Chapter 35 CNS Stimulants and Cognition Enhancers

CNS STIMULANTS

These are drugs whose primary action is to stimulate the CNS globally or to improve specific brain functions.

The CNS stimulants mostly produce a generalized action which may, at high doses, result in convulsions. Given below is a working classification based primarily on the clinical use, because clearcut differences do not exist.

CLASSIFICATION

1. *Convulsants* Strychnine, Picrotoxin, Bicuculline, Pentylenetetrazol (PTZ).
2. *Analeptics* Doxapram
3. *Psychostimulants* Amphetamines, Methylphenidate, Atomoxetine, Modafinil, Armodafinil, Pemoline, Cocaine, Caffeine.

Many other drugs are capable of causing CNS stimulation as side effect or at high doses.

I. CONVULSANTS

1. Strychnine It is an alkaloid from the seeds of *Strychnos nux-vomica,* and a potent convulsant. The convulsions are reflex, tonic-clonic and symmetrical. It has been labelled as a spinal convulsant because the dose producing convulsions is the same in spinal animals as in intact animals; actually it stimulates the whole cerebrospinal axis.

Strychnine acts by blocking *post-synaptic* inhibition produced by the inhibitory transmitter glycine. One of the sites that has been clearly demonstrated is the Renshaw cell-motoneurone junction in the spinal cord through which inhibition of antagonistic muscles is achieved. Due to loss of synaptic inhibition, any nerve impulse becomes generalized, resulting in apparent excitation and convulsions.

There are no valid uses of strychnine now. Accidental poisonings, especially in children, do occur. Treatment of poisoning is similar to that of status epilepticus (*see* Ch. 30).

2. Picrotoxin Obtained from 'fish berries' of East Indies *Anamirta cocculus*. It is a potent convulsant—convulsions are clonic, spontaneous and asymmetrical. The convulsions are accompanied by vomiting, respiratory and vasomotor stimulation. Though regarded as a medullary stimulant, it has little selectivity in site of action.

Picrotoxin acts by blocking *presynaptic* inhibition mediated through GABA. However, it is not a competitive antagonist; does not act on GABA receptor itself, but on a distinct site and prevents Cl^- channel opening (*see* p. 403). Diazepam, which facilitates GABAergic transmission, is the drug of choice for picrotoxin poisoning. Picrotoxin has no therapeutic indication now.

3. Bicuculline This synthetic convulsant has picrotoxin-like actions. It is a competitive $GABA_A$ receptor (intrinsic Cl^- channel receptor) antagonist, while $GABA_B$ receptor (G-protein coupled receptor) is insensitive to it. It is only a research tool.

4. Pentylenetetrazol (PTZ, Metrazol, Leptazol) It is a powerful CNS stimulant, believed to be acting by direct depolarization of central neurones. However, it has also been shown to interfere with GABAergic inhibition—may be acting in a manner analogous to picrotoxin.

Low doses cause excitation, larger doses produce convulsions which are similar in pattern to those caused by picrotoxin. Antagonism of PTZ induced convulsions is an established method of testing anticonvulsant drugs in laboratory animals (*see* Ch. 30).

II. ANALEPTICS (Respiratory stimulants)

These are drugs which stimulate respiration and can have resuscitative value in coma or fainting. They do stimulate respiration in subconvulsive doses, but margin of safety is narrow; the patient may get convulsions while still in coma. Mechanical support to respiration and other measures to improve circulation are more effective and safe.

The role of analeptics in therapeutics is very limited. Situations in which they may be employed are:

(a) As an expedient measure in hypnotic drug poisoning untill mechanical ventilation is instituted.
(b) Suffocation on drowning, acute respiratory insufficiency.
(c) Apnoea in premature infant.
(d) Failure to ventilate spontaneously after general anaesthesia.

However, the overall utility of analeptics is dubious.

Doxapram It acts by promoting excitation of central neurones. At low doses it is more selective for the respiratory centre than other analeptics. Respiration is stimulated through carotid and aortic body chemoreceptors as well. Falling BP rises. Continuous i.v. infusion of doxapram may abolish episodes of apnoea in premature infant not responding to theophylline. Other uses: *see* above.

Dose: 40–80 mg i.m. or i.v.; 0.5–2 mg/kg/hr i.v. infusion.
CAROPRAM 20 mg/ml in 5 ml amp.

Reflex stimulation Smelling ammonia or a drop of alcohol in the nose may be enough for hysterical fainting; analeptics should not be used.

III. PSYCHOSTIMULANTS

These drugs have predominant cortical action; their psychic effects are more prominent than those on medullary vital centres.

1. Amphetamines These are central sympathomimetics. Compared to amphetamine, higher central: peripheral activity ratio is exhibited by dextroamphetamine and methamphetamine. They stimulate mental rather than motor activity; convulsive doses are much higher. Their pharmacology and uses are described in Ch. 9.

2. Methylphenidate It is chemically and pharmacologically similar to amphetamine. Both act primarily by releasing NA and DA in the brain. Both produce increase in mental activity at doses which have little action on other central and peripheral functions. However, it is a CNS stimulant, and high doses can produce convulsions. Methylphenidate is considered superior to amphetamine for attention deficit hyperkinetic disorder (ADHD) because it causes lesser tachycardia and growth retardation. Behaviour and learning ability are improved in 3 out of 4 treated children. It can also be used for concentration and attention defect in adults, and for narcolepsy, but should not be employed to treat depression, dementia, obesity or to keep awake.

Methylphenidate is well absorbed orally, metabolized and excreted in urine, plasma t½ is 4–6 hours, but central effect lasts much longer. Twice daily dosing (morning and afternoon) is enough.

Side effects are anorexia, insomnia, growth retardation, abdominal discomfort and bowel upset.

Dose: Adults 5–10 mg BD; children 0.25 mg/kg/day initially, increased up to 1 mg/kg/day if needed.
RETALIN 5, 10, 20, 30 mg tab.

3. Atomoxetine This is a selective NA reuptake inhibitor, unrelated to amphetamine as well as to imipramine, which does not enhance DA release in the brain, and is neither a CNS stimulant nor an antidepressant. However, it has been found to improve attention span and behaviour in ADHD. It is indicated in children >6 years and in adults with concentration and attention problems.

Atomoxetine is absorbed orally, hydroxylated by CYP2D6 and excreted in urine, mainly as glucuronide. While majority of individuals are extensive metabolizers (EM), few are poor metabolizers (PM) due to polymorphism of CYP2D6. Inhibitors of CYP2D6 like fluoxetine, paroxetine, quinidine increase concentration and toxicity of atomoxetine. It should not be given with MAO inhibitors and is contraindicated in glaucoma.

Dose: 0.5 mg/kg/day in the morning, may be increased upto 1.2 mg/kg/day and split into morning and afternoon doses. Adults 40 mg OD, max 100 mg/day.
ATTENTROL 10, 18, 25, 40 mg caps AXEPTA 18, 25 mg caps.

Atomoxetine is relatively well tolerated, does not produce agitation, seizures, dependene or arrhythmias. Common side effect is dyspepsia, anorexia and other abdominal symptoms. Others are sleep disturbances, mood swings, emotional lability, rarely suicidal thoughts and hepatotoxicity. Growth retardation is possible in children.

4. Modafinil This newer psychostimulant is popular with night-shift (call centre) workers and other professionals who want to improve alertness and keep awake. It is claimed to increase attention span and improve accuracy that has been compromized by fatigue and sleepiness. Although, modafinil has been shown to inhibit NA and DA uptake as well as alter junctional concentration of glutamate and GABA, its actual mechanism of action is not known. The approved indications are day-time sleepiness due to narcolepsy, sleep-apnoea syndrome and shift-work disorder (SWD). It has also been found to reduce euphoria produced by cocaine and to suppress cocaine withdrawal symptoms; is being evaluated as a drug to prevent relapse of cocaine dependence.

The most common side effects are insomnia and headache. Others are nausea, dyspepsia, dizziness, confusion, amnesia, personality disorders, tremors and hypertension. Dependence is a possibility on long-term use.

Modafinil is absorbed within 2–4 hours of oral administration, and is eliminated with a t½ of 15 hours.

Dose: 100–200 mg morning and afternoon for day-time sleepiness due to narcolepsy or sleep-apnoea syndrome; or 200 mg 1 hour before starting night-shift work.
MODALERT, PROVAKE 100, 200 mg tabs.

Armodafinil A congener of modafinil which has been recently approved for improving wakefulness in patients with obstructive sleep apnoea (OSA), SWD and narcolepsy.

5. Pemoline Though chemically unrelated, pemoline has CNS stimulant actions similar to those of methylphenidate. Sympathomimetic and CVS actions are insignificant. Pemoline has been used in ADHD, narcolepsy and excessive day-time sleepiness, with benefits and side effects similar to methylphenidate. However, because of slow onset of action and hepatotoxicity, it has been discontinued in USA, and is not available in India.

6. Cocaine (*see* Ch. 26)

7. Caffeine Out of the three naturally occurring methylxanthines, only caffeine is used as a CNS stimulant. Its pharmacological actions are described in Ch. 16 along with those of theophylline.

Pharmacokinetics Caffeine has poor water solubility; is rapidly but irregularly absorbed after oral administration. It is < 50% bound to plasma proteins, distributed all over the body, and nearly completely metabolized in liver by demethylation and oxidation. Metabolites are excreted in urine; plasma t½ is 3–6 hours in adults.

Adverse effects Toxic effects of caffeine are extensions of its pharmacological actions. Caffeine poisoning is rare, and it is less toxic than theophylline.

Gastric irritation, nausea and vomiting may occur as side effects.

Excitatory and motor effects such as nervousness, insomnia, agitation, muscular twitching, rigidity, rise in body temperature, delirium and convulsions are produced at toxic doses.

Tachycardia, occasionally extrasystoles occur at high doses.

Caffeine is to be avoided in peptic ulcer patients. It is not contraindicated in gout because it is not converted in the body to uric acid. Moderate coffee drinking does not contribute to development of hypertension.

Uses

1. In analgesic mixture: caffeine benefits headache probably by allaying fatigue and boredom. It has no analgesic action of its own.
2. Migraine: Caffeine is used in combination with ergotamine for treatment of migraine attack. It appears to benefit by augmenting constriction of cranial vessels and by enhancing absorption of ergotamine from the g.i.t.
3. Apnoea in premature infants: as alternative to theophylline (*see* Ch. 16).

Caffeine is available only in combined formulations with ergotamine or analgesics in tablets.
CAFERGOT: Caffeine 100 mg + ergotamine 1 mg tab.
MICROPYRIN: Caffeine 20 mg + aspirin 350 mg tab.

Tonics containing caffeine are banned in India.

COGNITION ENHANCERS (Cerebroactive drugs)

These are a heterogenous group of drugs developed for use in dementia and other cerebral disorders. They do elicit pharmacological effects, but widely different mechanisms of action are claimed. Therapeutic benefits are limited, and at the best, short-lasting.

Dementia Refers to acquired global impairment of intellect, memory and personality (cognitive functions) in the absence of gross clouding of consciousness or motor involvement. Memory, capacity to solve problems of day to day living, performance of learned motor skills, social skills and control of emotions are primarily affected.

Alzheimer's disease (AD) A progressive neurodegenerative disorder which affects older individuals and is the most common cause of dementia. It may progress to a totally vegitative state. Atrophy of cortical and subcortical areas is associated with deposition of β-amyloid protein in the form of extracellular senile (amyloid) plaques and formation of intracellular neurofibrillary tangles. These abnormal proteins accumulate mostly due to reduced clearance, but in some cases, due to overproduction, and cause neuronal damage. There

is marked cholinergic deficiency in the brain, though other neurotransmitter systems, especially glutamate and neuropeptide, are also affected.

The indications of cognition enhancers include:

1. Alzheimer's disease (AD) and multi-infarct dementia (MID).
2. Mild cognitive impairment (MCI) or 'common symptoms' of the elderly; dizziness and episodic memory lapses.
3. Mental retardation in children, learning defects, attention deficit disorder.
4. Transient ischaemic attacks (TIAs), cerebrovascular accidents, stroke.
5. Organic psychosyndromes and sequelae of head injury, ECT, brain surgery.

Apart from some cholinergic activators and glutamate antagonist introduced lately, the above therapeutic field is barren and commercially highly profitable. A variety of drugs have been briskly promoted by manufacturers and wishfully prescribed by physicians. The mechanism by which they are believed to act are:

1. Increasing global/regional cerebral blood flow (CBF)
2. Direct support of neuronal metabolism.
3. Enhancement of neurotransmission.
4. Improvement of descrete cerebral functions, e.g. memory.

All cerebroactive drugs are tested for their vasodilator activity. The basic assumption has been that improvement in cerebral circulation is possible, real and therapeutically useful. However, precise measurements have shown that in many cases such claims are merely expectations. In stroke a global vasodilator effect may even be harmful by worsening cerebral edema and inducing 'steal' phenomenon, i.e. diversion of blood flow to non-ischaemic areas to the detriment of ischaemic area. Cerebral blood flow is reduced in AD, but this is probably a consequence of loss of neurones and not its cause.

The cerebroactive drugs may be grouped into:

a. *Cholinergic activators:*
Tacrine, Rivastigmine, Donepezil, Galantamine

b. *Glutamate (NMDA) antagonist:*
Memantine

c. *Miscellaneous cerebroactive drugs:*
Piracetam, Pyritinol (Pyrithioxine), Dihydroergotoxine (Codergocrine), Citicoline, Piribedil, Ginkgo biloba.

1. Cholinergic activators Since brain ACh levels are markedly reduced and cholinergic neurotransmission is the major sufferer in AD, various approaches to augment brain ACh have been tried. Precursor loading with choline or lecithin have failed because there is no shortage of these substrates in the brain. Cholinergic agonists (arecoline, bethanechol, oxotremorine) and conventional anticholinesterases (anti-ChEs) like physostigmine produce symptom improvement, but at the cost of marked peripheral side effects. Over the past two decades 4 cerebroselective antiChEs have been introduced and 3 are widely used in AD.

Tacrine It is the first centrally acting anti-ChE to be introduced for AD. In clinical trials tacrine produced significant improvement in memory, attention, praxis, reason and language. However, it does not alter the course of underlying disease process. Frequent side effects and hepatotoxicity have restricted its use.

Rivastigmine This carbamate derivative of physostigmine inhibits both AChE and BuChE, but is more selective for the G1 isoform of AChE that predominates in certain areas of the brain. Rivastigmine is highly lipid-soluble—enters brain easily. Greater augmentation of cholinergic transmission in brain is obtained with mild peripheral effect. The carbamyl residue introduced by rivastigmine into AChE molecule dissociates slowly resulting in inhibition of cerebral AChE for upto 10 hours despite the 2 hr plasma t½ of the drug.

In clinical trials an average of 3.8 point improvement in Alzheimer's Disease Assessment Scale (ADAS-cog) has been obtained compared to placebo. Other symptoms like apathy, delusions, hallucinations and agitation also improve, but to a lesser extent. Disease progression is briefly slowed or is not affected. Peripheral cholinergic side effects are mild. It has not produced liver damage. Rivastigmine is indicated in mild-to-moderate cases of AD, but not in advanced disease.

Dose: Initially 1.5 mg BD, increase every 2 weeks by 1.5 mg/day upto 6 mg/BD.
EXELON, RIVAMER 1.5, 3, 4.5, 6.0 mg caps.

Donepezil This cerebroselective and reversible anti-AChE produces measurable improvement in several cognitive as well as non-cognitive (activities of daily living) scores in AD, which is maintained at least upto 2 years. The benefit is ascribed to elevation of ACh level in the cortex, especially in the surviving neurones that project from basal forebrain to cerebral cortex and hippocampus. Therapeutic doses produce only weak peripheral AChE inhibition: cholinergic side effects are mild. Because of long t½ (~70 hr), donepezil is administered once daily at bed time; a distinct advantage over rivastigmine and galantamine which need twice daily dosing. Moreover, it can be used even in relatively severe case of AD. Donepezil is generally well tolerated and is not hepatotoxic.
Dose: 5 mg OD HS (max 10 mg OD);
DONECEPT, DOPEZIL, DORENT 5, 10 mg tabs.
Oral dispersible tablets of donepezil have also been approved for the benefit of patients who have problem in swallowing the regular tablet.

Galantamine It is a natural alkaloid which selectively inhibits cerebral AChE and has some direct agonistic action on nicotinic receptors as well. Galantamine has produced cognitive and behavioural benefits in AD which are comparable to rivastigmine and donepezil. It is well tolerated, but needs twice daily dosing.
Dose: 4 mg BD (max 12 mg BD)
GALAMER 4, 8, 12 mg tabs.

There is now firm evidence that rivastigmine, donepezil and galantamine afford similar, but modest symptomatic benefit in AD. Cognitive decline is slowed or halted for a short time, but not prevented. Their side effects, mostly g.i. smptoms, muscle pain and weird dreams, are also comparable among the three. There is now some evidence to support their use in MCI and non-Alzheimer dementia as well.

2. Memantine This new NMDA receptor antagonist, related to amantadine (that is also a NMDA antagonist), has been found to slow the functional decline in moderate-to-severe AD, but benefit in milder disease are unclear. It appears to block excitotoxicity of the transmitter glutamate in a noncompetitive and use-dependent manner. Beneficial effects have also been noted in parkinsonism.

Memantine is better tolerated than anti-AChEs used in AD. Side effects are constipation, tiredness, headache, dizziness, and drowsiness. It is indicated in moderate-to-severe AD, either to replace anti-AChEs or to supplement them. Memantine can be used for other types of dementia as well.
Dose: Initially 5 mg OD, increase gradually upto 10 mg BD; stop if no clinical benefit in 6 months.
ADMENTA, MENTADEM 5, 10 mg tabs, ALMANTIN 5 mg tab.

3. Piracetam This cyclic GABA derivative has no GABA-like activity and has been called 'nootropic' meaning a drug that selectively improves efficiency of higher telencephalic integrative activities.

Piracetam is not a vasodilator, does not affect total/regional CBF, but may reduce blood viscosity. In India and some other countries it has been promoted for cognitive impairment and dementia in the elderly as well as for mental retardation in children for over 30 years. However, a Cochrane Database review (2004) has concluded that published data does not support such use. Some later studies have demonstrated a neuroprotective effect of piracetam during coronary bypass surgery, and that it may benefit cognitive disorders of cerebrovascular and traumatic origin. In the UK, it is approved for adjunctive treatment of cortical myoclonus, but is not recommended for children. It is not approved in the USA.

Side effects are minor: gastric discomfort, nervousness, excitement, insomnia, dizziness and skin rash.
Dose: 0.8–1 g TDS oral; children 20 mg/kg BD–TDS; 1–3 g i.m. 6 hourly in stroke/head injury.
NORMABRAIN, NEUROCETAM, NOOTROPIL 400, 800 mg cap, 500 mg/5 ml syr., 300 mg/ml inj.

4. Pyritinol (Pyrithioxine) Pyritinol consists of two pyridoxine molecules joined through a disulfide bridge, but has no vit B_6 activity. It is claimed to activate cerebral metabolism by selectively increasing glucose transport across blood-brain barrier and improving regional blood flow in ischaemic brain areas. It has been promoted for:

- Sequelae of cerebrovascular accidents, head injury, prolonged anaesthesia.
- Infants and children with developmental disorders of CNS, delayed milestones.
- Concentration and memory defects, senility, organic brain syndromes.

However, therapeutic benefit, if any, is uncertain.

ENCEPHABOL 100, 200 mg tab. 100 mg/5 ml suspension; 200 mg dry powder with 2 ml solvent for i.v. infusion.

Dose: 100–200 mg TDS, children 50–100 mg TDS orally; 200–400 mg every 4–6 hours (max. 1 g/day) has been given i.v. for recovery from cerebral hypoxia due to cardiac arrest, anaesthesia, brain operations and stroke.

Side effects: Only mild g.i. upset was noted initially. Later skin rashes, itching and taste disturbances (attributable to the disulfide moiety) have been reported. It has been withdrawn in some countries.

5. Dihydroergotoxine (Codergocrine): It is a semi-synthetic ergot alkaloid having α adrenergic blocking property; claimed to increase cerebral blood flow selectively. It is believed to act by protecting altered brain metabolism. In a dose of 1.0–1.5 mg TDS oral/sublingual or 0.3 mg i.m. OD, it has been recommended for MCI and dementia, but therapeutic valve is not established.

HYDERGINE 1 mg tab, 0.3 mg/ml inj. CERELOID 1 mg tab.

Side effects: flushing, headache, nasal congestion, postural hypotension, g.i. disturbances and rashes.

6. Piribedil: It is a dopaminergic agonist claimed to improve memory, concentration, vigilance, giddiness and tinnitus in the elderly due to circulatory insufficiency, but benefit is unsubstantiated. Minor efficacy in parkinsonism has also been reported. Side effects are mild g.i. complaints.

Dose: 50 mg OD, BD; TRIVASTAL LA 50 mg tab.

7. Citicoline It is a compound derived from choline and cytidine, that is involved in biosynthesis of lecithin. Citicoline is believed to improve cerebral function by increasing blood flow to the brain and enhancing cerebral metabolism. Some studies have demonstrated short-term improvement in memory and behaviour in cerebrovascular disorders, but there is little evidence of clear-cut benefit. In the absence of effective medicines and under promotional pressure, citicoline is being commonly prescribed for impaired brain function due to ischaemic stroke, parkinsonism, head injury, etc.

Dose: 0.5–1 g/day i.m. or i.v. inj, 200–600 mg/day oral in divided doses.

CITILIN, CITINOVA 500 mg tab, 500 mg/2 ml inj, STROLIN 500 mg tab.

8. Ginkgo biloba The dried extract of this Chinese plant contains a mixture of ginkgoflavon glycosides (e.g. ginkgolide B) which have PAF antagonistic action. Since PAF has been implicated in cerebral thrombosis and infarcts, it is professed that *G. biloba* will prevent cerebral impairment in cerebrovascular insufficiency. It has been promoted for a variety of cognitive and behavioural disorders in the elderly, but a Cochrane metaanalysis (2007) concluded that *G. biloba* produced slight overall improvement in cognitive performance. However, most trials were small and results were inconsistant.

Side effects are mild upper g.i.t. symptoms, and increased risk of bleeding.

Dose: 40–80 mg TDS for a minimum period of 4 weeks; GINKOCER, BILOVAS, GINKOBA 40 mg tab.

☞ PROBLEM DIRECTED STUDY

35.1 A 75-year-old man was brought with a history of progressive functional decline, so much so that he now needs to be looked-after all the time. He misplaces his daily need articles, forgets what he said few minutes ago, is unable to perform simple calculations, mixes up what happened today and what happened yesterday, has poor control of emotions, but vision, hearing and other sensations are well preserved, and there is no gross ataxia. He was diagnosed to be having moderately advanced Alzheimer's disease and was prescribed Tab Donepezil 5 mg at bed time daily. After one week, his son reported that while his mental and functional state is unchanged, he has developed pain in abdomen, muscle ache, loud eructations, loose motion and is refusing to take the medicine.

(a) What could be the reason for no improvement in the mental and functional state of the patient? Are the new symptoms due to the medication? Should the drug be stopped, changed or another one added at this stage? What alternative drug could be used?

(see Appendix-1 for solution)