Lecture Note

Subject: HAP, 404T,
SEM-4th UNIT-IV
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DRUGS USED IN EPILEPSY

Epilepsy is a common neurological problem affecting about 0.5% of the population, the aetiology being unknown in most of the patients. An epileptic seizure or *'fit'* is caused by an episodic brief unphysiological synchronous high frequency discharge of impulses by a group of neurones in the brain. The abnormal local discharge may then spread to other areas of the brain. The locus of the primary abnormal neuronal discharge and the extent of its spread determines the nature of the symptoms. The abnormal electrical activity during a seizure can be recorded by an electroencephalograph (EEG), and the different types of seizures can be recognized on the basis of the locus, nature and spread of the abnormal discharge.

Epilepsy can be *categorized* into

(a) **Partial (focal) seizures.** The symptoms of these seizures depend upon the site of excessive neuronal discharge and the extent to which the abnormal electrical activity spreads to other brain neurones. Though initially localized, the seizures may later progress and intensify to become generalized tonic-clonic seizures.

(i) *Simple partial seizures.* Abnormal electrical activity is confined to a localized area of motor cortex so that the seizures are limited to one limb or a group of muscles controlled by that particular brain region. There is some sensory disturbance but no loss of consciousness. Also known as **Jacksonian epilepsy**. These seizures can occur at any age.

(ii) *Complex partial seizures* (psychomotor or temporal lobe epilepsy). There is complex sensory hallucinations, bizarre behaviour and loss of consciousness. Motor movements may be repetitive in nature (stereotypy). Incidence is usually below the age of 20 years.

(b) **Generalized seizures.** These seizures involve abnormal electrical discharge throughout both hemispheres. Though the seizures may be

convulsive or nonconvulsive, there is usually an *immediate loss of consciousness.*

(i) *Tonic-clonic* (**grand mal**) *seizures.* Commonest type of epilepsy. There is loss of consciousness followed by tonic, and then clonic, phases. The seizure is followed by a postictal period of confusion, muscle weakness and exhaustion.

(ii) *Absence* (**petit mal**) *seizures.* There is a brief, abrupt and self-limiting loss of consciousness, but no convulsions. The patient is usually prepubertal and exhibits vacant stare with rapid eye-blinking lasting for a few seconds.

(iii) *Myoclonic seizures.* These seizures consist of short episodic convulsions, which may reoccur after a few minutes. They may occur at any age and are usually due to underlying permanent neurologic damage.

(iv) *Febrile seizures.* Young children may exhibit convulsions concomitant with hyperpyrexia. They are of tonic-clonic type and are of short duration. They do not cause any neurologic damage and rarely require medication.

(v) *Status epilepticus.* These are rapid recurrent grand mal seizures. This is an emergency condition requiring immediate treatment.

1. Classification of antiepileptic drugs

Antiepileptic agents are conveniently classified according to their clinical use:

A. *Drugs used in partial seizures*

Phenytoin, and congeners, mephenytoin, ethotoin and phenacemide, **carbamazepine** and oxcarbazine, **phenobarbitone, primidone,** vigabatrin, lamotrigine, felbamate, gabapentin, topiramate, tiagabine, zonisamide, levetiracetam.

B. *Drugs used in generalized seizures*

(a) For tonic-clonic (grand mal) seizures: same rugs as used for partial seizures, **sodium alproate**

(b) For absence (petit mal) seizures: **hosuximide** and congeners phensuximide and thsuximide, **sodium valproate, trimethadione** congeners paramethadione and dimethadione, **clonazepam, clobazam, lamotrigine, ace zolamide** (as adjunct), topiramide

(c) For myoclonic seizures: **Sodium valpro clonazepam,** felbamate

(d) For infantile seizures (febri **Phenobarbitone,** primidone, clonazepam, AC had been used in non-febrile infantile seizures

C. *Drugs used in status epilepticus*

Diazepam (i.v.), lorazepam (i.v.), **phenyto** (i.v.), phenobarbitone (i.v.)

2. Mechanism of action

The mechanisms involved in antiepileptic d action are poorly understood. Basically, t mechanisms are likely to be involved, **stabiliz effect on excitable cell membranes** and re increase in seizure threshold, and **inhibition of spread of the seizure activity** by blocking synap transmission at some point. Thus, drugs which red Na^+ conductance and reduce Ca^{2+} influx w attenuate action potential generation in excitable and increase seizure threshold. The inhibition spread of the seizure activity may be mediat through an increase in the activity of the inhibit neurotransmitters like *GABA*, and possibly glyc Recent evidence suggests that inhibition of excita neurotransmitter (mainly *glutamate*) activity m also be responsible for attenuation of spread seizure activity. The role of catecholamin (noradrenaline and dopamine) and 5-HT are uncl However, phenytoin and some other antiepileptics known to inhibit release of noradrenaline and 5-H and promote the uptake of dopamine. The li mechanisms involved in antiepileptic drug action given in Table 8.12.

3. Pharmacokinetics

The parmacokinetic data of commonly antiepileptics are summarized in Table 8.10.

4. Therapeutic uses

The drugs of choice and their alternati the treatment of different types of epilepsy given in Table 8.11. The following guideli adopted to initiate and maintain therapy:

(a) Treatment should be **initiated w**

	Pharmacokinetic data
Phenobarbitone	Well absorbed from gut. *75% metabolized* in live rest excreted unchanged alkaline urine
Primidone	Well absorbed from gut. phenobarbitone
Phenytoin	Well absorbed from gut. *Metabolized* in liver by Rate of inactivation follo Genetic variations in rate
Carbamazepine	Well absorbed from gut. Initial half-life reduced o 30 to 15 hours due to enz Metabolites are also activ
Valproic acid	Well absorbed from gut. conjugate in urine. *90%* p
Ethosuximide	Well absorbed from gut. *bound*. Excreted in urine
Clonazepam	Gut absorption slow, errati
Clobazam	protein. Renal excretion of

drug, with careful monitoring of dosage. saliva or plasma drug concentrations assessed to ensure adequate the concentrations of

Partial simple	Phenytoin, carbamazepine	Phenobarbitone, primidone,
Partial complex	Phenytoin, carbamazepine	Gabapentin, vigabatrin, lamotrigine
Grand mal	Phenytoin, carbamazepine	Primidone
Petit mal	Ethosuximide, sodium valproate	Phenobarbitone, primidone, vigabatrin, lamotrigine, gabapentin
Myoclonic	Sodium valproate, clonazepam, clobazam	Clonazepam, clobazam, lamotrigine
Infantile febrile seizures	Phenobarbitone, clonazepam	Phenytoin, zonisamide
Status epilepticus	Diazepam, lorazepam, phenytoin	Primidone
		Phenobarbitone

5. Adverse reactions

All antiepileptic agents produce unwanted effects, particularly because of long term use. Individual adverse effects are given in Table. 8.12.

Pregnancy, lactation and antiepileptic drugs: All the antiepileptic agents used *cross the placental barrier* and are *excreted in mother's milk.* Antiepileptics, particularly phenobarbitone and phenytoin, have been implicated in causation of cleft palate, hare lip and cardiac malformations. *Folate deficiency* induced by phenobarbitone, and phenytoin, have been implicated in causation of cleft palate, hare lip and cardiac malformations. Folate deficiency induced by phenobarbitone, phenytoin, sodium valproate, and to a lesser extent carbamazepine, is held responsible for spina bifida. As such, *folate supplements* are essential. **Carbamazepine** appears to be the **safest** drug in epileptics **in the child bearing age** (*see* Chapter 16).

Phenobarbitone induces sedation, hypotonis and suckling defects in breastfed infants, a feature also noted with clonazepam. New born babies and breastfed infants of mothers on antiepileptic therapy, sometimes show reduction in vitamin K-sensitive clotting factors.

. Drug interactions

Most of the clinically relevant adverse drug-rug interactions between antiepileptics and other rugs are due to their pharmacokinetic properties. hus, they may **induce displacement** of other drugs from plasma protein binding sites, or **inhibit microsomal enzymes** and increase the t of other drugs, and often their own me well. Important drug interactions are gi 8.13.

7. Newer antiepileptic agents

(a) **Vigabatrin.** This drug (gam GABA) is an *irreversible inhibitor* o *aminotransferase* (GABA-T), the major responsible for GABA inactivation. A increasing GABA levels at synaptic sites, also potentiates GABA action by inhib GABA transporter. It is well absorbed follo administration and half-life is 6-8 ho minimally plasma protein bound and is e kidneys. It is *useful in treatment of parti* and to some extent in grand mal and seizures. Dosage is 500 mg twice daily, to a total daily dose of 2-3 g. *Toxicit* drowsiness, dizziness and weight gain, agitation, mental confusion and psyc existing mental disease is a major *contra* Long term use has been associated defects.

(b) **Lamotrigine.** Its actions *resem phenytoin* and the drug has some antifol well. It is well absorbed on oral adm moderately protein bound and e glucuronide conjugate by kidney. Ha hours and daily doses range between 10

hypersensitivity related skin rashes.

(c) **Gabapentin.** This drug, a *GABA analogue* does not act directly on GABA but increases synaptic GABA activity by its release and by inhibiting GABA It is fairly well absorbed after oral is not metabolized and excreted in urine. Half-life ranges between 5 to 8 has, therefore, to be administered 2-3 total dose being 2400 mg/day. It is *partial and grand mal seizures*, and *in neuropathic pain*. Adverse effects drowsiness, dizziness, tremors and ataxia.

(d) **Felbamate.** Its mechanism of action is but is *believed to block NMDA receptors via binding site*. It is absorbed orally and half-life of 20 hours. It is excreted mainly in form, and to some extent as conjugates, It increases plasma levels of phenytoin and valproate, but decreases that of mazepine. Felbamate is *effective mainly in seizures*. Adverse effects like aplastic and hepatitis limit its use.

Topiramate. It differs from other leptic agents being a substituted saccharide. It *appears to have multiple* including blockade of voltage-gated sodium potentiation of GABA activity and of kainate effect on AMPA receptors. The rapidly absorbed, minimally protein bound derately metabolized. Primary excretion is neys and half-life is 20-30 hours. It is *against partial and grand mal seizures*, but have an effect on absence seizures. anges from 200 to 600 mg/day. *Adverse* include drowsiness, dizziness, mental anxiety, paraesthesia, congnitive slowing

a half-life of 5-8 h
faeces and through u
as an adjunct drug
ranging from 16 mg
Adverse effects in
tremors, ataxia, me
rarely, psychosis an

(g) **Zonisamide**
which appears to *ac*
and calcium channe
partial and grand
in infantile seizur
absorbed, minima
excreted, with a ha
from 100 to 600 m
drowsiness, ataxia

(h) **Levetirace**
agent) analogue
unclear. Compl
administration,
excretion via urine
life is 6-8 hours
1000 mg twice
drowsiness, ataxia
in partial seizures

8. Treatment of s

Status epilep
The drugs used
treatment is instit
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given concurrentl
mg/min, maxi
Diazepam has
anticonvulsant
onset but sustai
persist, the i.v.
to 100 mg/min,
these drugs in
hypotension, ad

8.13.

7. Newer antiepileptic agents

(a) **Vigabatrin.** This drug (gamma-vinyl GABA) is an *irreversible inhibitor of GABA aminotransferase* (GABA-T), the major enzyme responsible for GABA inactivation. Apart from increasing GABA levels at synaptic sites, vigabatrin also potentiates GABA action by inhibiting GABA transporter. It is well absorbed following oral administration and half-life is 6-8 hours. It is minimally plasma protein bound and is excreted by kidneys. It is *useful in treatment of partial seizures* and to some extent in grand mal and infantile seizures. Dosage is 500 mg twice daily, increasing to a total daily dose of 2-3 g. *Toxicity* includes drowsiness, dizziness and weight gain, and rarely agitation, mental confusion and psychosis. Pre-existing mental disease is a major *contraindication*. Long term use has been associated with visual defects.

(b) **Lamotrigine.** Its actions *resembles that of phenytoin* and the drug has some antifolate action as well. It is well absorbed on oral administration, moderately protein bound and excreted as glucuronide conjugate by kidney. Half-life is 24 hours and daily doses range between 100 to 300 mg

is well absorbed after oral administration with nearly 100% bioavailability. It is highly protein bound with a half-life of 5-8 hours. Excretion is mainly via faeces and through urine. Tiagabine has been *used as an adjunct drug for partial seizures* in doses ranging from 16 mg to 56 mg/day in divided doses. *Adverse effects* include drowsiness, dizziness, tremors, ataxia, mental confusion, depression, and rarely, psychosis and skin rashes.

(g) **Zonisamide.** It is a sulphonamide derivative which appears to *act mainly on voltage gate sodium and calcium channels*. The drug is *effective against partial and grand mal seizures*, and also finds use in infantile seizures and myoclonus. It is well absorbed, minimally protein bound and renally excreted, with a half-life of 1-3 days. Doses range from 100 to 600 mg/day. *Adverse effects* include drowsiness, ataxia and congnitive impairment.

(h) **Levetiracetam.** It is a piracetam (nootropic agent) analogue whose mode of action remains unclear. Complete absorption after oral administration, minimal protein binding and excretion via urine mainly in unchanged form. Half-life is 6-8 hours and dosage ranges from 500 to 1000 mg twice daily. Adverse effects include drowsiness, ataxia, and asthenia. It is *used mainly in partial seizures.*

8. Treatment of status epilepticus

Status epilepticus is an **emergency condition**. The drugs used are given in Table 8.11. Drug treatment is instituted with **i.v. diazepam infusion** (2 mg/min, maximum dose given is 20 mg in adults) given concurrently with **phenytoin i.v. infusion** (50 mg/min, maximum dose 1000 mg in adults). Diazepam has rapid onset and short duration of anticonvulsant effect, while phenytoin has slow onset but sustained duration of action. If seizures persist, the i.v. dose of phenytoin can be increased to 100 mg/min, maximum dose 1500 mg. Since these drugs induce respiratory depression and hypotension, adequate measures have to be taken for **cardio-respiratory support**. EEG monitoring

Valproic acid	Well absorbed from gut. Excreted as glucuronide conjugate in urine. *90%* plasma protein *bound.*	
Ethosuximide	Well absorbed from gut. *Extensively* plasma protein *bound.* Excreted in urine as conjugates.	
Clonazepam	Gut absorption slow, erratic. *Moderate binding* to plasma protein. Renal excretion of conjugated metabolites.	Clon
Clobazam		Clo

drug, with careful monitoring of dosage. If possible, saliva or plasma drug concentrations should be assessed to ensure adequate therapeutic concentrations of the drug, and the dose is adjusted accordingly. Or else, the maximum tolerated dose of drug should be established.

(b) A **second drug is added** to the regimen if ures are not controlled despite maintaining uate therapeutic serum concentrations of first or if the first drug induces unacceptable adverse in the given dose. Addition of the second drug ake it possible to reduce the dose, and hence erse effects of the first drug.

Abrupt withdrawal of a given drug can ate seizures and even status epilepticus. **ithdrawal has to be gradual.**

If seizures are not controlled by a drug even after 3-4 months of use, the drug g combination is withdrawn and substituted r drug from a different chemical group.

Alternative drug controlled.

(e) Drugs are **daily doses.** Susta given once daily.

(f) **Dose incr** gradually at inte maximal tolerate plasma levels in concentrations hav

(g) **Plasma o monitoring** is desi renal disease, in o sodium valproate is

(h) **Withdrawa** *least 2 years after* should be slow over If there is relapse, for 2-3 years.

Table 8.12
Conventional antiepileptic agents: mechanism of action, uses and adverse effects

Drug	*Mechanism of action*	*Clinical use*	*Adverse effects*
Phenobarbitone and Primidone	Primidone is biotransformed into phenobarbitone. Reduce seizure discharge. Action unclear but inhibits sodium and calcium conductance, inhibits glutamate effect on AMPA receptors and enchance GABA effect on chloride channels	All types except absence seizures (may worsen)	See under barbiturates
Phenytoin	Inhibits spread of seizure discharge. Action unclear but known to affect sodium, calcium and potassium conductance, facilitate GABA activity and stabilize neuronal membranes. Blocks high-frequency repetitive firing of action potentials (post-tetanic potentiation) by blocking sodium channels.	All types except absence seizures	**Gum hyperplasia**, **nystagmus**, **folate deficiency**, osteomalacia, coarsening of facial features, skin rashes
Carbamazepine	Similar to phenytoin	Like phenytoin. Trigeminal neuralgia, mania	Ataxia, **diplopia**, **folate deficiency**, hepatic and idiosyncratic blood
Sodium valproate	Increases GABA by increased synthesis (stimulates glutamic acid decarboxylase) and reduced metabolism (inhibits GABA-T). May increase potassium conductance	Absence seizures. Grand mal, mixed grand mal-petit mal seizures	Commonly **gastro** complaints, alopecia, defects, hepatotoxicity, acute pancreatitis, **e** defects
Ethosuximide	Unclear. Reduces calcium conductance, inhibits Na^+/K^+ ATPase and GABA-T	Absence seizures	Gastric distress, **e** hallucinations, anxiety, **hypersensitivity reac** rashes, lupus, pancyto
Trimethadione	Active metabolite, dimethadione, acts like ethosuximide	Limited use in absence seizures	Sedation, **glare effect**, idiosyncratic dermatitis, pancytopenia, **nephro** syndrome
Clonazepam and clobazam	See under benzodiazepines	All types	*See* under benzodiaz

during pregnancy because of virtual absence of teratogenicity.

If seizures are not controlled, phenobarbitone (100-200 mg i.v.), *general anaesthesia*, preferably with *ether* (neuromuscular block), may be required. *paraldehyde* may be chosen where resuscitative facilities are not available, because it induces minimal respiratory depression and hypotension.

II. DRUGS USED IN PARKINSONISM OTHER MOVEMENT DISORDERS

A. DRUGS USED IN PARKINSONISM

Parkinson's disease is a progressive d movement due to degeneration of nig dopaminergic

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UNIT-V

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- Hexafluorenium prolongs the action of succinylcholine.
- Ca^{++} channel blockers prolong the action of both types of neuromuscular blockers.

☞ **Antagonism**

AntichE agents like neostigmine edrophonium are used to reverse the action of nondepolarizing blockers (*See* "Some therapeutic problems"). In the presence of prolonged acidosis it is difficult to reverse the action of nondepolarizing agents by antichE agents.

MORPHINE, OTHER OPIOID ANALGESICS AND OPIOID ANTAGONISTS

☞ **Morphine** is a high efficacy opioid analgesic used most commonly for analgesic and nonanalgesic purposes and it is obtained from opium.

☞ **Opium** is dried juice obtained from the unripe seed capsule of *Papaver somniferum*.

☞ Chemially opium contains two types of alkaloids :

1. **Phenanthrenes**

   Morphine 10-15%

   Codeine 0.5%

   Thebaine 0.2% (weak analgesic, potent convulsant not used clinically)

2. **Benzylisoquinolines**

   Papaverine 1% – Generalized smooth muscle relaxant, noncompetitive antagonist of histamine, ACh and 5HT with restricted therapeutic uses.

   Noscapine 6% used as **antitussive.**

☞ **Heterogenecity of opioid receptors :**

Atleast there are three opioid receptors in the central nervous system. Those are mu (μ), kappa (κ) and delta (δ) receptors. Each category has got two subtypes.

Mu (μ) receptor stimulation causes analgesia, respiratory depression, miosis, reduced gastrointestinal motility and euphoria.

Kappa (κ) receptor stimulation by agonist produces analgesia, dysphoria and psychomimetic effects.

Agonists and antagonists of opioid receptors :

- Morphine and Fentanyl are agonists of all types of opioid receptors.
- Pentazocine, Butorphanol and Nalbuphine are antagonists of mu (μ) receptor and agonists of kappa (κ) receptor respectively.
- Naloxone and Naltrexone and antagonists of all opioid receptors.
- Nalorphine is antagonist of mu (μ) receptor and agonist of kappa (κ) receptor (less than pentazocine).

☞ **Endogenous opioid peptides :**

Endorphins – Synthesized from large precursor molecule.

Enkephalins – Derived from proenkephalin A in adrenal cortex.

Dynorphins – Derived from proenkephalin B.

These peptides are chemically unrelated to morphine but they bind to and act via same opioid receptor.

☞ **Classes of narcotic analgesics :**

Natural
Morphine
Codeine

Semisynthetic derivatives
Metopon, Oxymorphone, Hydromorphone
Hydrocodeine, Dihydrocodeine
Buprenorphine (Thebaine derivative also partial mu(μ) ag

Synthetic
Meperidine (Pethidine)
Alfentanil
Methadone

Derivatives
Fentanyl, Sufentanil

Opioid with mixed action (Agonist - Antagonist/partial agonist)
Pentazocine, Cyclazocine, Nalorphine, Nalbuphine, Buprenorphine, Butorphanol, Metazinol, Dizocine.

☞ **Summary of pharmacological actions of Morphine :**

Central actions : On central nervous system morphine has got depressant and stimulant acti

* Depressant actions lead to analgesia, sleep, depression of respiration, vasomotor centre, temperature regulating centre and cough centre.
* Mood changes leading to euphoria or dysphoria
* Drug dependence
* Increased release of ADH and decreased release of ACTH, FSH and LH.

Stimulant actions lead to vomiting d to CTZ stimulation, miosis due to stimulation of Edinger Westphal nuc

Peripheral action : Vasodilation, reduction in peripheral resistance and hypotension
Histamine release
Bronchoconstriction
Increased smooth muscle tone and constipation
(*See* - "Some therapeutic problems")
Spasm of biliary tract

Mechanism of analgesic action :

Morphine is a potent narcotic analgesic. It relieves dull, continuous poorly localised pain be than sharp intermittent pain, which is relieved only in higher doses.

Morphine acts at supraspinal regions in midbrain, limbic system and cortex through mu receptors (specially mu_1) and at spinal region through kappa (κ) receptors and produces analg effect by following ways :

1. Reduces the emotional reactions (i.e. apprehension, fear, autonomic effects) to pain.
2. Elevates pain threshold and thereby reduces the perception of pain.
3. Induces sleep, which itself may raise the pain threshold.
4. Causes euphoria, which may contribute to its analgesic effect.
5. The patient's ability to tolerate pain is markedly increased, because pain no longer produ anxiety and fear.

6. In the spinal region, morphine acts on the substantia gelatinosa of the spinal cord and inhibits the release of excitatory transmitter from primary afferents carrying pain impulses and thus prevents entry of peripheral pain signals to CNS.

Therapeutic uses :

1. Severe painful condition associated with shock like burn
2. Myocardial infarction*
3. Pain of terminal illness (Cancer)

   The usual starting dose is 5–10 mg 4 hrly by oral route. Patients develop gradual tolerance. Some patients require a doubling of their dose as often as every 1–2 weeks.
4. Circulatory shock, accidents etc. to relieve anxiety.
5. Pulmonary oedema to relieve dyspnoea – Morphine causes reduction of preload and afterload, relieves anxiety and decreases sensitivity of respiratory centres to stimuli from congested lungs (**non analgesic use**).
6. Preanaesthetic medication, postoperative pain.
7. Tetanus – To combat sympathetic overactivity morphine is a suitable alternative of combined beta and alpha adrenergic blocking agent.

Contraindications :

1. Head injury
   - Increased respiratory depression
   - Increased intracranial pressure
   - Cerebral and spinal ischemic effects may aggravate
   - Judgement of clinical improvement becomes obscure because of miotic and vomiting effects of morphine
2. Bronchial asthma (*See* – "Some therapeutic problems")
3. Extremes of age :

   Old age
   - Central nervous system depressant action of morphine is prominent in old age due to increased sensitivity.

   Neonates
   - Incomplete BBB
   - Reduced metabolic process
4. Undiagnosed abdominal pain : Morphine may complicate clinical assessment.

Preparations and dosage :

1. Morphine sulfate inj

   S.C./I.M. – 10-20 mg for adult

   I.V. – 2.5 -10 mg for adult

Morphine salts are also used by oral, buccal, sublingual and rectal routes. Sustained formulations for oral and I.V. administration are also available.

2. Morphine sulfate tablets 10-30 mg for an adult

   0.1–0.15 mg/kg of body wt for a child.

☞ **Codeine** is available as codeine sulfate and codeine phosphate. For greater analgesic activity it is given with aspirin or acetaminophen (Paracetamol). Usual analgesic dose is 30–60 mg 4–6 hrly whereas cough suppressant dose is 15–30 mg/oral 4–6 hrly. For analgesic purpose high oral parenteral potency ratio (2 : 3) in comparison with that of morphine (1 : 6) and respect it has definite advantages over morphine. Its antitussive action probably involves receptors that bind codeine itself.

☞ **Meperidine** *(Pethidine)* : It is a synthetic opioid and binds to opioid receptors, particularly receptors. In general 75-100 mg of pethidine hydrocholoride inj parenterally is appro equivalent to 10 mg of morphine sulfate. It is available as pethidine hydrochloride inj., given S/C and I.V. Usual dose 75-100 mg I.V.

Meperidine differs from morphine in certain respects which are as follows : –

- Unlike morphine, in therapeutic doses meperidine does not delay the birth process.
- Has less respiratory depressant action in the neonates.
- Has less spasmogenic effects and better oral efficacy.
- Usually does not suppress cough.
- Has got little hypnotic action.
- Does not constipate.
- Has shorter duration of analgesic action.

☞ **Meperidine congeners** are

1. Diphenoxylate, Loperamide – These two as non analgesic doses slow gastrointestinal with definite constipating action, used in the treatment of diarrhoea (non specific antidia agents).
2. Fentanyl – 100 times more potent than morphine

   Sufentanil – 1000 times more potent that morphine with bradycardiac action

   Alfentanil – has got positive inotropic action.

   These are particularly used during and after surgery for anaesthesia and to relieve post op pain respectively.

☞ **Pentazocine :** It appears to be either a weaker antagonist or a partial agonist at mu receptors powerful agonist at kappa receptors. Its pharmacological action on CNS is generally simillar of morphine with the follow differences :

- In contrast to morphine (hypotension, bradycardia) in high dose it raises B.P. and tachycardia.
- In patients with coronary arterial diseases I.V. pentazocine increases cardiac work beca elevation of mean aortic pressure, left ventricular end-diastolic pressure and mean pulm artery pressure (due to increased plasma catecholamine conc.), so pentazocine is better avoided in cardiovascular diseases.
- In opioid dependence pentazocine induces withdrawl syndrome. Psychomimetic effec more than morphine.
- Dependence liability, respiratory depression, sedation and constipation are less than morp

Pentazocine can be administered both orally and parenterally (oral dose 25-100 mg 3-4 hrly I.M. inj 30-60 mg 3-4 hrly). A tablet preparation containi and 0.5 m naloxone is available. This oral tablet wil

in that case naloxone will produce aversive response. But this aversive response of naloxone will not occur when it is used orally because in that case naloxone will be detoxified by liver during first pass effect.

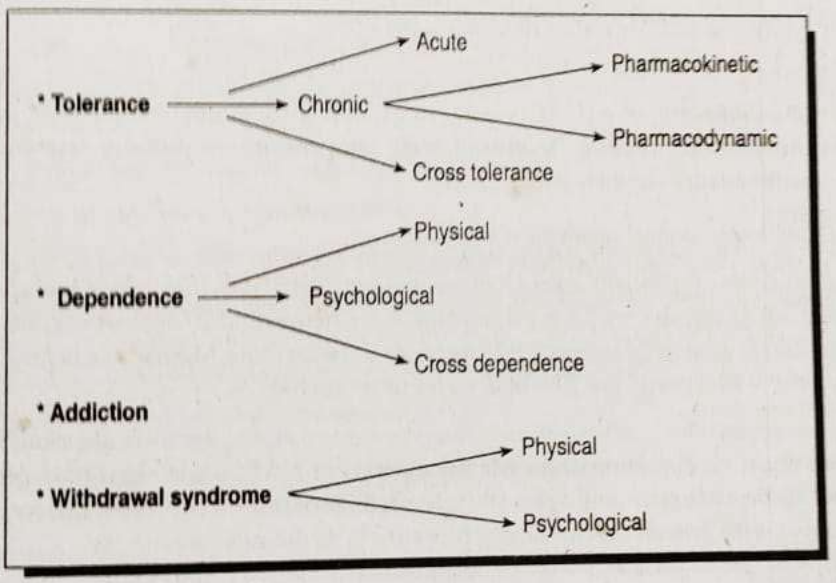
☞ **Nefopam :** It is an example of non opioid and non NSAID analgesic, useful for treatment of moderate pain in opioid addict. It does not cause constipation and respiratory depression. It is more potent analgesic than NSAID.

☞ **Drug abuse :** Drug abuse means the use of psychotropic substancs (stimulants and depressants) in excessive way that would constitute a public health and social problems.

Classes of drugs causing abuse :

1. Opioids (Morphine, Heroin and Meperidine)
2. Cannabis (THC)
3. Depressants (Alcohol and Barbiturates)
4. Psychodelics (LSD)
5. Arylcyclohexylamines
6. Nicotine
7. Stimulants (Amphetamine, Cocaine)
8. Caffeine
9. Solvents (Paint - thinner)

In connection with drug abuse following terms are important :



☞ Physical dependence means physical illness if the drug is withdrawn.

☞ Psychological dependence means the emotional distress when the drug is withdrawn. It appears first.

☞ Both psychological and physical dependence can co-exist.

☞ Psychological dependence may not be associated with physical dependence.

☞ **Addiction :** It is "behavioral pattern of drug abuse characterised by overwhelming involvement with the use of a drug, the securing of its supply and a high tendency to relapse after withdrawal". Addict may not be physically dependent. Under some special circumstances patients can be physically dependent on narcotics but not addicted.

Drugs	Physical	Psychological	Withdrawal syndrome
Narcotics	++++	++++	++++
Alcohol	++++	+++	++++
Phenobarbital	++++	+++	+
Amphetamine	+	+++	+
Cocaine	+	++	—
LSD	—	++	+
Nicotine	++	+	+
Caffeine	+		

+, ++, +++, ++++ = Increasingly more powerful

— = No evidence

☞ **Opiate abstinence syndrome :**

Onset of syndrome 5–15 hrs after the last dose

Peak of syndrome 36–72 hrs after discontinuation

Offset of syndrome 5–8 days

Syndrome manifestations include nausea, diarrhoea, lacrimation, rhinorrhoea, profuse sw... piloerection, muscle twitching; increased body temperature, respiratory rate and B.P.; ins... yawning with intense drug craving.

Treatment of the withdrawal syndrome (Detoxication):

- Readministration of sufficient opioid like methadone on first day, (***See*** "Some therapeutic proble... 1 mg methadone equates with 3 mg morphine, 1 mg heroin and 20 mg meperidine. The drug is ... tolerated and is used in dosage of 10–25 mg once or twice daily. Methadone is gradually with... usually over 5–10 days ((10 to 20% of dose is cut on each day).
- Non opiate approach for detoxication is done by central alpha$_2$ agonists like clonidine 100–30... 2–4 times daily. As clonidine decreases the outflow of NAD, some signs of overactivity migh... expected to be reduced. It is not well tolerated. Sedation and orthostatic hypotension ar... disadvantages. However, non addicting property is its definite advantage.
- Rehabilitation :

  Methadone maintenance

  Education and counseling which are important for improvement. Naltrexone, a long acting ... opiate antagonist is sometimes used for rehabilitation. Before administration of naltrexone, pati... should be free of opiates for a minimum of 5 days.
- **Neonatal addiction due to mother's drug abuse during pregnancy may be treated by ... administration of paregoric (Camphorated opium tincture) in a dose of 0.2 mg every 3–4 hrs init... followed by a dose in decreasing manner. Treatment lasts for a period of 10–20 days.**

☞ **Alcohols :**

Alcohol ***(Ethyl alcohol/Ethanol)*** **: It has both hydrophilic and lipophilic properties. Alcohol rea... passes through blood-placenta barrier into the fetal circulation. The metabolism is relative...**

independent of its conc. (*Zero-order kinetics*). Chronic ethanol consumption may induce microsomal mixed-function oxidases. Therefore, the metabolism of a variety of drugs may be impaired in chronic alcohilics.

Alcohol is primarily a CNS depressant and potentiates the effects of other CNS depressant drugs. In low conc. there is increase in gastric acid secretion. Higher conc. of alcohol produces certain ill effects on the absorption site and absorption of aminoacids, vitamins, minerals etc. Diuresis is also caused which is possibly due to inhibition of release of ADH. There may be alteration of sexual function because of reduced blood testosterone level.

Regarding its **medical uses,** the following are important :

1. When applied topically, antiseptic property is obtained (70% alcohol having maximum effect). In addition it cools skin and is useful to lower down high temperature.
2. In low-conc. alcohol beverages may improve appetite and sometimes useful in patients suffering from anorexia.
3. To provide relief of pain in certain neuralgias (tigeminal neuralgia) and inoperable carcinoma, absolute alcohol is injected to ganglia or nerves.
4. In methyl alcohol (Methanol) poisoning, larger amounts of ethyl alcohol is administered by I.V. It is also useful as I.V. infusion in the management of ethylene glycol poisoning.
5. I.V. alcohol is occasionally used to suppress uterine contractions and delay premature labour.
6. In acute pulmonary oedema resulting from left heart failure, ethanol mist has been used by inhalation to clear out the foam that may obstruct the respiratory airways.
7. As a night sedative in chronic alcoholics.

- **Treatment of alcohol withdrawal syndrome :**
- Thorough physical examination along with adequate rest and nutrition.
- The specific drug for alcohol is a long acting sedative-hypnotic. Benzodiazepines suit for the purpose. Chlordiazepoxide 10–15 mg or diazepam 10 mg is given every 4–6 hrs by I.V. on first day and then the dosage of either of the above drugs should be reduced gradully.
- B complex vitamins including thiamine.
- Rehabilitation

Motivation towards abstinence, maintenance of problem free life. As an adjunct, disulfiram is to be given as 250 mg daily at bed time. In the presence of ethyl alcohol disulfiram causes tremor, hypotension or hypertension, nausea and severe vomiting. Chronic alcohilics should be informed about the effects of the above drug. Disulfiram is contraindicated in diabetes mellitus, portal hypertension and heart diseases.

PHYCHOTROPIC DRUGS

A. Antipsychotic drugs
B. Anitdepressant drugs
C. Mood stabilising drugs (Antimanic)
D. Antianxiety drugs
E. Hallucinogens

A. Antipsychotics or Neuroleptics

Chlorpromazine	Chlorprothixene
Fluphenazine	Loxapine
Perphenazine	Newer agents e.g.
Haloperidol	Clozapine, Sulpiride

These are all dopamine antagonist.

Therapeutic uses :

Schizophrenia
Acute manic episodes (in combination with lithium)
Psychotic and agitated depression (in combination with antidepressants)

Adverse effects :

1. Sedation, lethargy and drowsiness — tolerance develops; drymouth, postural hypoten cycloplegia, constipation, urinary retention.
2. Troublesome side effects —
   Acute muscular dystonic reaction
   Extrapyramidal parkinson like syndrome
   (treated by Benztropine mesylate)
   Akathisia
   (reduction of dose and treated by beta blockers)
3. Most serious side effects :
   Tardive dyskinesia (20–40%)

B. Antidepressants :

There are three different groups of drugs used for the treatment of affective disorders :

1. Tricyclic antidepressants (TCAs) — most commonly used.
2. Monoamine oxidase inhibitors (MAOs) — Drug-drug and drug-food interactions have m these the second-line medication in the treatment of depressive disorders.
3. Selective serotonin re-uptake inhibitors (SSRIs) — useful for refractory and atypical case depression.

No antidepressant is ideal. They have got the following characteristics :
(a) Delayed onset of action (1–4 weeks), (b) Significantly sedative, anticholinergic, cardiot and weight gain producing and (c) Induction of manic episode (mood–reversal) in patien bipolar disorders.

Commonly used first generation antidepressants :

Drug	Action	Clinical features
Tricyclic derivatives		
Amitryptiline	Powerful blockade of 5HT uptake less blockade of NE uptake.	Prominent sedative and anticholinergic actions
Nortryptiline	Powerful blockade of NE uptake and less blockade of 5HT uptake.	Both sedative and anticholinergic actions are less than those of amitryptiline.
Imipramine	Equally powerful blockade of NE and and 5HT uptake.	Prominent anticholinergic action. No sedation may cause

Drug	Action	Clinical features
Desipramine	Very powerful inhibitor of NE uptake little or no blockade of 5HT uptake.	Minimal sedative and anticholinergic action.
Doxepine	Anxiolytic	Minimal adverse effect on CVS.
Dothiepin	Potent NE and 5HT blockade.	Marked sedation. Less side effect, hence better patient compliance.
MAOIs Phenelgine	Most commonly used MAO inhibitor in Depression.	Drowiness.
Tranylcypromine	Side chain cyclisation of amphetamine resulted in tranylcypromine. CNS stimulation.	Insomnia and tremors.
Isocarboxazid		Drowsiness.
Clorgyline	Specific MAO–B inhibitor	Same as other MAOIs.
Selegeline	Has influence on DA system as well.	Very useful in the treatment of Parkinsonism.

Commonly used second generation antidepressants

Drug	Action	Clinical features
Tricyclic derivatives		
Trimipramine	Powerful inhibitor of 5HT uptake. Some inhibitory action on NE and DA uptake.	Prominent seadtive action and moderate atropine-like action.
Amineptine	Potent NE and 5HT uptake inhibition and also DA blockade.	Less sedation. Less anticholinergic side effects. Useful in psychotic or endogenous depression.
Heterocyclics		
Amoxapine	Early onset of action within the firstweek is claimed.	Tardive dyskinersia, Parkinsonism.
Maprotiline		Fewer anticholinergic side effects. Lower dose is recommended. Blood dyscrasia.
Trazodone	High level of sedation and is useful as a hypnotic.	Increased risk of priaprism.
Selective serotonin reuptake inhibitors (SSRIs)		
Fluoxetine	Relatively selective 5HT reuptake inhibition. Early onset of action.	Nausea, diarroea, tremor weightloss, agitation, Anorgasmia.
Sertraline	Same as above	Lesser side effect profile. Less chance of overdosage and suicide.

Mechanism of action of TCAs :

1. Increased synaptic conc. of monoaminesgic neurotransmitters in the CNS by blocking the sypnaptic uptake of NE, 5HT and dopamine.
2. Regulation of postsynaptic receptor activity of monoaminergic neurones.
3. Down-regulation of neurotransmitter receptors.

Common side effects of TCAs :

Anticholinergic	Cardiovascular	Miscellaneous
Dry mouth Nausea, vomitting constipation, urinary retention, blurred vision.	Potural hypotension tachycardia, arrhythmia	Drowsiness, sleepiness, fine tremor, dizziness, ataxia, leucopenia.

Most common side effects are dry mouth, sedation, fine tremor of the hands and postural hypo

Mechanism of action of MAOIs :

Increased availability of one or more monoamines in the monoaminergic neurones of the CNS. is unexplained delay of antidepressant effects for 2–3 weeks although maximal inhibition of monoa metabolism is achieved within few days MAOIs are used when TCAs show unsatisfactory result or a tolerated or accepted by the patient. They are also of considerable benefit in atypical depressio depression associated with hyperphagia, hypersomnia etc.) in panic attacks, agoraphobia, social p psychalgia etc.

Common side effects of MAOIs :

Agitation, hallucinations, hyper-reflexia, insomnia and convulsion.

Drug interaction with MAOIs :

Indirectly acting sympathomimetics and cocaine cause hypertensive reactions.
(see " Cheese reaction ")

Q. 1. What to do if an antidepressant fails to bring clinical improvement?

Ans. Actually there are several methodological steps :

a) See whether the drug has been used in adequate dose for adequate time or not. It is bet use over-dose than under-dose in the treatment of depression.

b) See whether the patient has been taking the drug as per instruction or not — because us the patient compliance is poor due to undue sedation and other hyperadrenerg anticholinergic side effects.

c) If everything cited above goes right, the group of the drug may be changed, e.g. TCA to M or SSRI or vice-versa .

d) If still no improvement, go for 'potentiation'— i.e. clinical effects on addition of some o drugs like antipsychotics, lithium and thyroxine.

e) If no improvement, 'Re-evaluation of diagnosis' and other modes of therapy may be nee Some cases of depression may be secondary to pancreatic neoplasm, endocrinopathy or s SOL in the CNS, in which eradication of the primary cause is mandatory to bring out cli result.

C. **Mood stabilising drugs :**

a) Lithium carbonate — A drug of low therapeutic index.

b) Carbamazepine

c) Sodium valproate

d) Propranolol.

Drugs (b) and (c) are used when lithium fails to bring optimum clinical benefit, i.e. in cases of lithium non-responders and also in rapid cycling mood disorders.

Lithium carbonate

Mechanism of action :

1. Lithium partly replaces sodium specially in hyperexcitable tissues (of CNS, kidney and heart) and it has a relatively small gradient of distribution across the cell membranes. Although lithium can replace Na^+ to support a single actionpotential in a nerve cell, it is not an adequate substrate for the the Na^+ pump and so cannot maintain membrane potential . Lithium thus inhibits the release of NAD, dopamine but not serotonin at the synapse.
2. In mania, hyperactive neurones require excess amount of inositol for its activity. Lithium inhibits the hydrolysis of inositol monophosphate to free inositol. Supply of free inositol from extracellular sources is very poor, so the hyperactive neurones suffer from deficiency of free inositol and excitability is reduced.

Pharmacokinetics

Route of administration	Oral
Bioavailability	100%
Half-life	18-20 hrs. (longer in elderly)
Therapeutic phasma conc.	0.8–1.2 mmol/L in mania.
	0.4–0.8 mmol/L (Prophylactic)
Response starts after	2–4 weeks.

Therapeutic uses :

1. Acute manic/hypomanicepisodes.
2. Prophylactic for recurrent episodes of mania and depression in bipolar illness.
3. Prophylaxis for recurrent unipolar depressive disorders.
4. In certain cases of pre-menstrual tension syndrome.
5. SIADH.
6. In certain childhood behaviour disorders, e.g. autism.
7. Hyoplastic anemia (because of its stimulatory effects on the bone marrow — one nonpsychiatr condition.)

Drug interactions :

1. Diuretics increase serum lithium conc. due to more reabsorption of lithium from p convoluted tubules.
2. Indomethacin increases serum lithium conc.
3. Haloperidol causes encephalopathic syndrome.

Treatment of lithium poisoning :

1. Mannitol I.V. to accelerate renal excretion (Amiloride also increases lithium excretion)
2. Dialysis in severe poisoning.

☞ **Drugs causing anxiety**

Caffeine – intoxication
Sedative – hypnotic withdrawl
Amphetamine
Glucocorticoids

Drugs causing depression

Reserpine
Glucocorticoids
Oral contraceptives
Amphetamine
Indomethacin

☞ **Drugs for some neurological disorders :**

Conditions	Amitriptyline Drugs
Muscle spasticity	Baclofen, Dantrolene, Diazepam
Essential tremor	Propranolol
Hypokalemic paralysis	Propranolol
Hyperkalemic paralysis	Salbutamol inhalation
Pain following nerve injury	Tricyclic antidepressants Doxepin Imipramine Nortriptyline Desimipramine (Desipramine)
Tinnitus	Lignocaine
Trigeminal neuralgia	Anticonvulsants Phenytoin, Carbamazepine, Clonazepam

N.B. – **Antihistamine (H_1 receptor blocker) hydroxyzine potentiates the action of narcotic analgesic increasing the sedative action.**

– **Dextroamphetamine enhances analgesia and makes and patients more alert when used in pa are excessively sedated by narcotics.**