetics

The analeptic stimulants are a diverse chemical class of agents ranging from plant alkaloids, such as picrotoxin and strychnine, to synthetic compounds, such as pentylenetetrazol and doxapram. The wide range of chemical structures makes this particular class somewhat difficult to categorize with respect to absorption, distribution, and metabolism. However, most analeptic stimulants can be absorbed orally and have short durations of action. The pharmacological effect of most of these compounds is terminated through hepatic metabolism rather than renal excretion of unchanged drug.

Mechanism of Action

Perhaps the most unifying concept concerning the mode of action of these agents comes from studies of the γ-aminobutyric acid (GABA) receptor–chloride ionophore interaction. It has long been recognized that the inhibitory action of many amino acid neurotransmitters (e.g., GABA) involves an increase in chloride conductance. Thus, GABA and other inhibitory amino acids actively promote an increase in chloride influx by activation of the chloride channel in the neuronal membrane. An increase in chloride conductance generally leads to mem-

brane *hyperpolarization* and a reduction in the probability of action potential generation (i.e., inhibition of neuronal activity). With GABA in particular, the interaction appears to occur through specific membrane-associated GABA$_A$-receptors that form an integral part of the chloride channel (see Chapter 24). The chloride channel appears to contain other regulatory sites with high affinity for such agents as the benzodiazepines, picrotoxin, alcohol, neuroactive steroids, and the barbiturates.

Chloride movement across neuronal membranes can be regulated at this ion channel by at least three distinct molecular entities: (1) a GABA-binding site, (2) a benzodiazepine-binding site, and (3) a picrotoxin-binding site. GABA and other agonists open the chloride channel (i.e., increase chloride conductance). Benzodiazepine-induced facilitation of GABA-mediated increases in chloride conduction are antagonized by pentylenetetrazol and possibly by the methylxanthines, while picrotoxin closes the chloride channel. Other agents that appear to promote chloride conductance through this channel include the barbiturates and alcohol.

The existence of the chloride channel as a major site of drug action permits a single molecular event (control of chloride ion movement) to be involved in the mechanism of action of a diverse class of agents.

Strychnine is an analeptic stimulant with a well-defined mechanism of action that is unrelated to interaction with GABA receptors or other sites that modulate the activity of the chloride ionophore. Strychnine appears to be a specific competitive postsynaptic antagonist of glycine. Glycine, like GABA, is a known inhibitory transmitter in the mammalian CNS. Whereas GABA is likely to be more important in the brain, glycine is more important in the spinal cord. Glycine mediates inhibition of spinal cord neurons and is intimately involved in the regulation of spinal cord and brainstem reflexes. *Strychnine directly antagonizes this inhibition, allowing excitatory impulses to be greatly exaggerated.*

Clinical Uses

As indicated, most of the analeptic stimulants were used as pharmacological treatments for overdosage of CNS depressants. Doxapram (*Dopram*) *is sometimes used to counteract postanesthetic respiratory depression and as an aid in chronic obstructive pulmonary disease.* Pentylenetetrazol (*Metrazol*) was used experimentally on rare occasions to "activate" the electroencephalogram. Strychnine is used almost exclusively in animal studies as a tool for studying CNS mechanisms because it is a relatively specific glycine antagonist.

Adverse Effects

Most of the CNS stimulants produce adverse reactions that are extensions of their therapeutic effect. These
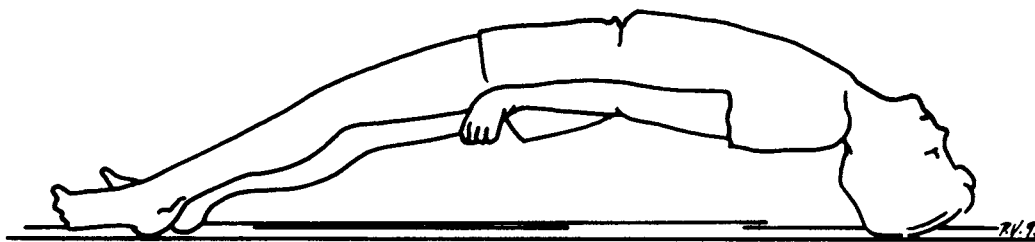
FIGURE 29.1
Patient in opisthotonos.

agents produce convulsions that can be followed by coma and death. Convulsions produced by this class of agents (with the exception of strychnine) are usually tonic–clonic and are uncoordinated. In some cases, the convulsions are preceded by marked stimulation of respiration, tachycardia, and excessive pressor effects.

The uncontrolled excitation that occurs after accidental or intentional strychnine ingestion (in the absence of normal inhibition) results in characteristic convulsions. In humans, in whom extensor muscles are normally dominant, tonic extension of the body and all limbs is observed. This hyperextension is known as *opisthotonos;* at its extreme, it consists of a characteristic posture in which the back is arched and only the back of the head and the heels are touching the surface on which the victim is lying. Figure 29.1 illustrates a patient in opisthotonos. Under the influence of strychnine, all sensory stimuli produce exaggerated responses. The primary therapeutic consideration after strychnine poisoning is to prevent convulsions, which may be fatal. Diazepam and clonazepam (see Chapter 33) appear to be moderately effective in preventing strychnine convulsions, and either of these is the agent of choice. Barbiturates are often used to treat overdoses of all of the analeptic stimulants. Generally, however, antidotal therapy is not required.

PSYCHOMOTOR STIMULANTS

Pharmacokinetics

Many psychomotor stimulants possess activities similar to those of amphetamine and have been discussed previously (see Chapter 10). Of primary importance to our discussion of the psychomotor stimulants are amphetamine (*Adderall, Benzedrine, Dexedrine*), methamphetamine (*Desoxyn*), and methylphenidate (*Concerta, Ritalin, Metadate, Methylin*).

All of these compounds are well absorbed after oral administration, leaving injectable forms with few legitimate applications. Although several catabolic pathways metabolize the amphetamines, a considerable portion

of untransformed drug is excreted in the urine. Thus, it is possible to ion-trap this weak organic base by acidifying the urine, thereby reducing its reabsorption in the renal tubules and enhancing its clearance.

Mechanism of Action

There is good evidence that the facilitation of peripheral sympathetic nervous system transmission produced by the amphetamines also occurs in the CNS. The possibility that amphetamines act indirectly (i.e., by releasing monoamines) at monoaminergic synapses in the brain and spinal cord seems likely. However, amphetamine has effects beyond displacement of catecholamines; these include inhibition of neuronal amine uptake, direct stimulation of dopamine and serotonin receptors, antagonism of catecholamine action at certain subtypes of adrenoceptors, and inhibition of monoamine oxidase. Interestingly, none of these actions explains the therapeutic benefit of the amphetamines in hyperkinetic children.

Clinical Uses

The therapeutic indications for the psychomotor stimulants are quite limited. They are beneficial in the treatment of the *hyperkinetic syndrome* (attention deficit–hyperactivity disorder with minimal brain dysfunction). This is generally a childhood disease characterized by hyperactivity, inability to concentrate, and impulsive behavior. Amphetamines and the more extensively used methylphenidate paradoxically are quite effective in calming a large proportion of children with this disorder. Pemoline (*Cylert*) is also used in the treatment of attention deficit disorder with hyperkinetic behavior. The mechanism by which these compounds are effective in this disorder is not known.

Narcolepsy is another medically recognized indication for the use of the psychomotor stimulants. This disorder is characterized by sleep attacks, particularly during the day, sudden loss of muscle tone (*cataplexy*), sleep paralysis, and vivid visual and auditory nightmares that may persist into the waking state. Drugs that influence the central action of adrenomimetic amines re-

markably affect narcolepsy. Monoamine oxidase inhibitors (e.g., selegiline) and amphetamines are both quite effective in preventing sleep attacks and improving cataplexy. Modafinil (*Provigil*) is a nonamphetamine compound whose mechanism of action is not known but that has been shown to be successful in the treatment of narcolepsy. However, amphetamine and methylphenidate are still considered among the drugs of choice in this disorder.

Previously, another use of the amphetamines and other centrally acting adrenomimetics has been in the management of obesity and weight reduction. Although the amphetamines have a significant anorexic effect, tolerance to this action develops within a few weeks. In addition, insomnia restricted their use during the latter part of the day. The combined drawbacks of the development of tolerance and potential for drug abuse have convinced much of the medical community that *the use of amphetamines in weight control is inappropriate.*

Fenfluramine (*Pondimin*) and phentermine (*Adipex-P, Fastin*) are anorexigenic drugs that produce *depression* of the CNS and at one time were used (Fen-phen) in the treatment of obesity. Sibutramine (*Meridia*) is also available for the treatment of obesity.

Adverse Effects

The acute effects of psychomotor stimulant overdoses are related to their CNS stimulant properties and may include euphoria, dizziness, tremor, irritability, and insomnia. At higher doses, convulsions and coma may ensue. These drugs are cardiac stimulants and may cause headache, palpitation, cardiac arrhythmias, anginal pain, and either hypotension or hypertension. Dextroamphetamine produces somewhat less cardiac stimulation. Chronic intoxication, in addition to these symptoms, commonly results in weight loss and a psychotic reaction that is often diagnosed as schizophrenia.

These agents produce addiction, including psychological dependence, tolerance, and physical dependence. Psychic dependence also has been seen following high doses of methylphenidate. The abstinence syndrome seen after abrupt discontinuation of amphetamines is neither as dramatic nor as predictable as that observed during withdrawal from the barbiturates or opioids. With the amphetamines, the abstinence syndrome consists primarily of prolonged sleep, fatigue, and extreme hunger (*hyperphagia*). These symptoms may be accompanied by profound and long-lasting depression. Amphetamine abuse is discussed more completely in Chapter 35.

XANTHINES

The compounds known as xanthines, methylxanthines, or xanthine derivatives constitute a particularly interesting class of drugs. Since they possess diverse phar-

macological properties, there is always a question of where most appropriately to discuss them in a pharmacology text. The xanthines are clearly CNS stimulants, although not all have this characteristic equally. While the xanthines have legitimate therapeutic uses, by far the greatest public exposure to them is in xanthine-containing beverages, including coffee, tea, cocoa, and cola drinks. The popularity of xanthine-containing drinks appears to be related to its subtle CNS stimulant effect. It is primarily for this reason that xanthines are listed as CNS stimulants in this text.

Chemistry and Pharmacokinetics

Three xanthines are pharmacologically important: *caffeine, theophylline,* and *theobromine.* All three alkaloids, which occur naturally in certain plants, are widely consumed in the form of beverages (infusions or decoctions) derived from these plants. Coffee primarily contains caffeine (about 100–150 mg per average cup); tea contains caffeine (30–40 mg per cup) and theophylline; and cocoa contains caffeine (15–18 mg per cup) and theobromine. Cola drinks also contain significant amounts of caffeine (about 40 mg/12 oz). *The CNS stimulation associated with these beverages is predominantly due to the caffeine.*

The xanthines are readily absorbed by the oral and rectal routes. Although these agents can be administered by injection (*aminophylline* is a soluble salt of theophylline), *intravascular administration is indicated only in status asthmaticus and apnea in premature infants.* Intramuscular injection generally produces considerable pain at the injection site.

The compounds are extensively metabolized, primarily to uric acid derivatives. There is, however, no indication that methylxanthines aggravate gout.

Mechanism of Action

The mechanism of action of methylxanthine-induced stimulation of the CNS has been the subject of much investigation, and at least two other possible mechanisms of action of the methylxanthines have been suggested. The first derives from the ability of the methylxanthines to act as antagonists of the naturally occurring compound adenosine, a substance that can inhibit both neuronal activity and behavior through direct postsynaptic action on neurons and through indirect action involving presynaptic inhibition of neurotransmitter release. The A1 subtype of the purine receptors mediates these actions of adenosine. Thus, as an equilibrium-competitive antagonist of adenosine, the methylxanthines may produce excitation either by direct blockade of inhibitory effects of adenosine at the neuron or by an antagonism of the presynaptic inhibitory effect of adenosine on the release of an excitatory substance (e.g., acetylcholine).

Another suggested mechanism of action involves the chloride channel. As discussed previously, the chloride channel is intimately associated with neuronal inhibition, and its activity appears to be modulated at many different sites. Caffeine can compete for binding at the benzodiazepine site and would therefore be expected to reduce chloride conductance. Thus, caffeine may act functionally like the analeptic stimulants that limit chloride channel activation.

Clinical Uses

Central Nervous System

Xanthines, primarily as the intramuscularly administered combination of *caffeine* and *sodium benzoate,* have been used in the treatment of CNS depressant overdosage. Black coffee has been used to physiologically antagonize alcohol intoxication, although many physicians believe that this ineffective therapy simply produces a wide-awake drunk.

Many over-the-counter preparations are aimed at relieving fatigue through CNS stimulation. Such compounds are often referred to as wake-up tablets, but these methylxanthine-containing products do little to offset physical fatigue, so they place individuals using them at risk for accidental injuries.

Diuresis

All the xanthines, but especially theophylline, are capable of producing some degree of diuresis in humans. This specific action of the methylxanthines is discussed in greater detail in Chapter 21.

Bronchial Asthma

Theophylline is frequently used as a bronchodilator in the treatment of asthma. The importance of the methylxanthines in the management of bronchial asthma is discussed more fully in Chapter 39. Caffeine as the citrate salt (*Cafcit*) is used for the short-term management of apnea in premature infants (28–33 weeks of gestational age).

Cardiac Uses

Theophylline, given as the soluble ethylenediamine salt aminophylline, offers some help in relieving the paroxysmal dyspnea that is often associated with left heart failure. A major portion of its efficacy may be due to the relief of bronchospasm secondary to pulmonary vascular congestion. Theophylline increases myocardial contractile force and has occasionally been used in the treatment of refractory forms of congestive heart failure. Theophylline also has shown some benefit in the treatment of neonatal apnea syndrome.

Miscellaneous Uses

Xanthines (usually caffeine) are frequently combined with aspirin in the treatment of headaches. In combination with an ergot derivative, methylxanthines have been used to treat migraine. These effects are likely due to their ability to produce vasoconstriction of cerebral blood vessels. Aminophylline is useful in the relief of pain due to acute biliary colic.

Adverse Effects

Toxicity associated with the methylxanthines usually takes the form of nervousness, insomnia, and in severe cases, delirium. Cardiovascular stimulation is seen as tachycardia and extrasystoles. Excessive respiratory stimulation may occur, and diuresis may be prominent.

The intravenous administration of aminophylline (or theophylline) may present some problems if the drug is given too rapidly. In such cases, severe headache, hypotension, and palpitation accompany drug administration. Subsequently the patient may show signs of excessive CNS stimulation, shock, and even death. Children appear to be especially prone to this toxicity.

Abuse of Xanthines

The use of some xanthine-containing beverages is customary in most cultures, and moderate use of such beverages does not appear to cause problems in most people. There is little question, however, that such use is habituating. For example, it has been observed that chronic coffee drinkers who suddenly abstain frequently have headaches and a general feeling of fatigue that may last for several days. Although it has not been established that these symptoms constitute any kind of abstinence syndrome, it remains a possibility. There is no good evidence for the development of tolerance to the CNS stimulant effects of caffeine.

Drug Interactions

An interaction of potential clinical significance involves the xanthines and the coumarin anticoagulants. Xanthines by themselves shorten clotting time by increasing tissue prothrombin and factor V and in this regard may be expected to antagonize the effectiveness of oral anticoagulants. However, the usual therapeutic doses of xanthines cause no significant effect on the patient's response to oral anticoagulants.

Study QUESTIONS

1. Opisthotonos is a convulsive condition that is often associated with the ingestion of strychnine. This condition is associated with all of the following EXCEPT
   (A) Antagonism of the inhibitory amino acid neurotransmitter glycine
   (B) The predominance of glycine as an inhibitory amino acid transmitter in the spinal cord
   (C) Antagonism of the inhibitory amino acid neurotransmitter GABA
   (D) The convulsions lead to tonic extension of the body and all limbs

2. Which of the following classes of agents is useful in the treatment of attention deficit hyperkinetic disorder?
   (A) Analeptic stimulants
   (B) Benzodiazepines
   (C) Xanthines
   (D) Psychomotor stimulants
   (E) Phosphodiesterase inhibitors

3. Which of the following mechanisms of action account for the effects of all analeptic stimulants except strychnine?
   (A) Antagonism of chloride ion influx at the GABA receptor–chloride channel complex
   (B) Increased release of catecholamines from CNS neurons
   (C) Inhibition of cholinesterase leading to increased acetylcholine levels
   (D) Antagonism of CNS adrenoceptors to reduce inhibition produced by catecholamines
   (E) Antagonism of nicotinic receptors that inhibit motor neuron activity

4. The CNS stimulation produced by methylxanthines, such as caffeine, is most likely due to the antagonism of which of the following receptors?
   (A) Glycine receptors
   (B) Adenosine receptors
   (C) Glutamate receptors
   (D) GABA receptors
   (E) Cholinergic muscarinic receptors

5. Cardiac stimulation is an adverse effect associated with the use of the psychomotor stimulants, such as amphetamine. Which of the following mechanisms is most likely responsible for this peripheral effect?
   (A) Inhibition of vagal tone through an action in the CNS
   (B) Indirect sympathomimetic effects in the periphery due to release of norepinephrine
   (C) Inhibition of a GABA-mediated negative chronotropic effect at the heart
   (D) Antagonism of muscarinic receptors in the heart
   (E) Blockade of ganglionic transmission at sympathetic ganglia in the periphery

ANSWERS

1. **C.** Glycine is the major inhibitory amino acid transmitter in the spinal cord, and strychnine is a relatively selective antagonist of glycine. Strychnine has very little if any action at the GABA receptor–chloride channel complex.

2. **D.** Attention deficit–hyperkinetic disorder and attention deficit disorder are among only a few approved uses of the psychomotor stimulants of the amphetamine type.

3. **A.** Analeptic stimulants, such as pentylenetetrazol and picrotoxin, act by inhibiting chloride influx at the $GABA_A$ receptor–chloride channel complex. This antagonism can occur through interaction with one of several binding sites or allosteric modifiers of receptor–channel function.

4. **B.** Methylxanthines have been proposed to be inhibitors of phosphodiesterase, which would elevate intracellular levels of cAMP. However, the concentration of cAMP that is required for such action is above the threshold of CNS stimulation. Since the methylxanthines are relatively potent antagonists of adenosine and since adenosine has been shown to be a reasonably potent inhibitor of both central and peripheral neurons, the most likely mechanism by which CNS stimulation occurs is through antagonism of adenosine receptors.

5. **B.** Psychomotor stimulants such as amphetamine are also indirectly acting sympathomimetics that increase the release of catecholamines from sympathetic nerve terminals. While amphetamine and other congeners possess additional actions on peripheral sympathetic nerves, this is the most likely explanation for the cardiac stimulation observed following the administration of these agents.

SUPPLEMENTAL READING

Barnard EA. The molecular biology of $GABA_A$ receptors and their structural determinants. In Biggio C, Sanna E, and Costa E (eds.). $GABA_A$ Receptors and Anxiety: From Neurobiology to Treatment. New York: Raven, 1992.

Costa E. From $GABA_A$ receptor diversity emerges a unified vision of GABAergic inhibition. Annu Rev Pharmacol Toxicol 1998;38:321–350.

Daval, J-L, Nehlig A, and Nicolas F. Physiological and pharmacological properties of adenosine: Therapeutic implications. Life Sci 1991;49:1435–1453.

Fredholm BB et al. International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. Pharmacol Rev 2001;53: 527–552.

Linden J. Structure and function of A_1 adenosine receptors. FASEB J 1991;5:2668–2676.

Sieghart W. Structure and pharmacology of γ-aminobutyric acid$_A$ receptor subtypes. Pharmacol Rev 1995;47:181–234.

Smith GB and Olsen RW. Functional domains of GABA$_A$ receptors. Trends Pharmacol Sci 1995;16:162–168.

C A S E Study Daytime Sleepiness

W. M. is a 55-year-old highly successful businessman who often spends long hours at the office or in his automobile traveling to meet new clients and partners. Since his days in college, W. M. has had frequent episodes of daytime somnolence, which he attributed to overwork and fatigue. Over the past several years, the number of daytime episodes has begun to increase, and he recently began to lose mobility in his arms and legs during the periods of somnolence. He also barely avoided a significant automobile accident for which the local sheriff's deputy cited him for failure to maintain control of his vehicle. During questioning by the police, W. M. indicated that he had no memory of any of the events surrounding the incident; he tested negative for any intoxicating substances. As a result of this most recent episode, W. M. has come to you, his family physician, to determine the cause of the excessive daytime sleepiness (EDS) and to find a way to manage this condition. Your examination reveals an individual who is in otherwise excellent health and mentation with no apparent significant pathology. He indicates that he has several periods of EDS during the day and that the frequency of these events is beginning to increase. While he feels well rested upon waking, he is especially concerned about the recent loss of skeletal muscle function and fears that he may be developing some degenerative progressive disease that will leave him disabled and unable to continue working. What types of pathological conditions can lead to excessive somnolence? What is the appropriate therapeutic management of these pathological conditions?

ANSWER: Three disorders are most often associated with EDS. *Sleep apnea* is characterized by pauses in respiration during sleep and usually excessive snoring. Patients with sleep apnea have EDS but often awake without feeling rested. Sleep apnea is managed by treating the nighttime episodes of apnea. *Narcolepsy* is characterized by episodic EDS. Patients with this pathology often exhibit periods of irresistible instantaneous REM sleep and may also progress to cataplexy, or sudden loss of tone in skeletal muscles (usually bilaterally). A final type of disorder that displays periods of EDS is *idiopathic hypersomnia,* in which patients usually have periods of EDS usually associated with non-REM sleep. W. M. most likely has *narcolepsy,* which could be more clearly defined by determining whether he has a specific human leukocyte antigen associated with the disorder (HLA-DR2). Management of narcolepsy is accomplished with psychomotor stimulants of the amphetamine type. *Methylphenidate, modafinil, pemoline,* and *dextroamphetamine* all are effective in managing the EDS periods, while *imipramine* and *clomipramine* can be used to manage any cataplexy.