HYPNOTICS
DRUGS USED IN TREATING MOTOR DISORDERS

J. Mojžiš

Hypno-sedative drugs

terminology

Sedation

can be defined as a supression of responsiveness to a constant level of stimulation, with decreased spontaneous activity

Hypnotic effects

involve more pronounced depression of the CNS than sedation, and this can be achieved with most sedative drugs simply increasing the dose.

Hypno-sedatives

I. generation – barbiturates (obsolete)

II. generation – benzodiazepines (BZD)

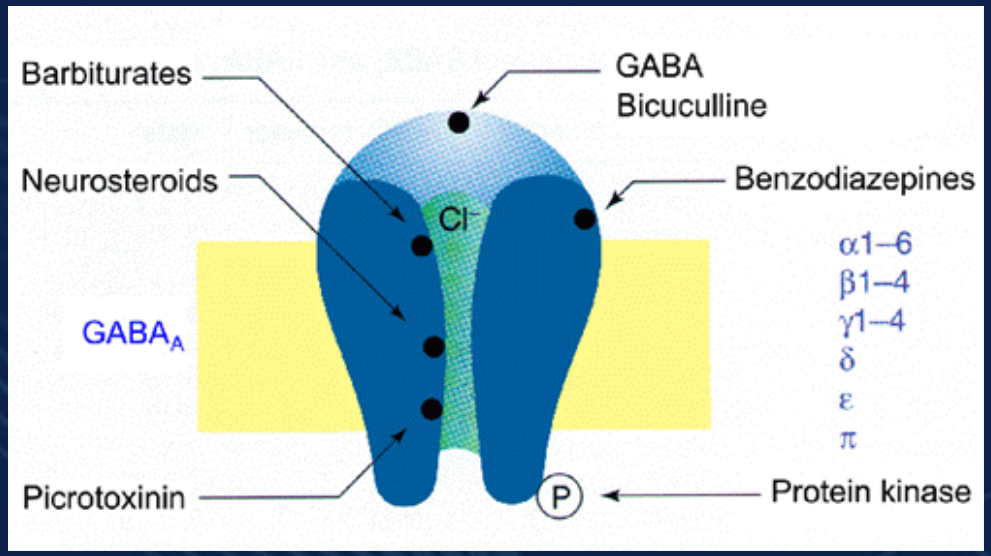
III. generation – zolpidem, zaleplon

Benzodiazepines

- act selectively on gamma-aminobutyric acid ($GABA_A$) receptors, which mediate fast inhibitory synaptic transmission through the CNS
- they bind specifically to a regulatory site of the receptor, distinct from the GABA binding site and act allosterically to increase the affinity of GABA for the receptors
- by facilitating the opening of GABA activated chloride-channels BZ enhance the response to GABA

Benzodiazepines – Mechanism of Action

GABA Receptor



GABA-A receptors – highly variable (i.e., consist of different complements of alpha, beta, and gamma subunits).

= different sensitivities to benzodiazepines.
= α2 subunit is critical in sedative effects.

Benzodiazepines do **NOT** activate the receptor directly.

= increase frequency of chloride-channel opening produced by GABA.

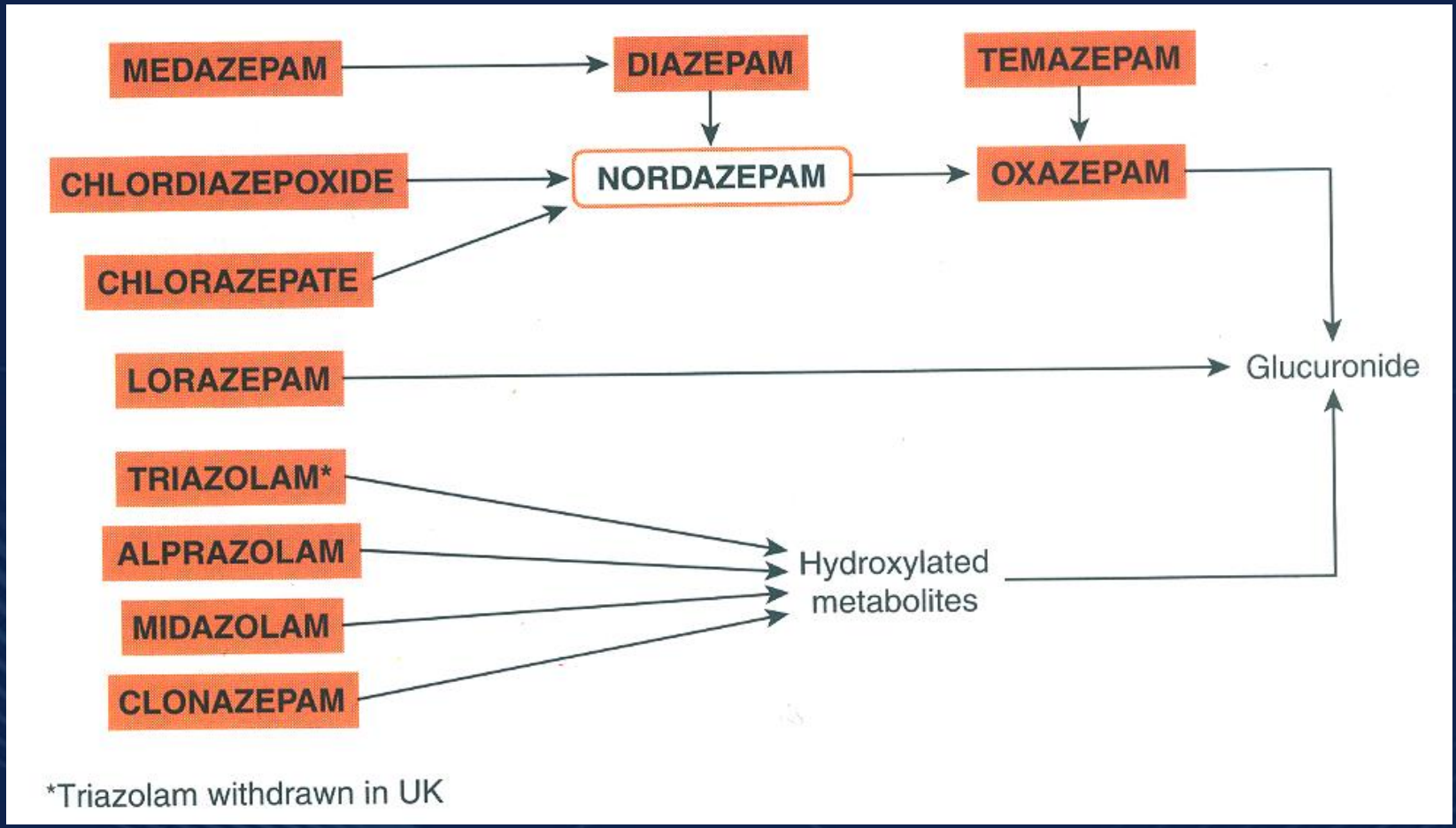
Benzodiazepines

absorption: **well absorbed if given orally , C_{max} reached in about 1 h**

binding: **strongly bound to plasma proteins**

distribution: **large Vd: accumulation in body fat (high lipid sol.)**

metabolism: **hydroxylation, conjugation with glucuronic acid**


MEDAZEPAM
DIAZEPAM
TEMAZEPAM
CHLORDIAZEPOXIDE
NORDAZEPAM
OXAZEPAM
CHLORAZEPATE
LORAZEPAM
Glucuronide
TRIAZOLAM*
ALPRAZOLAM
Hydroxylated metabolites
MIDAZOLAM
CLONAZEPAM
*Triazolam withdrawn in UK

Benzodiazepines

Pharmacological effects and uses

The main effects

- **reduction of anxiety and agression**
- **sedation and induction of sleep**
- **reduction of muscle tone and coordination**
- **anticonvulsant effects**

Benzodiazepines

Indications

- **reduction of anxiety and agression**

Note: BZD may *paradoxically* produce an increase in irritability and aggression in some individuals (particularly if short- acting drugs are given (triazolam)

- **sedation and induction of sleep**

BZDs *decrease the time taken to get to sleep*
increase the total duration of sleep (only in subjects who normally sleep for less than about 6 hours each night)

Benzodiazepines

Non-rapid eye movement(NREM) sleep: 70%-75%
Rapid eye movement(REM) sleep

REM sleep (rapid eye movement) is less affected if compared with the same effect of other hypnotics.

Is that important? Yes, artificial interruption of REM sleep causes irritability and anxiety even if the total amount of sleep is not reduced.

Benzodiazepines

- **reduction of muscle tone and coordination**

may be clinically useful: increased muscle tone is a common feature of anxiety states and may contribute to pains (headache). Influence of manual skills (!)

- **anticonvulsant effects**

clonazepam to treat epilepsy

diazepam (i.v.) status epilepticus to control life-threatening seizures

Pharmacological Effects of Benzodiazepines are Concentration-Dependent.

- Nanomolar Concentrations
  - Anxiolytic sedation – via α2 subunit.
  - Action effectively blocked by flumazenil.

- Micromolar Concentrations
  - Anesthesia – diazepam, midazolam, lorazepam.
  - Activity due to binding of benzodiazepines to low-affinity site on GABA-A receptor.

Benzodiazepines

Unwanted effects

- **effects occuring during normal therapeutic use**
- **acute overdosage**
- **tolerance and dependence**

Unwanted effects occuring during therapeutic use

Influence of manual skills (such as driving performance) due to drowsiness, confusion, amnesia and impaired coordination

enhance of depressant action of other drugs (in a more than additive way)

- They vary greatly in duration of action, and can be roughly divided into
  - **Short-acting compounds**: triazolam, oxazepam($t_{1/2}$ 2-3 h)
  - **Medium-acting compounds**: estazolam, nitrazepam ($t_{1/2}$ 5-8 h)
  - **Long-acting compounds**: diazepam (biphasic half-life of about 1–3 and 2–7 days for the active metabolite desmethyldiazepam), flurazepam (50h)

Benzodiazepines

acute overdosage (BZs are relatively safe in overdose)

- BZs produce prolonged sleep, without serious depression of respiration or cardiovascular function

- severe even life-threatening respiratory depression may appear in BZ combination with **other CNS depressants**, **particularly alcohol.**

- acute overdosage can be counteracted with **flumazenil**

Benzodiazepines

tolerance, dependence

tolerance occurs with all BZs; it appears to represent a change at the receptor level

Discontinuation of benzodiazepine therapy in tolerant patients **MUST** be gradual.

dependence – in human subjects and patients, stopping BZ treatment after weeks and months causes an increase in symptoms of anxiety, together with tremor and dizziness.

Addiction (craving -severe psychological dependence) is not a major problem.

New drugs

Zolpidem

- binds selectively to the α_1 subtype of BZ receptors and facilitates GABA-mediated neuronal inhibition
- like the BZs, the actions of zolpidem are antagonised by flumazenil
- minimal muscle relaxing and anticonvulsant effects
- the risk of development of tolerance and dependence with extended use is less than with the use of other BZs

Zaleplon

- rapid onset and short duration of action are favorable properties for those patients who have difficulty falling asleep.

ANTIPARKINSONICS

History of Parkinson´s disease (PD)

- First described in 1817 by an English physician, James Parkinson, in “An Essay on the Shaking Palsy.”

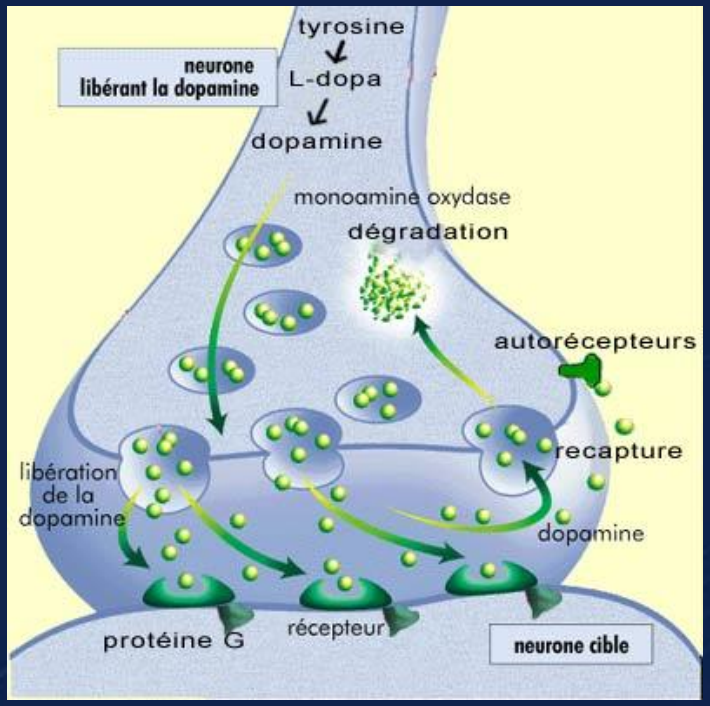
- The famous French neurologist, Charcot, further described the syndrome in the late 1800s.

Epidemiology of PD

- **The most common movement disorder affecting 1-2 % of the general population over the age of 65 years.**
- **2.5% of the population older than 85**
- **The second most common neurodegenerative disorder after Alzheimer´s disease (AD).**

Parkinsonism:

- degenerative disease of CNS
- symptomatic



- hypokinesia
- muscle rigidity
- tremor
- postural lability

Parkinson's Disease Symptoms

- Secondary features of the disease:
  - **Depression**
  - **Dementia**
  - **Dysphagia**
  - **Anxiety**
  - **Orthostatic hypotension**
  - **Constipation**

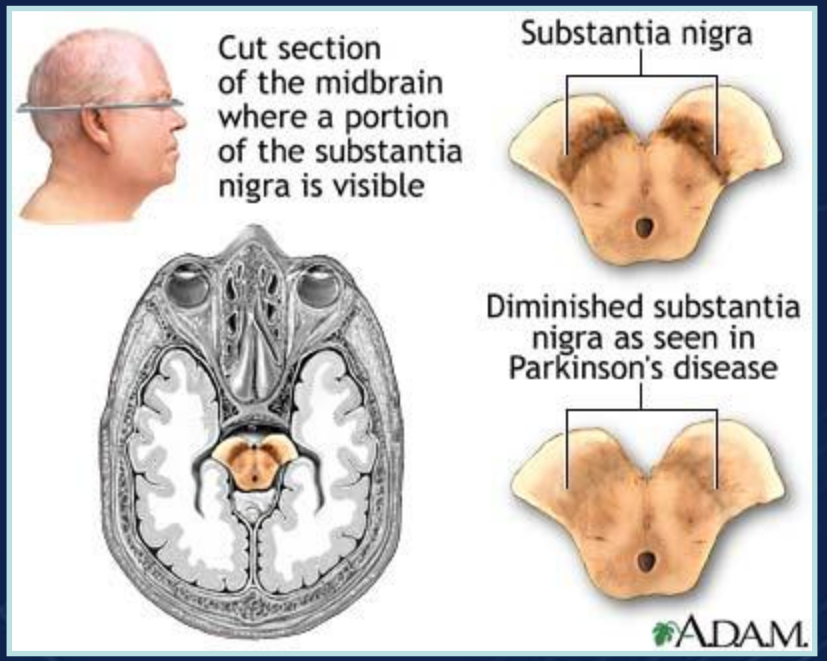
Diagnostic Features

- Four Cardinal Signs
  - T remor
  - R igidity
  - A kinesia and bradykinesia
  - P ostural instability

» Signs start in one limb, usually an arm, and spread to the other limb on that side

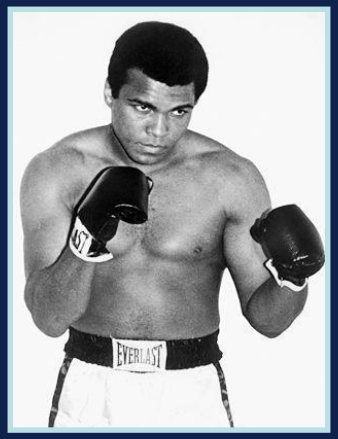
Etiology

- Parkinson disease is caused by the death of the nerve cells in the substantia nigra, which produce the neurotransmitter **dopamine**.



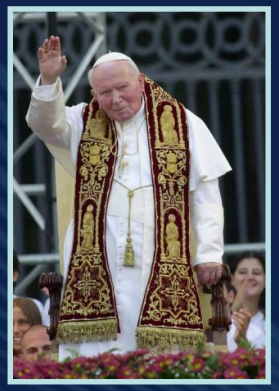
Famous Faces of Parkinson

Michael J. Fox



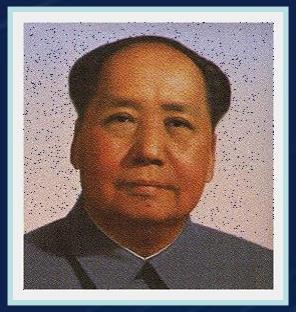
Muhammad Ali

Katharine Hepburn



Pope John Paul II

Johnny Cash

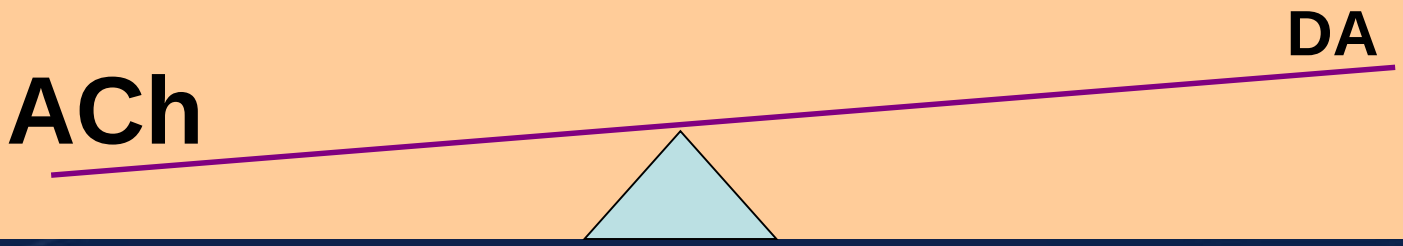


Mao Tse Tung

Primary Known Causes

- **Idiopathic—majority of cases**
- **Genetic**
- **Drug induced—Calcium Channel Blockers**
- **Toxins**
- **Head Trauma**
- **Cerebral Anoxia**

Imbalance primarily between the excitatory neurotransmitter **Acetylcholine** and inhibitory neurotransmitter **Dopamine** in the Basal Ganglia



Pharmacotherapy (strategy)

- **dopamine saturating agents:**
  levodopa
- **dopamine receptor agonists**
  bromocriptine, ropinirol, pramipexol
- **agents increasing dopamine effect:**
  rasagiline, tolcapon, entacapon
- **agents increasing dopamine release:**
  amantadine
- **acetylcholine bloking agents:**
  biperiden, procyclidine, trihexyfenidil




Dopamine-saturating agents

Levodopa (L-DOPA)

1. **choice drug**

L-DOPA

- L-DOPA can cross blood-brain barrier, when dopamine cannot. This led to the idea of using L-DOPA as treatment for PD.

- First used in the 1960's, with daily increase dosage program.

- L-DOPA used in combination with Carbidopa in 1967.
  - Increases potency of L-DOPA up to 4-fold.

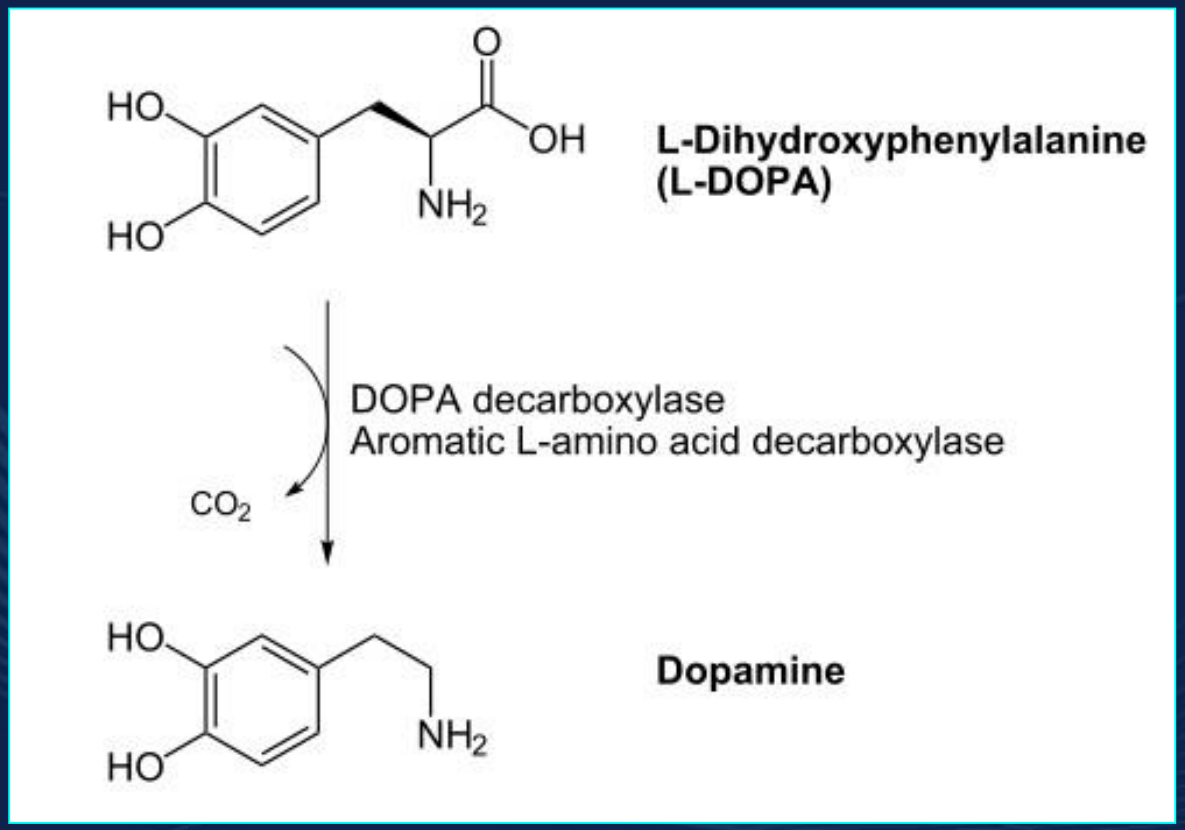
Mechanism of action

- dopamine receptors D_1 a D_2
- dopaminergic antiparkinsonics – stimulation of D_2 receptors

Pharmacokinetics

- ***L-DOPA*** **- rapid GIT absorption**
- **brain distribution - 1-3% only**
- **majority metabolised to dopamine in extracerebral tissues**
- **combination with carbidopa (inhibitor of dopa-decarboxylase) – 10% enter CNS**

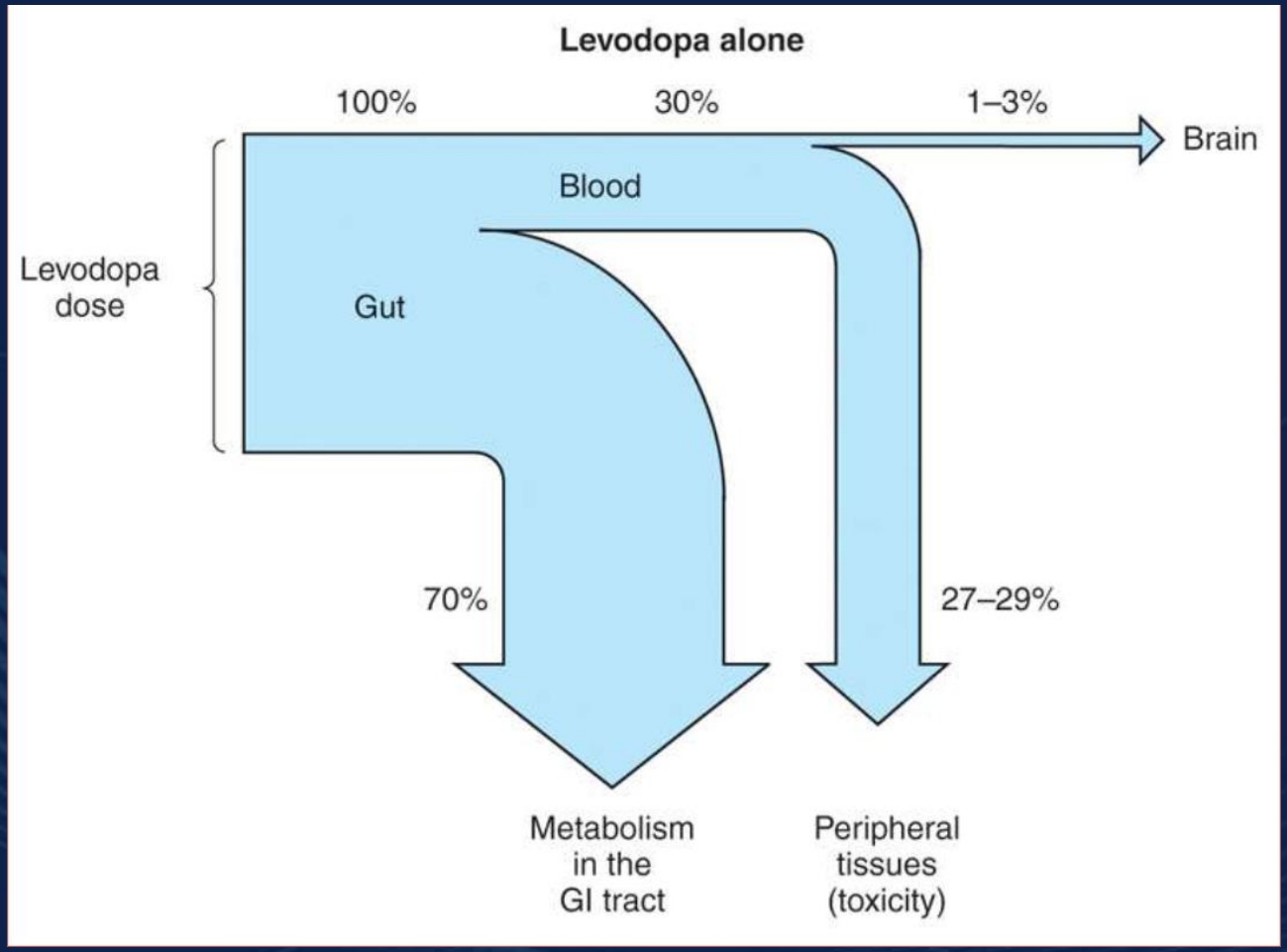
- L-DOPA is converted to dopamine by DOPA decarboxylase

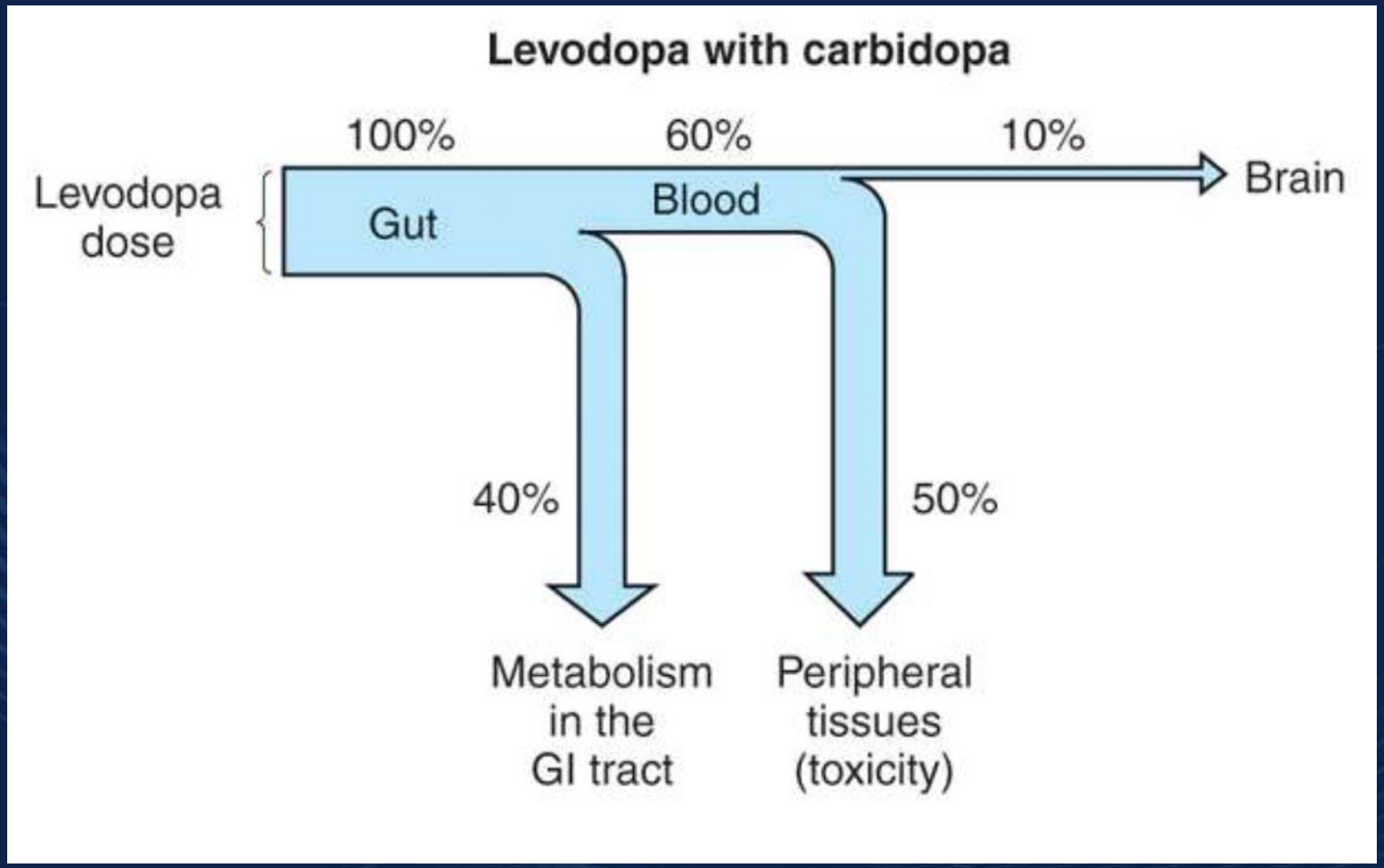


Carbidopa

- **Carbidopa is an inhibitor of dopa decarboxylase.**

- **Because it is unable to penetrate the blood-brain barrier, it acts to reduce the peripheral conversion of levodopa to dopamine.**


Levodopa alone
100%
30%
1–3%
Brain
Blood
Levodopa dose
Gut
70%
27–29%
Metabolism in the GI tract
Peripheral tissues (toxicity)


Levodopa with carbidopa
100%
60%
10%
Levodopa dose
Gut
Blood
Brain
40%
50%
Metabolism in the GI tract
Peripheral tissues (toxicity)

Carbidopa - cont.

Virtue:

a. It can decrease the dosage of levodopa.

b. It can reduce toxic side effects of levodopa.

c. A shorter latency period precedes the occurrence of beneficial effects.

Clinical use

- ***L-DOPA*** **can change all symptoms of parkinsonism**
- **effective mainly in rigidity, hypokinesia**
- **65-70% patients answer in the begining of therapy**
- **decreased effectiveness – after few years**

Side effects 1

- **GIT**

- about 80% of patients - nausea, vomiting
- divide doses, apply with meal
- tolerance – after few weeks
- application with dopa-decarboxylase inhibitors – about 20% vomiting

- **CVS**

- increase in catecholamine production in periphery:

- **arrhythmias**
- **orthostatic hypotension**
- **hypertension**

Side effects 2

- **Diskinesia**
- **Behavioral changes**
  - depression
  - anxiety, agitation
  - insomnia
  - euforia

  - mainly in *L-DOPA + carbidopa* combination
- **Other**
  - mydriasis
  - taste or smell abnormality

Levodopa-note

- **Sudden discontinuation can result in fever, rigidity, and confusion.**

- **The drug should be withdrawn gradually over 4 days.**

Dopamine receptor agonists or agents increasing dopamine effect

Bromocriptine

Ergot alcaloid derivative

Claviceps purpurea

Mechanism of action

- 2. choice drug
- acts as partial agonist on D_2 – receptors in CNS

Clinical use

- can be combined with *L-DOPA*
- therapeutic level should be reached in 2-3 months
- the dose of *L-DOPA* should decrease

Side effects

- **GIT**

- nausea, vomiting, anorexia, constipation

- **CVS**

- hypotension, vasospasms (fingers), arrhythmias

- **Diskinesia**

- **Mental disorders**

- confusion, halucinations

II. generation of dopamine receptor agonists

- ***Ropinirol*** **- D_3/D_2 agonist:**

  - similar effects as *L-DOPA*

- ***Carbegoline*** **- D_2 agonist**

- ***Pramipexol*** **- D_3/D_2 agonist**

  - monotherapy, in severe forms combination with L-DOPA

MAO-B inhibitors

Rasagiline

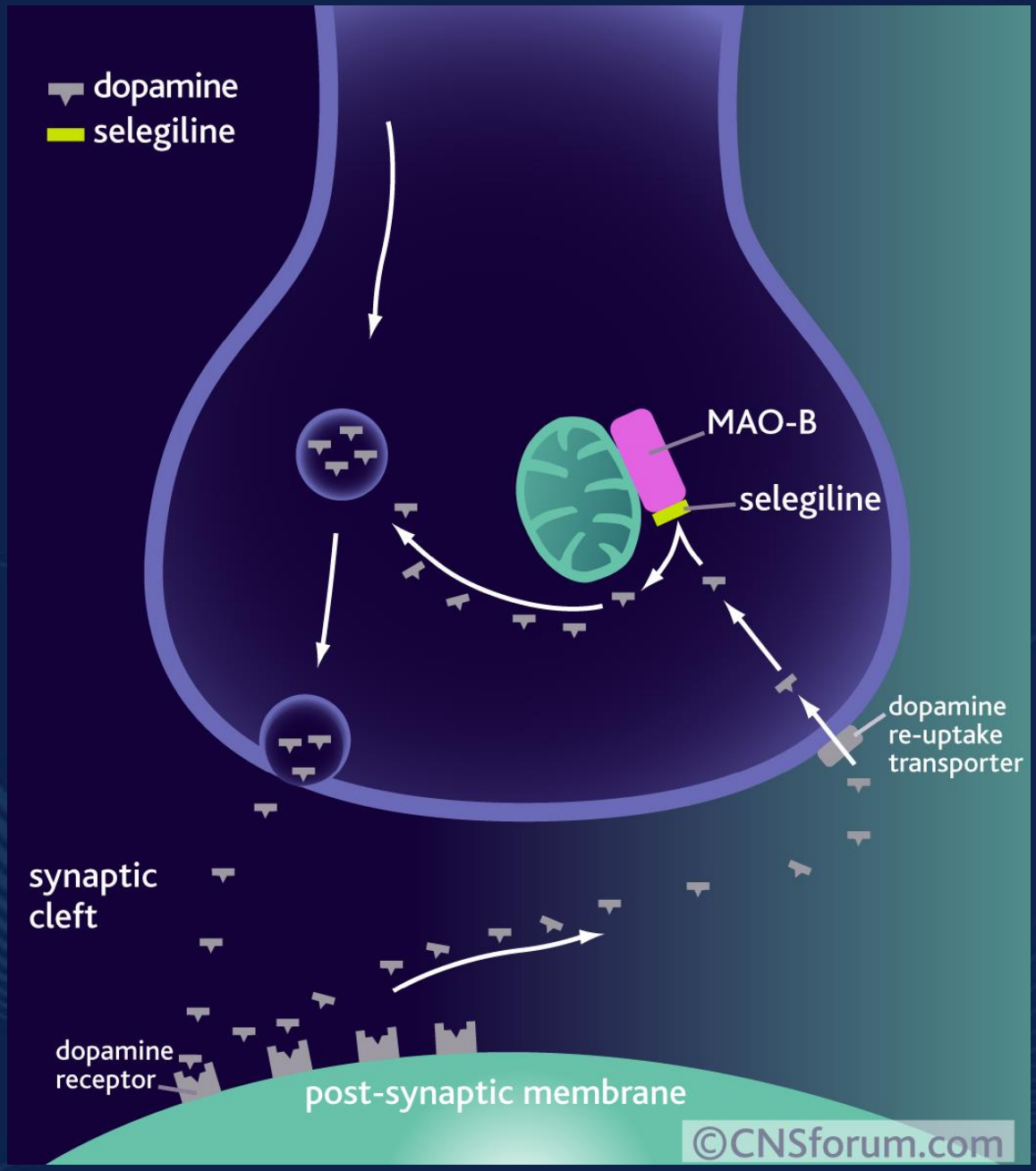
- **inhibition of MAO B**
- **it prolongs *L-DOPA* effect ⇨ dose diminution**
- **Used as monotherapy or in conjunction with L-DOPA, it can reduce the dosage of L-DOPA by 15%.**

MAO-B Inhibitors

- **MAO-B is an enzyme that metabolizes dopamine.**
- **From the breakdown of dopamine, hydrogen peroxide is produced, which the oxidative stress can damage dopaminergic neurons in the substantia nigra. (Possibly neuroprotective)**
- **MAO-B inhibitor delays or reduces the metabolism of dopamine.**

Rasagiline (selegiline)

- combination of rasagiline and levodopa is more effective than levodopa along in relieving symptoms and prolonging life


dopamine
selegiline
MAO-B
selegiline
dopamine
re-uptake
transporter
synaptic
cleft
dopamine
receptor
post-synaptic membrane
©CNSforum.com

- **Side effects of L-DOPA may be enhanced by selegeline.**
- **Nausea and dizziness.**

COMT Inhibitors

- COMT catalyses methylation of L-DOPA.
- Addition of COMT inhibitor along with L-DOPA and carbidopa prolongs the half-life of L-DOPA and increases the amount in the CNS.
  - This increases “on” time for L-DOPA.

COMT- inhibitors

Entacapon

- peripheral COMT- inhibitor
- Decrease of L-DOPA degradation
- additive to *L-DOPA+carbidopa*
- *L-DOPA* dose diminution
- nausea, vomiting, hallucination

Tolcapon

- strong peripheral & central COMT inhibitor
- similar as *entacapon* (in patients with weak response to *L-DOPA+carbidopa*
- possible severe hepatotoxicity (nausea, vomiting, abdominal pain, unusual fatigue, loss of appetite, yellow skin or eyes, itching, dark urine; death)

Agents increasing dopamine release

Amantadine

- antiviral agent
- increases dopamine release from nerve endings and also it blocks NMDA receptors
- short action, disappears after few weeks
- positive effects on rigidity, tremor
- can induce CNS disorders - depressions, sleep disturbancies

Amantadine

- **Amantadine may be more efficacious in PD than the anticholinergic atropine derivatives but is less effective than levodopa.**

- **It has been used alone to treat early PD and as an adjunct in later stages.**

Acetylcholine blocking agents

Biperiden, procyclidine, trihexyfenidil

- progressive begining of therapy
- influence rigidity, tremor
- important side effects
- continual discontinuation of therapy

ANTIEPILEPTICS

Definition

- A **chronic neurologic disorder** manifesting by **repeated epileptic seizures** which result from **paroxysmal uncontrolled discharges of neurons** within the central nervous system (grey matter disease).

Pathogenesis

- The 19th century neurologist Hughlings Jackson suggested “a sudden **excessive** disorderly **discharge of cerebral neurons**“ as the causation of epileptic seizures.

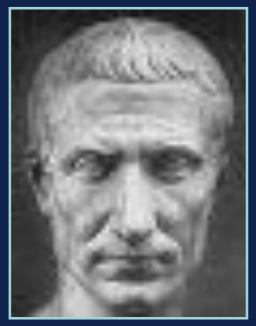
- Recent studies in animal models of focal epilepsy suggest a central role for the excitatory neurotransmiter **glutamate** (increased in epi) and inhibitory gamma amino butyric acid (**GABA**) (decreased)

Epilepsy

Etiology:

- **symptomatic epilepsy**
- **idiopatic epilepsy (mainly in young adults - 75%)**
- **ideal antiepileptic drug – nonsedative!**

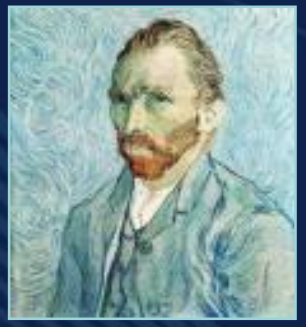
Famous Faces of Epilepsy



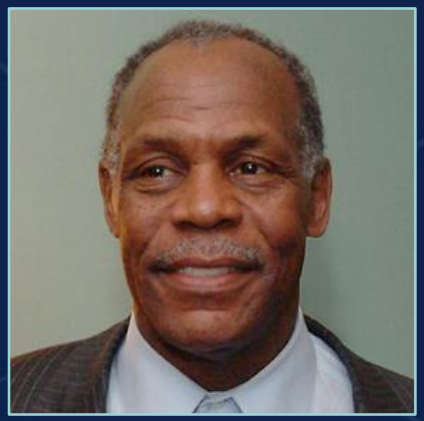
Caesar

Napoleon

Lenin



Van Gogh



Danny Glover

Prince

Trigger mechanisms of epilepsy

- **hyperpyrexia (infections)**
- **CNS infections**
- **metabolic disorders (hypoglycemia, phenylketonuria)**
- **toxic agents (strychnine, lead, alcohol, cocaine)**
- **brain hypoxia**
- **expansive processes (tumors, bleeding)**
- **CNS developmental disorders**
- **brain trauma**
- **anaphylactic reactions**

Attack classification

partial attacks

- simplex partial attacks
- complex partial attacks

generalised attacks

- generalized tonic-clonic attacks (grand mal)
- absences (petit mal)
- tonic attacks
- atonic attacks
- clonic & myoclonic attacks

Epilepsy - Treatment

- The majority of pts respond to drug therapy (anticonvulsants). In intractable cases surgery may be necessary. The treatment target is seizure-freedom and improvement in quality of life!
- The commonest drugs used in clinical practice are:
  Carbamazepine, Sodium valproate, Lamotrigine (first line drugs)
  Levetiracetam, Topiramate, Pregabaline (second line drugs)
  Zonisamide, Eslicarbazepine, Retigabine (new AEDs)
- Basic rules for drug treatment: Drug treatment should be simple, preferably using one anticonvulsant (monotherapy). “Start low, increase slow“.
  Add-on therapy is necessary in some patients…

Barbiturates

Phenobarbital

- belongs to the oldest antiepileptics (OBSOLETE)
- acts through inhibitory neurotransmitters (GABA)
- inhibits the effect of excitatory neurotransmitters (glutamate)
- in high doses ⇨ blocks Ca^{2+} channels

Clinical use

- rarely used (sedative effect)
- partial seizures
- grand mal

Side effects

- sedative
- allergic reactions
- megaloblastic anemia
- increased porphyrine synthesis (CI in porphyria)
- overdose, intoxication
- tolerance, dependence

Other barbiturates

Primidon

metabolised to phenobarbital

- **Clinical use**
  - partial seizures
  - grand mal

- **Side effects**
  - as phenobarbital

Hydantoin derivatives

Phenytoin

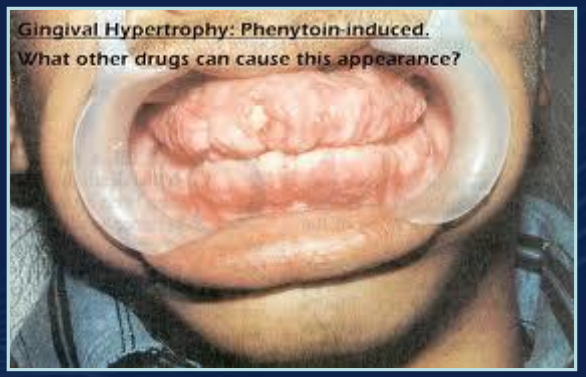
- **introduces in 1938**
- **significantly influences the movement of ions across the membrane (Na^+, K^+, Ca^{2+})**
- **binds to membrane lipids ⇨ membrane stabilization**

Clinical use

- partial attacks
- generalised tonic-clonic seizures
- antidysrrhythmic

Side effects

- nystagmus (early side effect)
- diplopia, ataxia, headache – dose adjustment
- hyperplasia of gums, hirsutism
- chronic application ⇨ avitaminosis (D) ⇨ osteomalatia
- folic acid metabolism disorders ⇨ megaloblastic anemia
- allergic reactions ⇨ skin
- teratogenic effects



Iminostilbens

Carbamazepine

chemically similar to tricyclic antidepressants

- **effect similar to *phenytoin***
- **blocks sodium channel**
- **inhibits synaptic transmission**

Clinical use

- **drug of choice in partial attacks**
- **effective also in grand mal**
- **neuralgia trigemini**
- **painful seizures in diabetic neuropathy**

Side effects

- diplopia & ataxia
- GI intolerance
- restlessness, sleepness
- in elderly - fatal aplastic anemia, agranulocytosis
- inducer of microsomal enzymes

Suxinimides

Ethosuximide

- **Mechanism of action**

  ⇨ **calcium channels T-type**

  ⇨ **calcium current responsible for induction of cortical impulses in petit mal**

- **Clinical use**

  - petit mal

Side effects

- GIT disorders (start therapy with low doses)
- fatigue
- headache, vertigo, euphoria (rare)

Valproic acid

Valproic acid & sodium valproate

- **mechanism of action - not fully understood**
- **inhibits GABA-transaminase**
- **⇓ aspartate level in brain**
- **possible change in membrane permeability for K^+ ⇨ hyperpolarisation**

Clinical use

- absences
- myoclonic seizures
- generalised tonic-clonic seizures
- partial seizures (rarely)

Side effects

- **nausea, vomiting, abdominal pain**
  (progressive dose increase)
- **weight ⇑ & alopecia**
  (about 10 % of patients)
- **hepatotoxicity !!!**
  (liver function monitoring)
- **possible teratogenic effect**
  (⇑ incidence of spina bifida)

Benzodiazepines

- *diazepam* – drug of choice in acute epileptic attack (10 mg i.v.)

- *lorazepam* - as diazepam, more effective
- *clonazepam* – long acting, absences, myoclonic seizures, highly effective antiepileptic drug
- *nitrazepam* – some forms of myoclonic seizures

Side effects

- **important sedative effect** **(use limitation)**

- **tolerance**

Newer antiepileptics

- GABA transaminase inhibitor: ***vigabatrin***
- Na^+ channel blocker: ***lamotrigine***
- GABA analogue: ***gabapentine***
- Aspartate excitatory effects antagonist: ***felbamate***
- As phenytoin with less side effects: ***topiramate***

GABA transaminase inhibitor

Vigabatrin

- irreversible inhibitor of GABA-transaminase
- ⇑ concentrations of GABA

- **Clinical use**
  - drug of choice in complex partial seizures

- **Side effects**
  - sleepness, weight gain
  - vertigo, confusion

Na^+ channel blocker

Lamotrigine

- inhibits also release of EA in brain cortex

- **Clinical use**

  - broad spectrum antiepileptic

  - drug of choice in partial & generalised tonic-clonic seizures

  - preferentially in non responders to other therapy

- **Side effects**

  - ataxia, vertigo, headache, diplopia, skin affections

GABA analogue

Gabapentine

- easily crosses blood-brain barrier, enhances GABA release

- **Clinical use**
  - drug of choice in partial seizures
  - first line for pain due diabetic neuropathy an postherpetic neuralgia
- **Side effects**
  - well tolerated
  - fatigue, vertigo, headache, nausea,

Aspartate excitatory effects antagonist

Felbamate

- in non-responders to other therapy

- **Clinical use**
  - in partial seizures
  - in children in seizures in Lennox-Gaustat sy (generalised myoclonic epilepsy with mental retardation)

- **Side effects**
  - nausea, insomnia, irritability – low incidence
  - aplastic anemia & hepatopathia – very rare but fatal

Na^+ channel block, GABA potentiation

Topiramate

- similar as phenytoin, less side effects
- inhibits also glutamate receptors
- in children and adults

- **Clinical use**
  - in partial seizures (simplex, complex)
  - in children in seizures in Lennox-Gaustat sy
- **Side effects**
  - CNS depression
  - suspect teratogenic effect

New AEDs

Inhibition of neurotransmitter release

Levetiracetam

- **It binds to SV2A (synaptic vesicle glycoprotein), and inhibits presynaptic calcium channels**
- **Reducition of neurotransmitter release**
- **Treatment of focal epilepsy and generalized tonic-clonic epilepsy**

Adverse reactions

- **The most common adverse effects - somnolence, decreased energy, headache, dizziness, mood swings and coordination difficulties**

Antagonists of an excitatory effect of glutamate

Perampanel

- Selective non-competetive antagonist of AMPA receptors (for glutamate)

Indications

- Partial seizures
- generalized tonic-clonic epilepsy

Adverse reactions

- Psychical disorders (euforia, irritability, aggresivity, psychosis, suicidal tendencies)

- **Zonisamid – MoA - ?, Na^+, Ca^{2+} GABA**

- **Eslikarbazepín – stabilisation of inactiveNa+ channels**
- **Retigabín – mostly via opening of neuronal K^+ channels – stabilisation of membrane potential**

- **Pregabalín – blockade of presynaptic Ca^{2+} channels - ⇩ release of NE, Subst. P, glutamate**

Therapeutic choices

Seizure type	1st choice	alternative or add-on
Tonic-clonic	carbamazepine	clobazam
	phenytoin	lamotrigine
	valproic acid	topiramate
Absence	ethosuximide	clobazam
	valproic acid	lamotrigine
		topiramate
Partial (simple or complex)	carbamazepine	clobazam
	phenytoin	lamotrigine
		valproic acid
		phenobarbital

Acute epileptic attack: ***diazepam, lorazepam***

Antiseizure drugs

Use of antiseizure drugs in other non-seizure conditions

Carbamazepine

mania, trigeminal neuralgia (possibly behavioural disturbances in dementia)

Gabapentin

neuropathic pain (possibly mania)

Lamotrigine

(possibly mania, migraine)

Phenytoin

(possibly neuropathic pain, trigeminal neuralgia)

Valproic acid

Mania, migraine (possibly behavioural disturbances in dementia)

Status epilepticus

0-5 min - history, physical examination, intubation?, ECG

5-10 min – start 2 large bore IV saline, dextrose, thiamine, lorazepam or diazapam IV

10-30 min - Phenytoin or phenobarbital IV

30-60 min - If seizures persist after phenytoin, use phenobarbital or vice versa. Admit to CCU, get EEG, consider thiopental, propofol

The Virgin Mary as advocate for a girl with epilepsy (portrayed having a tonic seizure)