1st seminar

Sedatohypnotic-anxiolytic drugs, Alcohols; Antiepileptics

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Sedatohypnotics, anxiolytics

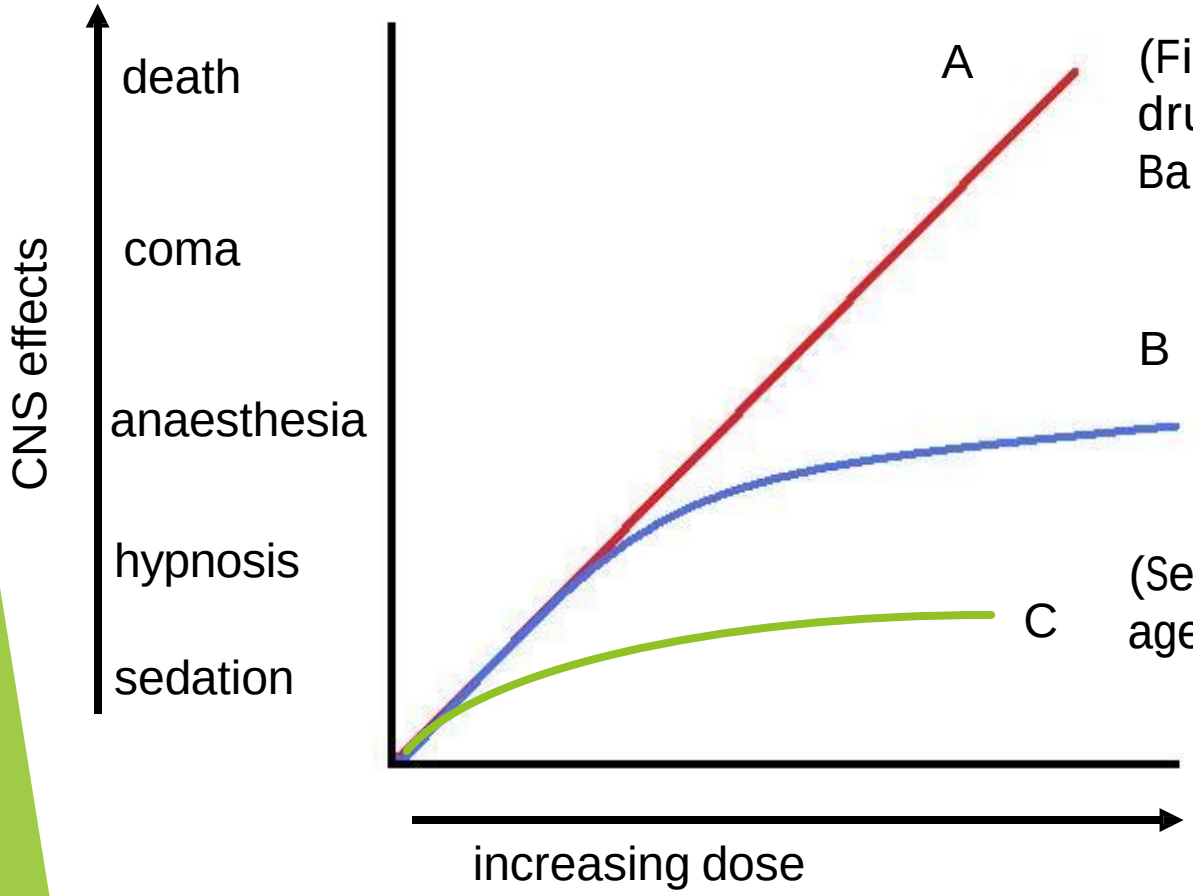
- sedative-hypnotic-anxiolytic effects
- anxiety disorders:
  - GAD (generalised anxiety disorder)
  - panic disorder
  - phobias
  - PTSD (post-traumatic stress disorder)
  - OCD (obsessive-compulsive disorder)
- hypnotic disorders
  - insomnia

Sedatohypnotic, anxyolytic drugs

- Classification:

  - benzodiazepines
    - Chlordiazepoxide (Elenium®, Librium®)
    - Diazepam (Valium®, Seduxen ®)
    - Medazepam (Rudotel®)
    - Clonazepam (Rivotril®)
    - Triazolam (Halcion®)
    - Alprazolam (Xanax ®, Frontin ®)
    - Midazolam (Dormicum ®)
    - Nitrazepam (Eunoctin ®)
    - Flunitrazepam (Rohipnol ®)
    - Cinolazepam (Gerodorm ®)
    - Brotizolam (Lendormin ®)
    - Temazepam (Signopam®)
    - Clobazam (Frisium®)
    - Tofisopam (Grandaxin®)
    - Lorazepam (Rilex®)
    - Oxazepam (Serax®)
  - barbiturates
    - phenobarbital (Sevenal®, Sevenaletta®)
    - pentobarbital (Nembutal ®)
    - thiopental (Trapanal ®)
    - secobarbital
  - „Z compounds”
    - zolpidem (Stilnox ®)
    - zopiclon (Imovan ®)
    - Zaleplon
  - 5HT receptor agonists
    - buspirone (Buspar ®)
  - melatonin receptor agonist
    - ramelteon

„Ideal” sedatohypnotics



(First generation drugs, e.g. Barbiturates)

(2nd generation drugs, e.g. Benzodiazepines)

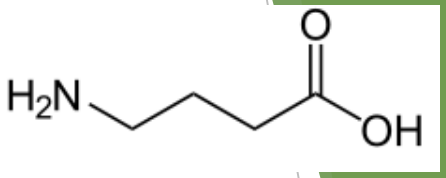
(Selective anxiolytic agents, e.g. buspirone)

Overdose effect of an ideal sedatohypnotic should not include generalized CNS depression

Therapeutic index (LD50/ED50), i.e. margin of safety:
greater for 2nd generation agents than for 1st generation agents

Physiologic background

GABA (γ-aminobutyric acid)



- main NT in the CNS (inhibitory effect)
- Synthesis: GAD (glutamic acid decarboxylase)
- Break-down: GABA transaminase
- Reuptake: GAT (GABA transporters)
- GABAerg neurons: cerebellum, the striatum and in the spinal cord; astrocytes

- Receptors
  - $GABA_A$:
    - ionotropic
    - ligand gated Cl^- channel→Cl^-influx→hyperpolarisation
    - pentamer structure ($\alpha_2\beta_2\gamma_1$)
  - $GABA_B$:
    - linked via G-proteins to K+ channels ➔ opens K+ channels ➔ hyperpolarisation &
    - Gi: inhibits adenylyl cyclase (cAMP↓) &
    - G_0 alpha-subunit: Inhibiting Voltage Gated Ca^{2+} ch.
    - Location: both pre/post-synaptically

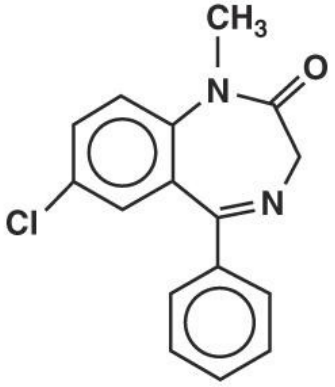
Benzodiazepines

history: 1960's – chlordiazepoxide

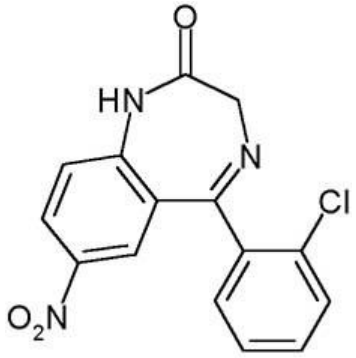
structure:

benzene ring
+ diazepine ring (7 membered heterocyclic)
+ 5-aryl substituent ring
(+ oxazole/triazole ring – oxazolam/ alprazolam, triazolam)

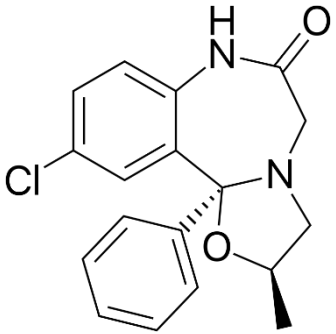
diazepam



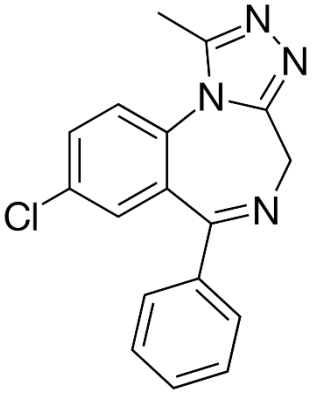
clonazepam



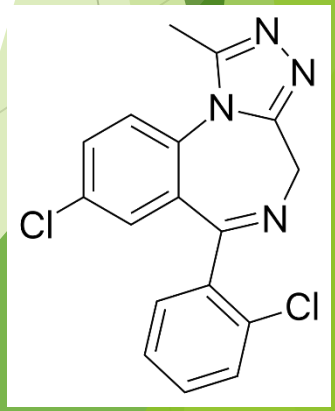
oxazolam



alprazolam



triazolam



Benzodiazepines

- Chlordiazepoxide (Elenium®, Librium®)
- Diazepam (Valium ®, Seduxen ®)
- Medazepam (Rudotel®)
- Clonazepam (Rivotril ®)
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- Clobazam (Frisium®)
- Tofisopam (Grandaxin®)
- Lorazepam (Rilex®)
- Oxazepam (Serax®)

Classification

- chemical structure
  - basic:
    - diazepam, chlordiazepoxide, clonazepam, midazolam
  - triazole ring:
    - triazolam, alprazolam
  - oxazole rings
    - oxazolam, cloxazolam
- potency (of anxiolytic effect)
  - high potential (eff. dose < 10mg/day) (alprazolam, clonazepam, lorazepam, triazolam)
  - low potential (eff. dose > 10mg/day) (chlordiazepoxide, midazolam, nitrazepam, cinolazepam, oxazepam, temazepam)
- duration of action
  - ultrashort: midazolam, triazolam
  - short: lorazepam, oxazepam
  - medium: alprazolam
  - long: diazepam, clonazepam, flunitrazepam

Benzodiazepines

mechanism of action:
specific regulatory site on $GABA_A$ receptor

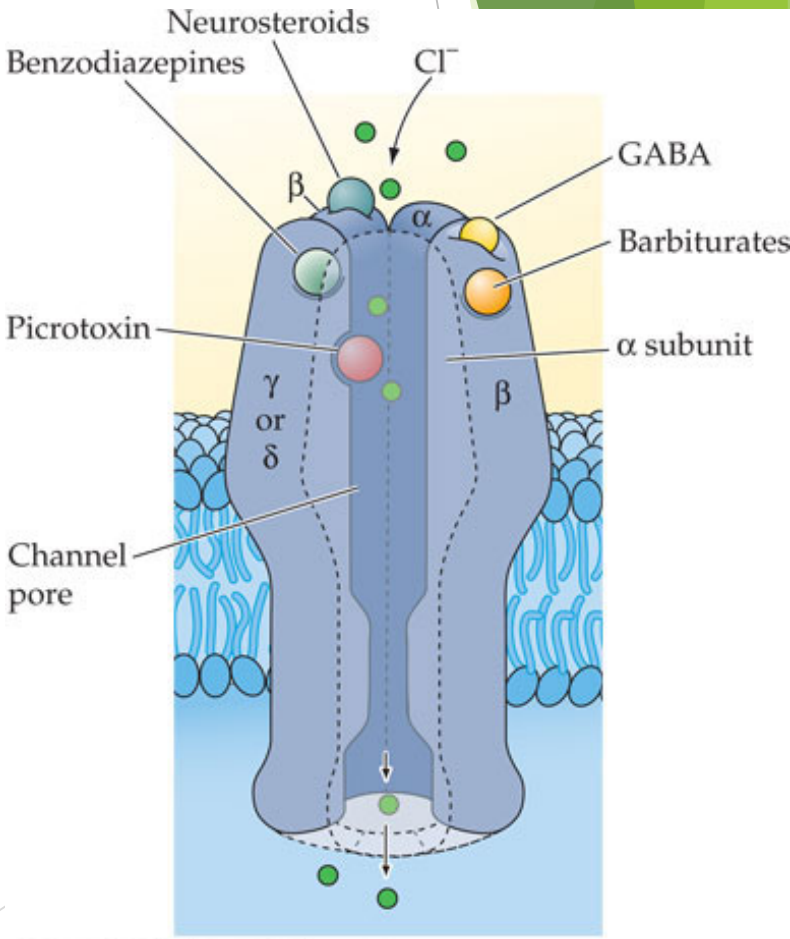
$GABA_A$ receptor: Cl^- channel, inhibitory function - hyperpolarisation in CNS
pentamer structure (usually 2α, 2β, ɤ),
16 different subunits: α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, π, θ
Possible composition is over 1 M

Has binding site for:

GABA (ɤ-amino butyric acid),
BZD, barbiturates } ALLOSTERIC MODULATION

BZD R (also called ω R) is composed of either
α_1: hypnosis, sedation; α_5: amnesia; OR
$\alpha_{2,3}$: anxiolytic, anticonvulsant; subunits

Effect of BZDs on BZD R:
↑ frequency of channel opening!!!



Drugs acting on BZD receptor

- BZD receptor agonists: benzodiazepines, „Z compounds”
- BZD receptor antagonist: flumazenile (Annexate®) –
  - competitive antagonist
  - short half life ($t_{1/2}$: 0.7-1.3 hours)→intoxication relapse
  - for diagnostic and therapeutic purposes
  - antidote! (complex therapy of intoxication)
  - 0.2-0.4 mg
- BZD receptor inverse agonist:
  - β-carbolines
  - experimental application

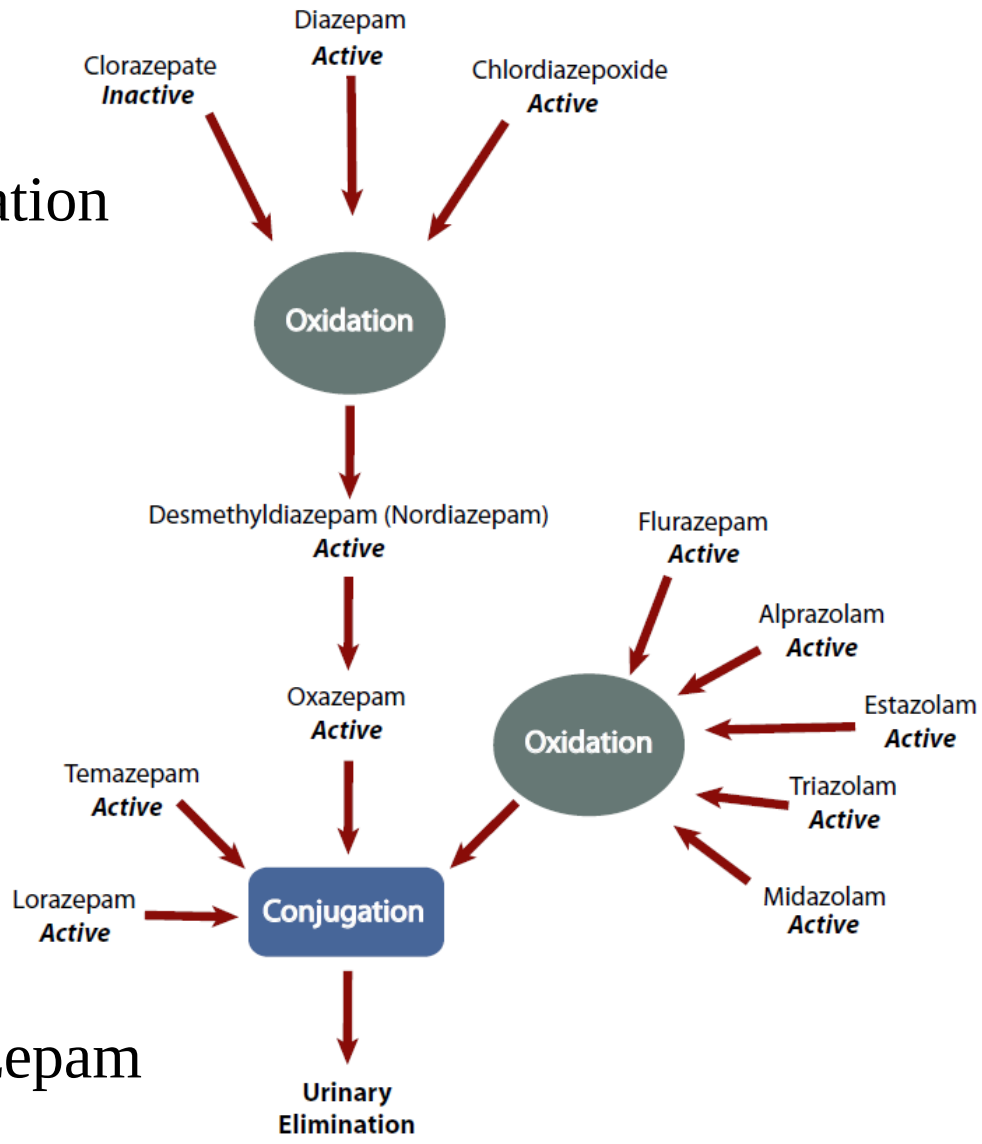
Pharmakokinetic features of Benzodiazepines

absorption: 80-100%, oral application

lipid solubility ↑ - penetrating, accumulating in CNS

metabolised by CYP3A4, CYP2C19 (ketoconazole, H_2 rec blockers, makrolides)

active metabolite: desmethyl-diazepam (diazepam, chlordiazepoxide)
$t_{1/2}$: 40-60 h → prolonged effect!

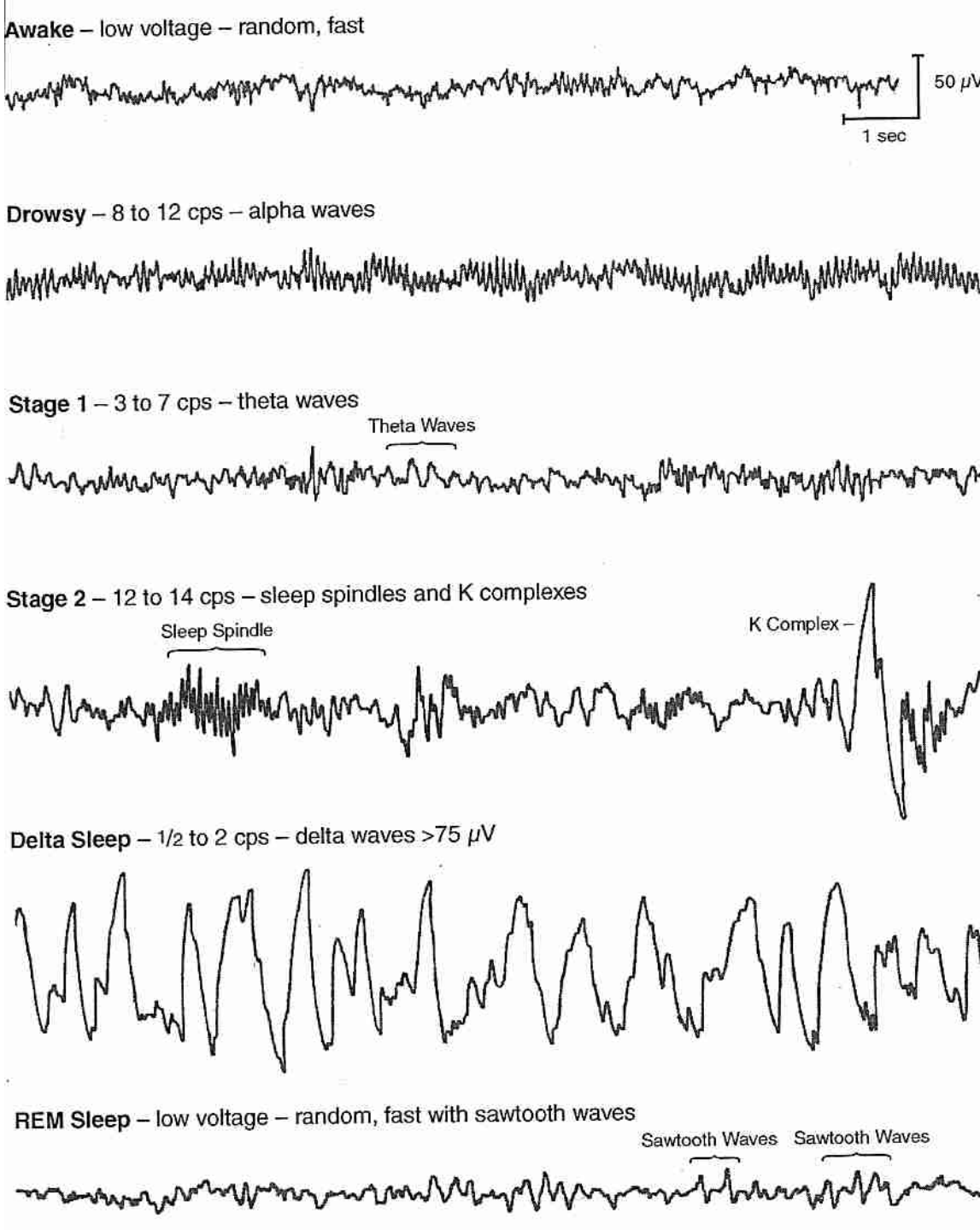


Effects of Benzodiazepines

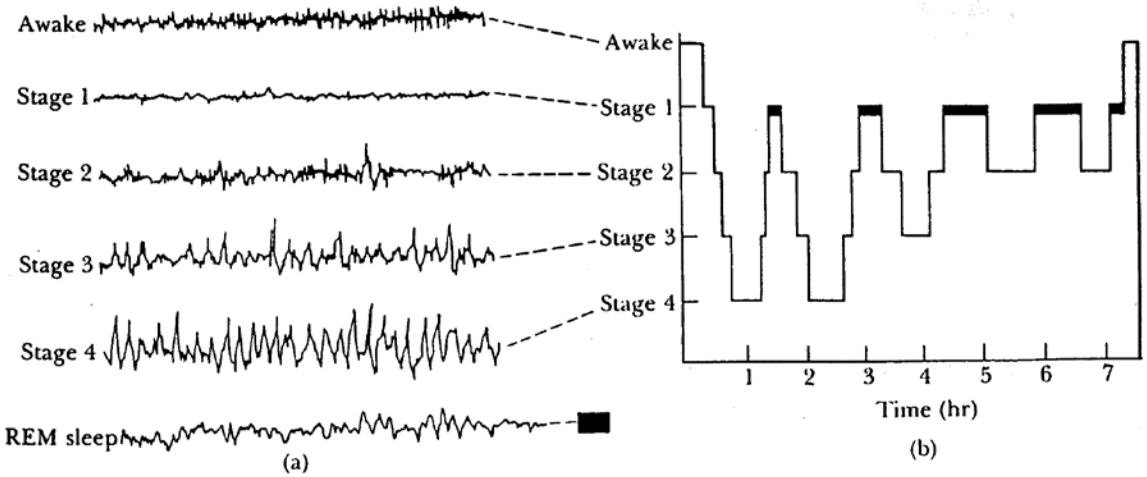
- sedative, anxiolytic:
  - calming effects, produce drowsiness
- anaesthetic:
  - premedication: ET intubation, etc. (e.g. midazolam)
- amnestic:
  - anterograd and retrograd amnesia
- anticonvulsant:
  - anti seizure effect
- muscle relaxant
- hypnotic:
  - ↓ latency of sleep onset
  - ↑ duration of NREM
    (but increase the 1. stage of sleep = superficial non-REM sleep)
  - ↓ duration of REM

Stages of sleep

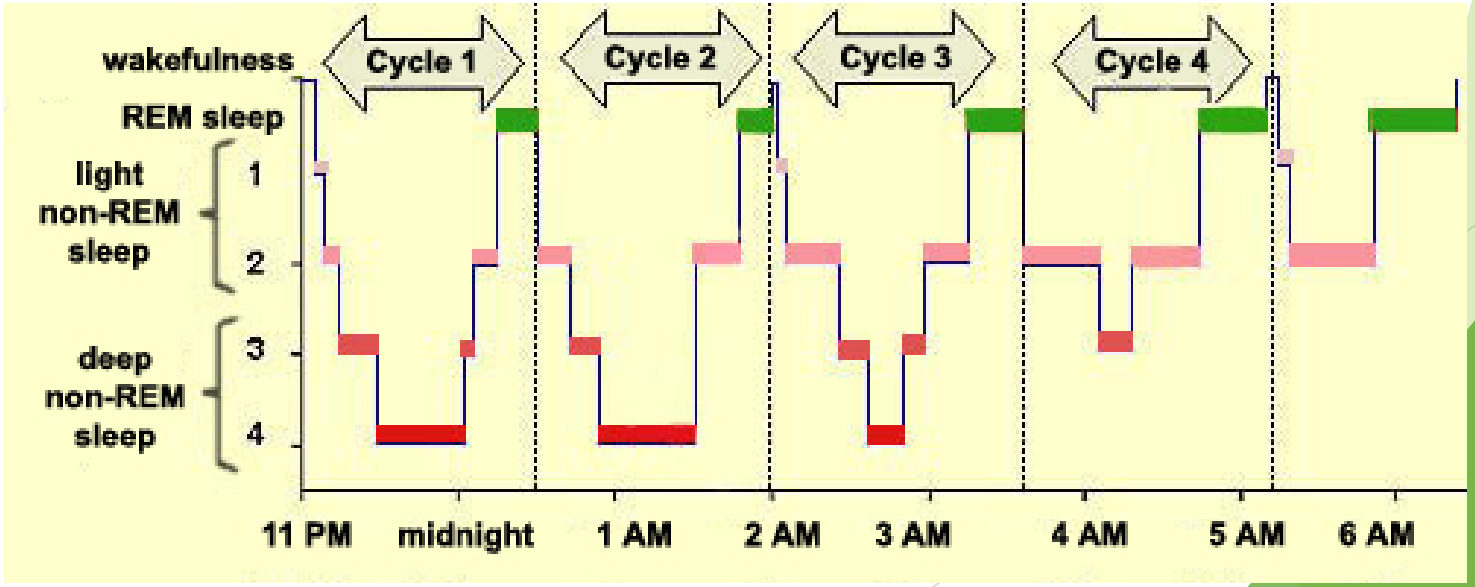
- A whole cocktail of neurotransmitters are involved in driving wakefulness and sleep including:
- histamine,dopamine, norepinephrine, serotonin, glutamate, orexin, melatonin and acetylcholine
- during sleep synchronisation of EEG waves can be observed (on multi-lead EEG)



Sleep hypnogram - periodicity



Mammalian sleep occurs in repeating periods: non-REM and REM sleep. REM stands for "rapid eye movement", but involves many other aspects including virtual paralysis of the body.



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  - ↓ latency of sleep onset
  - ↑ duration of NREM
    (but increase the 1. stage of sleep = superficial non-REM sleep)
  - ↓ duration of REM

Adverse effects of Benzodiazepines

- cardiovascular/respiratory depression
  - (impaired cardiac/metabolic/respiratory function)
- tolerance→abuse→dependence
- withdrawal syndrome
  - psychological
  - physical

Benzodiazepines

Therapeutical use/Clinical indication:

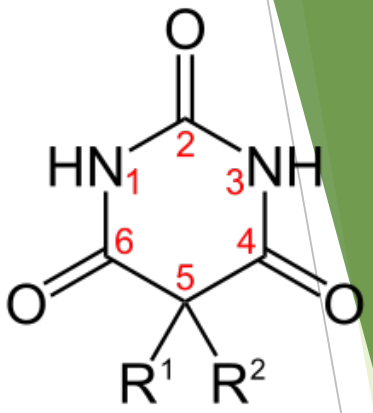
- relief of anxiety (GAD, Phobias, OCD)
- insomnia
- sedation and amnesia before and during medical and surgical procedures (Anaesthesia, Preoperative phases)
- main component of balanced anaesthesia (i.v.)
- treatment of epilepsy and seizures (GTCS)
- control of ethanol or other sedative-hypnotic withdrawal states

Names, Routes of Administration, and Therapeutic Uses of Benzodiazepines

Compound (Trade Name)	Routes of Administration*	Examples of Therapeutic Uses†	Comments	$t_{1/2}$, Hours‡	Usual Sedative-Hypnotic Hypnotic Dosage, mg¶
Alprazolam (XANAX)	Oral	Anxiety disorders, agoraphobia	Withdrawal symptoms may be especially severe	12±2	—
Chlordiazepoxide (LIBRIUM, others)	Oral, IM, IV	Anxiety disorders, management of alcohol withdrawal, anesthetic premedication	Long-acting and self-tapering because of active metabolites	10±3.4	50–100, qd–qid§
Clonazepam (KLONOPIN)	Oral	Seizure disorders, adjunctive treatment in acute mania and certain movement disorders	Tolerance develops to anticonvulsant effects	23±5	—
Clorazepate (TRANXENE, others)	Oral	Anxiety disorders,seizure disorders	Prodrug; nordazepam formed by decarboxylation in GI tract	2.0±0.9	3.75–20, bid–qid§
Diazepam (VALIUM, others)	Oral, IM, IV, rectal	Anxiety status epilepticus, skeletal muscle relaxation, anesthetic premed	Prototypical benzodiazepine	43±13	5–10, tid–qid§
Estazolam (PROSOM)	Oral	Insomnia	Contains triazolo ring; adverse effects may be similar to those of triazolam	10–24	1–2
Flurazepam (DALMANE)	Oral	Insomnia	Active metabolites accumulate with chronic use	74±24	15–30
Lorazepam (ATIVAN)	Oral, IM, IV	Anxiety disorders, preanesthetic medication	Metabolized solely by conjugation	14±5	2–4
Midazolam (VERSED)	IV, IM	Preanesthetic and intraoperative medication	Rapidly inactivated	1.9±0.6	—#
Oxazepam (SERAX)	Oral	Anxiety disorders	Metabolized solely by conjugation	8.0±2.4	15–30, tid–qid§
Quazepam (DORAL)	Oral	Insomnia	Active metabolites accumulate with chronic use	39	7.5–15
Temazepam (RESTORIL)	Oral	Insomnia	Metabolized mainly by conjugation	11±6	7.5–30
Triazolam (HALCION)	Oral	Insomnia	Rapidly inactivated; may cause disturbing daytime side effects	2.9±1.0	0.125–0.25

*IM, intramuscular injection; IV, intravenous administration; qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day.
†The therapeutic uses are identified as examples to emphasize that most benzodiazepines can be used interchangeably. In general, the therapeutic uses of a given benzodiazepine are related to its half-life and may not match the marketed indications. The issue is addressed more extensively in the text.
‡Half-life of active metabolite may differ. See Appendix II in the 11th edition of the parent text for additional information.
¶For additional dosage information, see Chapter 13 (Anesthesia), Chapter 17 (Anxiety), and Chapter 19 (Seizure Disorders).
§Approved as a sedative-hypnotic only for management of alcohol withdrawal; doses in a nontolerant individual would be smaller.
#Recommended doses vary considerably depending on specific use, condition of patient, and concomitant administration of other drugs.

Barbiturates



history: - 1912, barbituric acid ($R^{1,2}$= H)

classification: (based on duration of action)

- ultrashort: thiopental (Trapanal®)
- short: cyclobarbital
- medium: secobarbital
- long: phenobarbital (Sevenal®, Sevenaletta®)

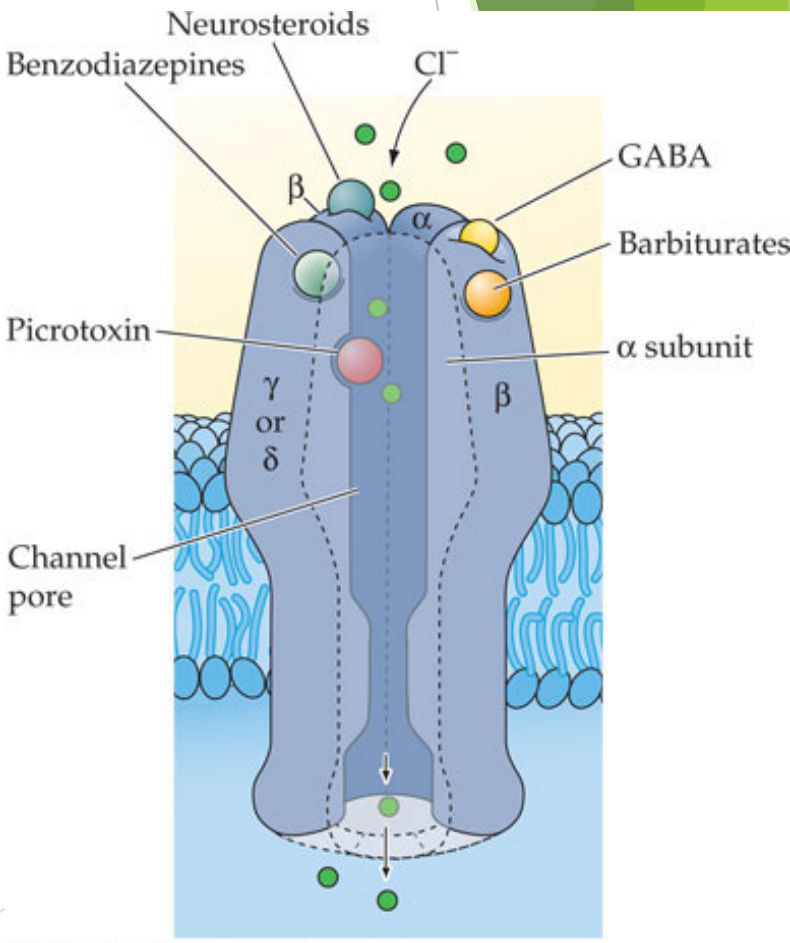
Barbiturates

<u>mechanism of action:</u>

specific regulatory site on $GABA_A$ receptor

binding site for

barbiturates



allosteric modulator effect:

↑ duration of channel opening!!!

Barbiturates

Effects:

- similar to BDZ

  but! extremly depressant on CNS

- cardiovascular/respiratory depression

- hepatic enzyme induction (phenobarbital)
  - coumarin, phenytoin, digitalis (serum cc.↓)

Barbiturates

Therapeutical use:

- obsolete drugs!!!
- anti-seizure therapy: infants, children→phenobarbital
- sedation and amnesia before and during medical and surgical procedures → thiopental (ultrashort-acting)
- main component of balanced anaesthesia (i.v.) → thiopental
- therapy of neonatal jaundice → phenobarbital
- Used when benzo class drugs fail or in underdeveloped countries

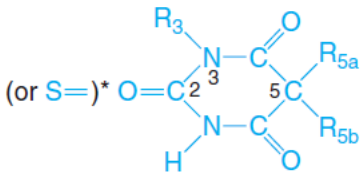
Barbiturates

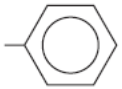
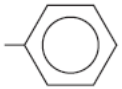
Adverse effects:

- tolerance→dependence/addiction→abuse
  → respiratory depression, coma (ethanol!)
- withdrawal syndrome
  - psychological
  - physical
- more marked than, BZDs

Structures, Trade Names, and Major Pharmacological Properties of Selected Barbiturates

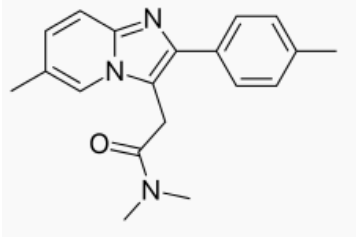
General Formula:

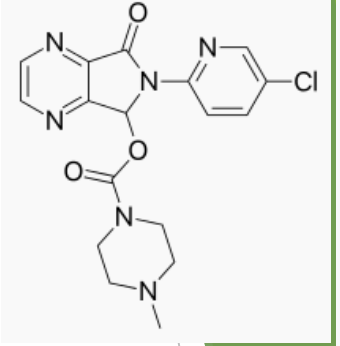


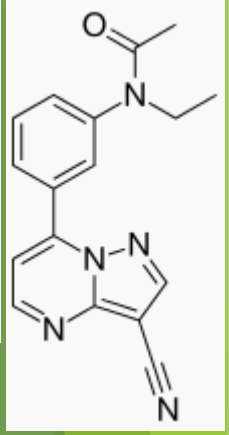
Compound (Trade Names)	R_3	R_{5a}	R_{5b}	Routes of Administration†	$t_{1/2}$, Hours	Therapeutic Uses	Comments
Amobarbital (AMYTAL)	—H	$-C_2H_5$	$-CH_2CH_2CH(CH_3)_2$	IM, IV	10–40	Insomnia, preoperative sedation, emergency management of seizures	Only Na^+ salt administered parenterally
Butabarbital (BUTISOL, others)	—H	$-C_2H_5$	$-CH(CH_3)CH_2CH_3$	Oral	35–50	Insomnia, preoperative sedation	Redistribution shortens duration of action of single dose to 8 hours
Butalbital	—H	$-CH_2CH=CH_2$	$CH_2CH(CH_3)_2$	Oral	35–88	Marketed in combination with analgesics	Therapeutic efficacy questionable
Mephobarbital (MEBARAL)	$-CH_3$	$-C_2H_5$		Oral	10–70	Seizure disorders, daytime sedation	Second-line anticonvulsant
Methohexital (BREVITAL)	$-CH_3$	$-CH_2CH=CH_2$	$-CH(CH_3)C\equiv CCH_2CH_3$	IV	3–5‡	Induction and maintenance of anesthesia	Only Na^+ salt is available; single injection provides 5–7 minutes of anesthesia‡
Pentobarbital (NEMBUTAL)	—H	$-C_2H_5$	$-CH(CH_3)CH_2CH_2CH_3$	Oral, IM, IV, rectal	15–50	Insomnia, preoperative sedation, emergency management of seizures	Only Na^+ salt administered parenterally
Phenobarbital (LUMINAL, others)	—H	$-C_2H_5$		Oral, IM, IV	80–120	Seizure disorders, status epilepticus, daytime sedation	First-line anticonvulsant; only Na^+ salt administered parenterally
Secobarbital (SECONAL)	—H	$-CH_2CH=CH_2$	$-CH(CH_3)CH_2CH_2CH_3$	Oral	15–40	Insomnia, preoperative sedation	Only Na^+ salt is available
Thiopental (PENTOTHAL)	—H	$-C_2H_5$	$-CH(CH_3)CH_2CH_2CH_3$	IV	8–10‡	Induction/maintenance of anesthesia, preop sedation, emergency management of seizures	Only Na^+ salt is available; single injections provide short periods of anesthesia‡

*O except in thiopental, where it is replaced by S. †IM, intramuscular injection; IV, intravenous administration.
‡Value represents terminal $t_{1/2}$ due to metabolism by the liver; redistribution following parenteral administration produces effects lasting only a few minutes.

„Z compounds”



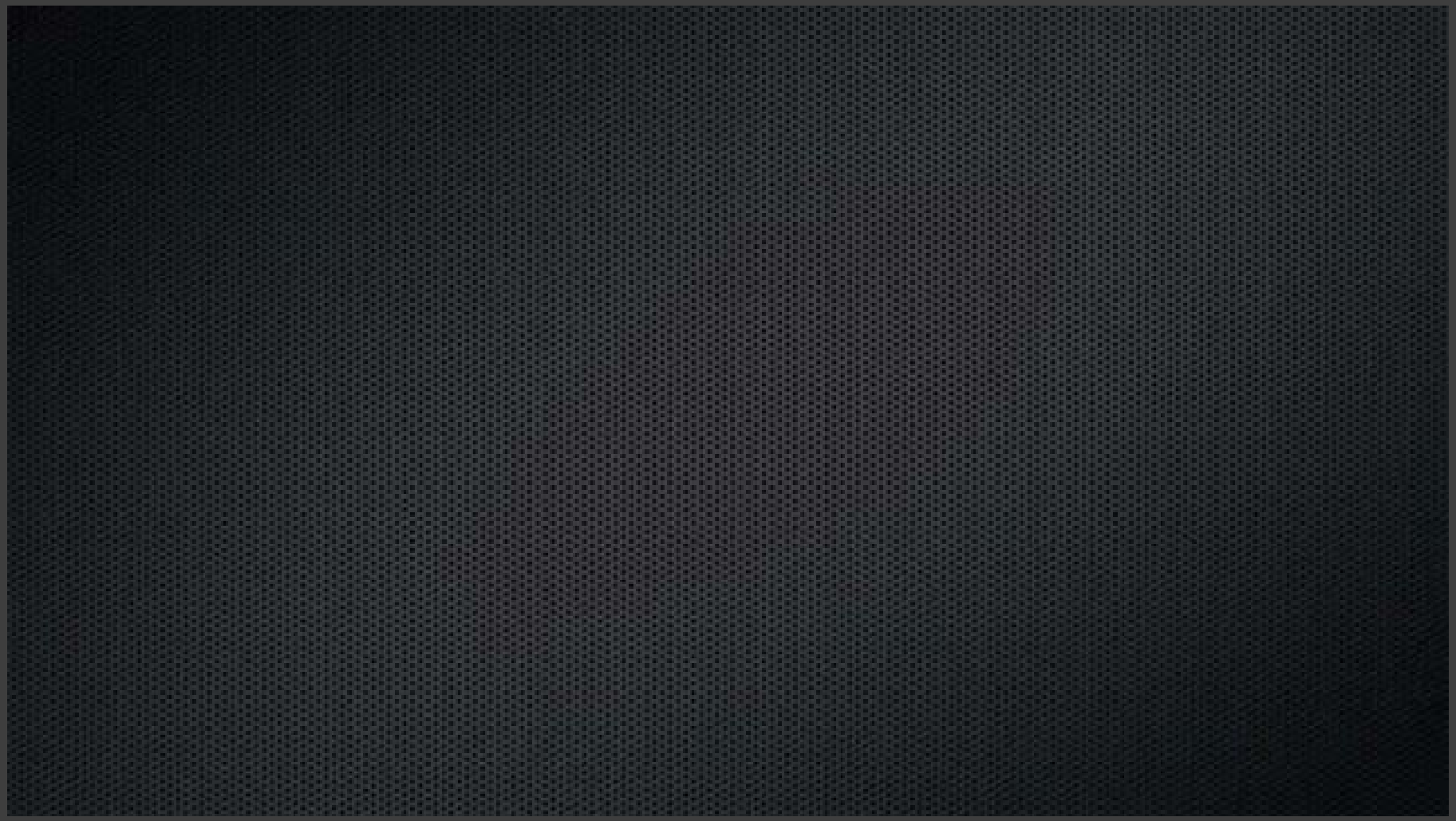




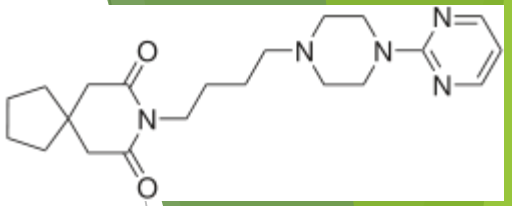
- zolpidem, zopiclon, zaleplon
  - selective ω_1 receptor agonist (bind selectively to α_1 subunit)
  - ω_1 receptor: cortex, hippocampus
  - novel hypnotic effects – no CNS depression
  - no anxiolytic, sedative, muscle-relaxant effects
  - can be antagonized by flumazenil
  - For short-term treatment of insomnia (max 2-4 weeks)
  - Transient treatment of aphasia (zolpidem)

Zolpidem = Stilnox® Sanval ®, Ambien ®
Zopiclon = Somnol ®, Imovane ®
Zaleplon = Andante ®

Transient effect of Zolpidem on aphasia, 0:00-0:20, 0:45-1:10



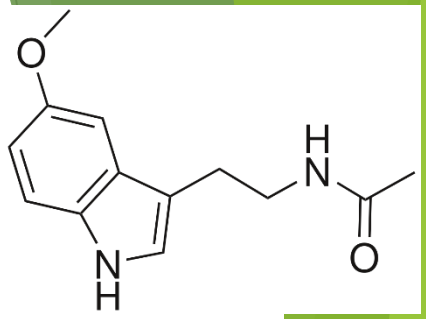
5 HT receptor agonists



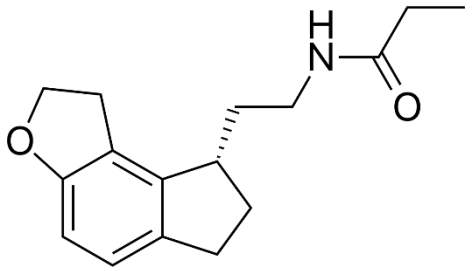
- Buspirone (Spitomin®)
  - partial agonist on $5HT_{1A}$ receptor (also binds to dopamin-R)
  - sedative, hypnotic, euphoric effects
  - no anticonvulsant, no muscle relaxant properties
  - no withdrawal symptoms, no abuse
  - Delayed onset of action (2-3 weeks) Slow onset of action, metabolized by CYP3A4
  - active metabolite: α_2R antagonism, BP↑
  - other drugs: gepirone, ipsapirone

Melatonin receptor agonists

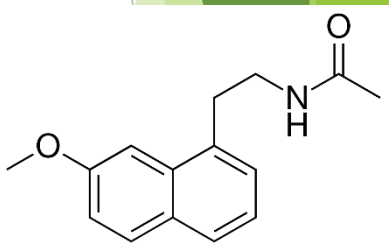
- Ramelteon:
  - agonists on MT_1, MT_2 melatonin receptors (suprachiasm. nucl.)
  - no direct effects on GABAerg neurons
  - hypnotic drug
    - treatment of insomnia
  - no anxiolytic, sedative, muscle-relaxant effects
  - oral administration
    - rapid absorption, excessive first-pass metabolism
  - adverse effects:
    - dizzines, fatigue
    - endocrine changes: testosterone↓ prolactin↑
  - no withdrawal symptoms, no abuse
  - Others: agomelatine, tasimelteon
  - Melatonin (Circadin®, Bio-Melatonin®)



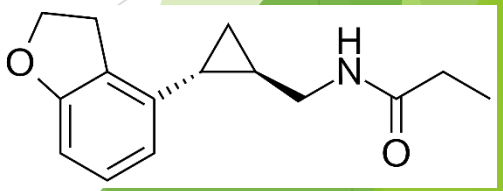
melatonin



ramelteon



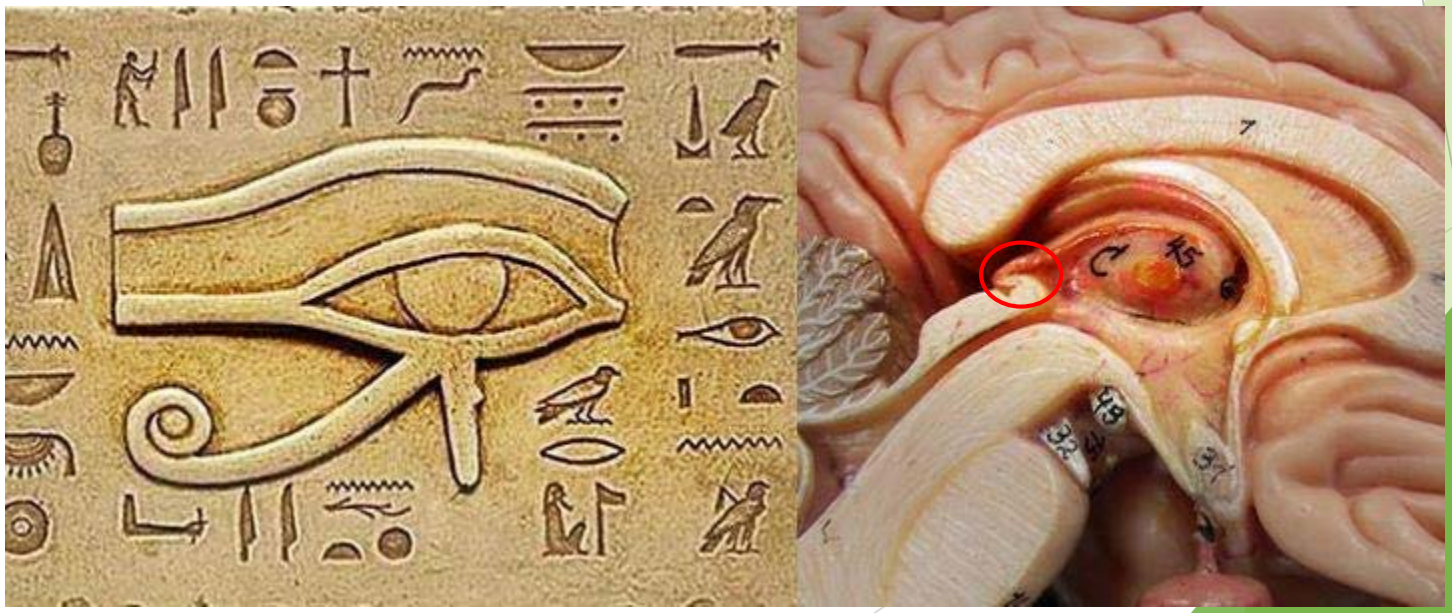
agomelatine



tasimelteon

Circadian rhythm

- suprachiasmatic nucleus (SCN) = circadian "clock",
  a pair of distinct groups of cells located in the hypothalamus
- Retina ➔illumination = length of day ➔ SCN ➔
  pineal gland ➔ melatonin secretion
- Secretion of melatonin peaks at night and negligible during the day
- dim-light melatonin onset – DLMO at roughly 21:00 (9 p.m.)
  melatonin can be measured in the blood, saliva



Circadian rhythm II.

- Chronopharmacology: relationship between drugs and circadian rhythm
- Chronotherapy: the use of circadian or other rhythmic cycles in the application of therapy
- Chronotherapy is used in different fields, examples:
  - asthmatic attack is more common at dawn
  - Cancer-therapy (therapy of ALL is more effective in the evening)
  - Morning angina, rise in blood-pressure at dawn ➔ timing of anti-anginal and anti-hypertensive agents
  - multiple types of depression
  - ACTH level highest in the morning ➔ steroid-therapy in the morning
  - Peak of cholesterin-synthesis is in the evening ➔ statins night

Other drugs producing sedatohypnotic-anxiolytic effects

- Chloralhydrate, paraldehyde (historical significance)
- promethazin, cyclizin (1st gen. H_1-rec blocker antihistamines)
- Carbamates: Ethinamate; Meprobamate (Andaxin)
- Piperidinediones: Glutethimide, Methyprylon

$GABA_A$-agonists

- TCA (imipramine) (due to H_1-rec blocking effect)
- Alcohols

Alcohols

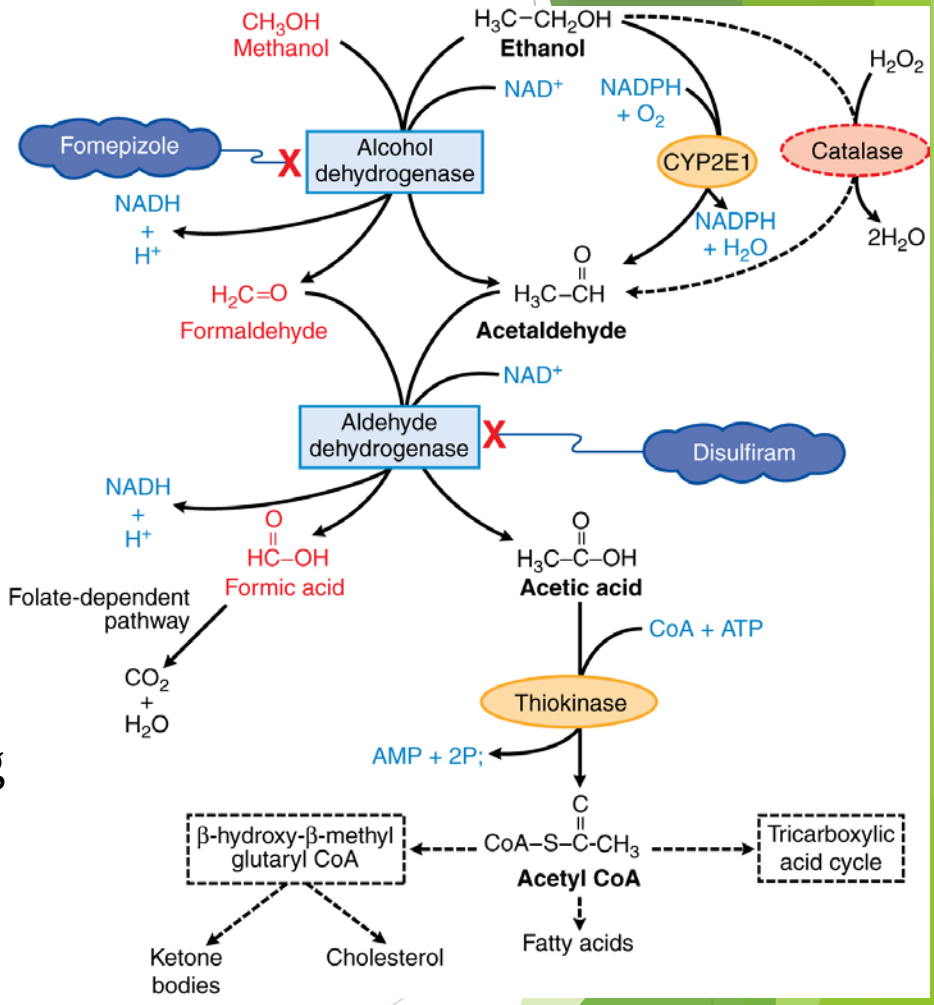
- history: Ancient Egypt
  Roman Empire
  Medieval ages
  Industrial revolution

„most commonly abused drug”
„French paradox”

- main types:
  - ethyl-alcohol (ethanol)
  - methyl-alcohol (methanol)
  - ethylen-glycol

Ethanol

- Pharmacokinetic aspects
  - water-soluble
  - rapid absorption (stomach, small intestine)
  - rapid distribution, CNS („well perfused”)
  - metabolized in the liver
    - Alcohol Dehydrogenase (ethanol→acetaldehyde), ADH1A, ADH1B, ADH1C
    - Microsomal Ethanol Oxidating System (MEOS = CYP2E1) (when ADH is saturated)
    - Aldehyde Dehidrogenase (acetaldehyde →acetic acid), (mutation:ALDH2*2)
  - excreted by kidney, lungs



Ethanol (acute consumption)

- mechanism of action
  - CNS:
    - inhibiting glutamate R (NMDA channel)
    - enhancing the action of GABA on $GABA_AR$
    - blocking voltage gated Na/Ca channels
    - activating voltage gated K-channels
    - release of β endorfins
  - Heart
    - cardiodepressive effect
  - Respiratory system
    - depression
  - Smooth muscle
    - vasodilation

BAC (mg/dl)	symptoms
50-100	sedation, „subjective high”, slower reactions
100-200	impaired motorium, slurred speech, ataxia
200-300	emesis, stupor
300-400	coma, blackout
>500	respiratory depression, death

Ethanol (chronic consumption)

- Liver and GIT
  - fatty liver, alcohol induced hepatitis, cirrhosis
  - enzyme induction (early phases)
  - chronic pancreatitis
  - malabsorption syndrome

- CNS
  - neurotoxicity (Wernicke-Korsakoff syndrome) (first inhibition of NMDA-rec; later upregulation and over-activation ➔ Glu-excitotoxicity)
  - tolerance – dependence – alcohol withdrawal syndrome
    - delirium tremens
    - Due to $GABA_A$ downregulation and NMDA-rec upregulation

- Cardiovascular system
  - cardiomyopathy
  - heart failure
  - arrhythmia
  - Coronary Heart Disease

- Blood/Immune system
  - anaemia
  - infections

- Fetal alcohole syndrome
  - intrauterine growth retardation
  - microcephaly
  - abnormalities in development of midfacial region

Ethanol

Management of acute alcohol intoxication

- prevent respiratory depression
- prevent aspiration (vomitus)
- glucose i.v.
- thiamine i.v. (Vitamin B_1)
- prevent electrolyte disturbances: antiemetic drugs (metoclopramide, Vitamin B_6)

Ethanol

Management of alcohol withdrawal syndrome

- sedation, anxiolysis, anti-seizure therapy
  - diazepam, clonazepam, chlordiazepoxide
- antipsychotic
  - haloperidol, carbamazepine, mepobramate
- neuroprotection
  - thiamine (Vitamin B_1)
  - glucose
- electrolyte, saline supplementation

Ethanol

Treatment of alcoholism

- disulfiram (Antaethyl®)
  - blocking ALDH → acetaldehyde↑, „hangover”
  - sweating, facial flushing, nausea, vomiting, hypotension, confusion
- acamprosate
  - NMDA antagonist, $GABA_AR$ PAM
  - effects based on receptor occupancy – partial agonism
- Naltrexone
  - Opioid-receptor antagonist
  - Preventing beta-endorphine effects

Methanol

- industrial application, detergents
- accidental/suicide intoxication
- Absorbed well from skin, GIT
- metabolized by ADH, ALDH
  (methanol→formaldehyde→formic acid)

- Symptoms
  - visual disturbances (snow storm)→(retina destruction)
  - nausea, vomitus, seizures (metabolic acidosis)
  - respiratory distress, coma

Intoxication of methanol

- Therapy
  - decontamination
  - ethanol (p.o., i.v.) – saturating ADH
  - fomepizole – inhibitor of ADH
  - alkalization (Na_2HCO_3)
  - haemodialysis
  - support of respiration
  - anti seizure therapy

Ethylene glycol

- windshield washing, anti-freeze formulations
- accidental/suicide intoxication (sweet taste ➔ children as well)
- rapid absorption from GIT
- metabolized by ADH
  (Ethylene glycol →glycolic-acid→oxalic-acid)
- (nowadays propylene-glycol is used, because its unpleasant taste and it is metabolized to lactic acid)

- Symptoms:
  - headache
  - nausea, vomitus, seizures (metabolic acidosis)
  - acute renal failure
  - respiratory distress, coma

Intoxication of ethylene glycol

- Therapy
  - decontamination
  - ethanol (p.o., i.v.) – saturating ADH
  - fomepizole – inhibitor of ADH
  - alkalization (Na_2HCO_3)
  - haemodialysis
  - support of respiration
  - anti seizure therapy

Antiepileptic (anticonvulsive, antiseizure) drugs

Epilepsy, seizures

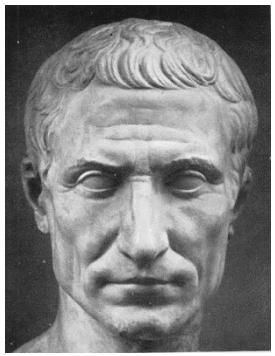
- Epilepsy:
  - is a heterogeneous symptom complex – a chronic neurological disorder characterized by recurrent and unpredictable seizures

- Seizures:
  - are finite episodes of brain dysfunction with a transient alteration of behavior resulting from abnormal, excessive discharge of cerebral neurons, a hypersynchronous neuronal activity in the brain

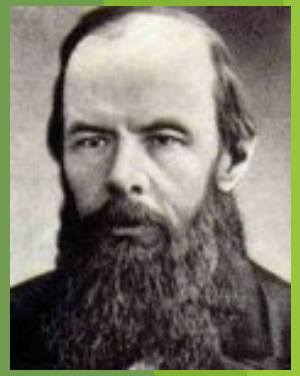
Epilepsy, seizures

- history:
  - most common neurology disorder
  - epilepsy – 0,1% of population
  - „morbus sacer” = the "sacred disease" because of the belief that those who had seizures were possessed by evil spirits or touched by the gods and should be treated by invoking mystical powers.
- (epilepsy and genius were often closely connected?)
  - Alexander the Great
  - Julius Caesar
  - Saint Paul
  - Jeanne D’Arc
  - Blaise Pascal
  - Isaac Newton
  - Alfred Nobel
  - Vincent Van Gogh
  - George Frideric Handel
  - Fyodor Dostoyevsky
  - Agatha Christie
  - Ludwig van Beethoven
  - Pyotr Ilyich Tchaikovsky
  - Michelangelo Da Vinci
  - Lewis Carol (Alice in Wonderland)
  - Aristotle
  - Napoleon
  - Hugo Weaving

Alexander the Great
Macedonian King

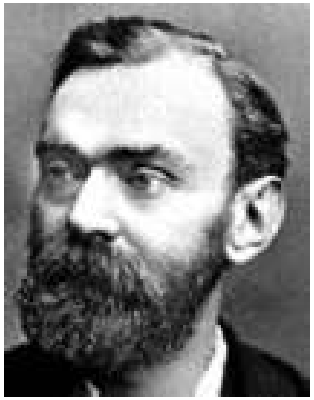


G. Julius Caesar
Roman Statesman

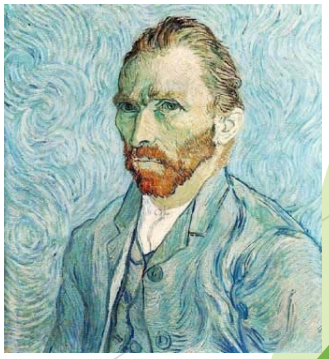


F.M. Dostoyevsky
Russian Writer

Napoleon Bonaparte
French Emperor



Alfred Nobel
Swedish Chemist



Vincent van Gogh
Dutch painter

Epilepsy, seizures

- background:
  - localized or generalized discharge of the cerebral neurons (epileptogenic focus)
  - (seizures = somatic manifestations of the CNS discharge)

- definition
  - epileptiform /epileptic seizure (accidental, temporary)
    - fever (neonates, children) – „hyperpyretic seizure/convulsion”
    - hypoglycaemia
    - drug/alcohol withdrawal
    - hyperventillation
    - hypoxia

  - epilepsy (as disease) – at regular intervals, repetitive, periodic
    - idiopathic (genuine), primer
    - Symptomatic, secunder
      - trauma (CNS)
      - neoplasia
      - meningitis
      - malformations in CNS

Seizure types

Partial seizures (motoric, sensoric, vegetative) (60%)

- simple partial seizure (preservation of consciousness)
- complex partial seizures (complex – the patient lose consciousness, often start with deja vu, smelling weird odours)
- partial seizures secondarily generalized to GTCS

Generalized seizures (40%)

- absence seizures (petit mal)
- generalized tonic-clonic seizures (GTCS) (grand mal)
- myoclonic seizures
- atonic/akinetic seizures

clinical forms!

- epileptic attack – (ictus epilepticus)
- repeated seizures
- status epilepticus – („permanent epileptic state”)

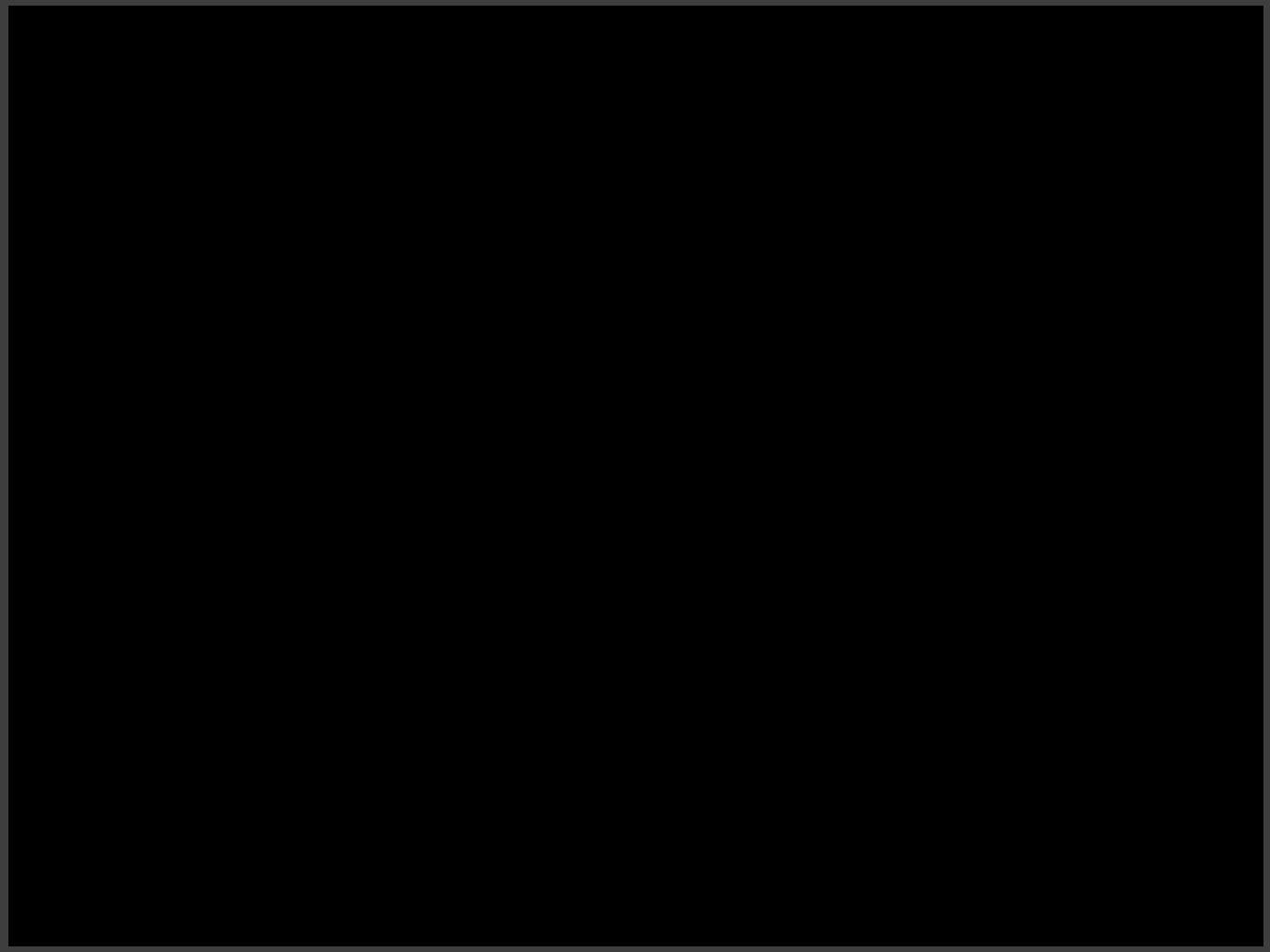
Seizures

Absence seizure (petit mal) (1:00)

Tonic-clonic seizure (grand mal) (0:17)

2. Tonic-clonic seizure (grand mal)

Secondariliy generalised complex partial seizure (0:35) (1:36) (2:18)



Pathomechanism

1. excitation – PDS* – spontaneous depolarization
2. propagation – spreading into diferrent CNS structures
3. hypersynchronization
4. seizures (somatic manifestation)

Hypothesis:

glutamate ↑

GABA ↓

***PDS**: Neurons from which the epileptic discharge originates display an **unusual type of electrical behaviour** termed the paroxysmal depolarising shift (PDS), during which the membrane potential suddenly increases by about 30 mV and remains depolarised for up to a few seconds before returning to normal.

Mechanisms of action of antiseizure drugs

- Enhanced γ-aminobutyric acid (GABA) mediated synaptic inhibition.
  - $GABA_A$ agonist effect, or enhancing GABA effect (e.g. BZDs)
  - increasing the amount of GABA by
    - inhibiting GABA metabolism (e.g. vigabatrin)
    - inhibiting GABA reuptake (e.g. tiagabin)
- Inhibition of glutamate (excitatory amino acid) mediated synaptic excitation
  - NMDA Glu-rec. Inhibition (e.g. felbamate)
  - AMPA Glu-rec. Inhibition (e.g. lamotrigin)
  - Inhibiton of presynaptic relelase (Ca-dependent see below)
- Inhibition of ion channels
  - T-type (transient) Ca^{2+} channels (e.g. ethosuximid)
  - voltage-activated Na^{+} channels (e.g. phenytoin)

One classification of antiepileptic drugs (~pharmacologic)

GABAergics

$GABA_AR$ PAMs:
- Barbiturates
- BZDs
- Carbamates
- NaBr/KBr

GABA-T inhibitors:
- Fatty acids
- Vigabatrin

GABA-R Agonists:
- Progabide

GAT-1 inhibitors:
- Tiagabine

Channelergics

Sodium channel blockers:
- Hydantoins
- Fatty acids
- Carboxamides (Iminostilbenes)
- Lamotrigine
- Topiramate
- Sulfonamides (e.g.Zonisamide)

Calcium channel blockers:
- Succinimides
- Gabapentinoids
- Lamotrigine
- Topiramate
- Zonisamide

Potassium channel openers:
- Retigabine

CA inhibitors

Sulfonamides:
- Acetazolamide
- Topiramate
- Zonisamide
- Sultiame

Other

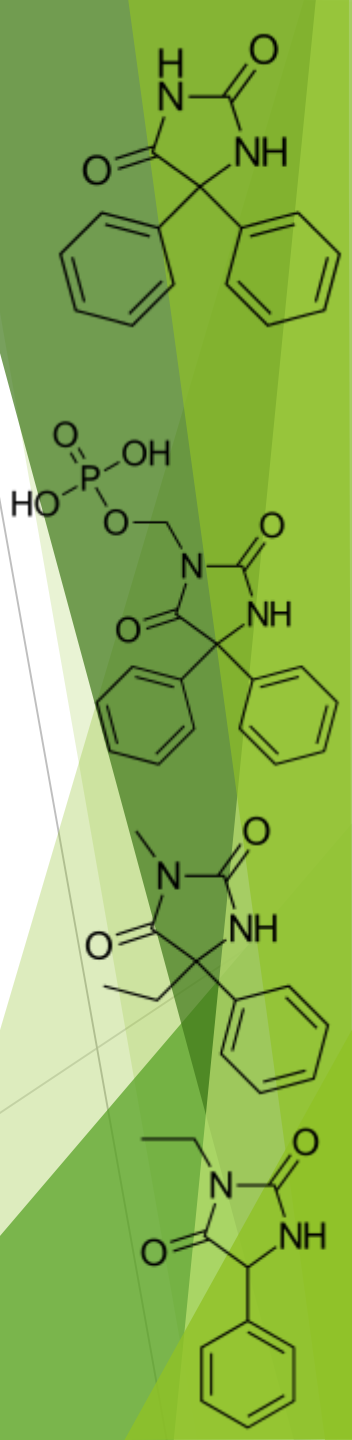
Levetiracetam

Chemical classification of antiepileptics

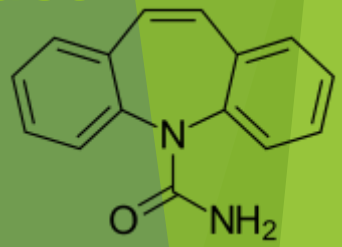
- Barbiturates
  Phenobarbital (1912).
  Methylphenobarbital (1935). ,
  Barbexaclone (1982).
- Benzodiazepines
  Clobazam (1979). , Clonazepam (1974).,
  Clorazepate (1972)., The following
  benzodiazepines are used to treat status
  epilepticus:, Diazepam (1963).., Midazolam
  (1975). , Lorazepam (1972).
- Bromides
  Potassium bromide (1857).
- Carbamates
  Felbamate (1993), Retigabine (2011)
- Carboxamides (iminostilbenes;
  dibenzoazepines)
  Carbamazepine (1963). , Oxcarbazepine
  (1990). , Eslicarbazepine acetate (2009)
- Fatty acids
  valproic acid (1967)., Vigabatrin (1989).,
  Progabide, Tiagabine (1996)., (Vigabatrin
  and progabide are also analogs of GABA.)
- Fructose derivatives
  Topiramate (1995).
- GABA analogs
  Gabapentin (1993)., Pregabalin (2004).
- Hydantoins
  Ethotoin (1957)., Phenytoin (1938).,
  Mephenytoin, Fosphenytoin (1996).
- Pyrimidinediones
  Primidone (1952). (=desoxy-phenobarbital)
- Pyrrolidines
  Brivaracetam, Levetiracetam (1999).,
  Seletracetam
- Succinimides
  Ethosuximide (1955)., Phensuximide,
  Mesuximide
- Sulfonamides
  Acetazolamide (1953)., Sultiame,
  Methazolamide, Zonisamide (2000).
- Triazines
  Lamotrigine (1990).
- Valproylamides (amide derivatives of
  valproate)
  Valpromide, Valnoctamide

Antiseizure drugs - hydantoins

- Phenytoin (Epanutin®, Diphedan®), fosphenytoin, mephenytoin, ethotoin
  - (di)phenyl-hydantoin-derivatives
  - one of the oldest antiseizure drugs
  - pharmacodynamic features
    - blocking VG Na^+ channels (I/B type antiarrhythmic drugs)
  - pharmacokinetic features
    - well absorbed
    - Highly plasma-protein bound ➔ increases free plasmal level of other protein-bound agents e.g.: phenylbutazon, warfarin, sulfonamide
    - CYP3A4 and CYP2C19 enzyme inductor!
  - adverse effects
    - pro-arrhythmic
    - hyperthyreosis (affinity to thyroxine binding globuline)
    - diplopia (= double vision)
    - ataxia
    - gingiva hyperplasia (impaired collagen metabolism)
  - clinical use
    - partial seizures (simplex, complex)
    - GTCS
    - 15-20 mg/kg



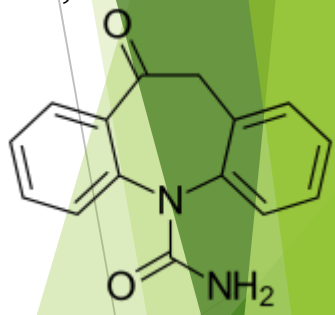
Antiseizure drugs – Iminostilbenes/Carboxamides

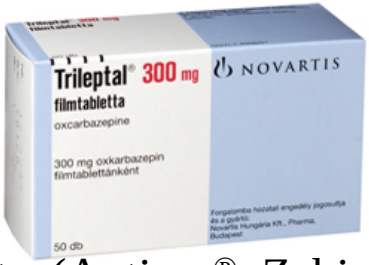


Carbamazepine (Tegretol ®, Neurotop®)

tricyclic structure (just like the structure of tricyclic antidepressants):
di-benzo-azepin

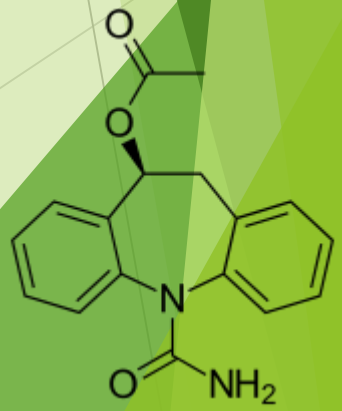
- pharmacodynamic features
  - blocking VG $Na^{+,}$ channels → limits the repetitive firing
- pharmacokinetic features
  - well absorbed
  - plasma protein binding ≈ 70%
  - induces CYP3A4 (like phenobarbital) , ↓ serum cc. of phenytoin, valproic acid, OAC
- adverse effects
  - teratogenic
  - drowsiness,
  - aplastic anaemia, agranulocytosis
- clinical use
  - partial seizures (simplex, complex)
  - GTCS
  - trigeminal neuralgia
  - effective dose: 600-800 mg/day



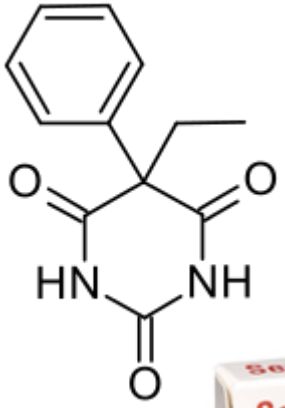


Oxcarbazepine (Trileptal®) Eslicarbazepine acetate (Aptiom®, Zebinix®)

- similar to carbamazepine
- less potent CYP3A4 enzyme inductor than carbamazepine
- CYP2C19 inzyme inhibitor!

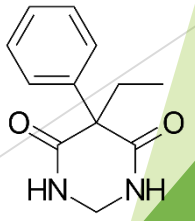


Antiseizure drugs – Barbiturates



Phenobarbital

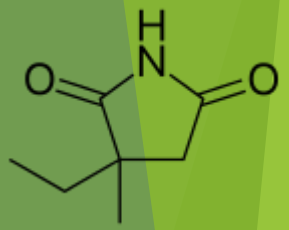
- pharmacodynamic features
  - GABA R PAM ➔ PDS↓
- pharmacokinetic features
  - well absorbed
  - hepatic enzyme induction! CYP3A4, (unwanted pregnancy!)
- adverse effects
  - sedation
  - cardiovascular/respiratory depression
- clinical use
  - partial seizures (simplex, complex)
  - GTCS

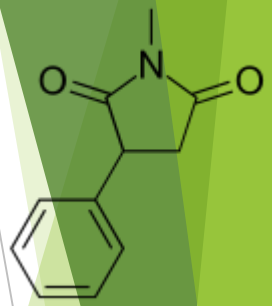


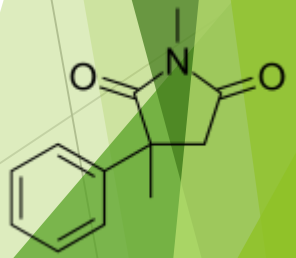
Primidon (Sertan®)

- A dezoxy-barbital, metabolises into phenobarbital

Antiseizure drugs - Succinimides







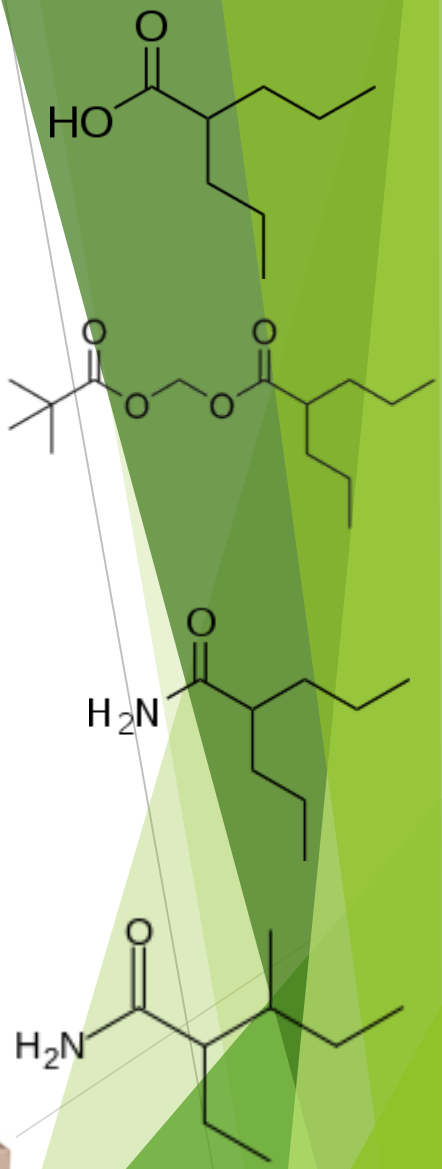
<u>Ethosuximide, Phensuximide, Mesuximide</u>

- pharmacodynamic features
  - blocking T-type Ca^{++} channels (especially in thalamic neurons)
- pharmacokinetic features
  - rapidly absorbed
  - half life: 40 hours
- adverse effects
  - gastric distress
  - nausea, vomitus
  - paresthesias (abnormal sensation)
- clinical use
  - absence seizures (first-line treatment)
  - 250-500 mg

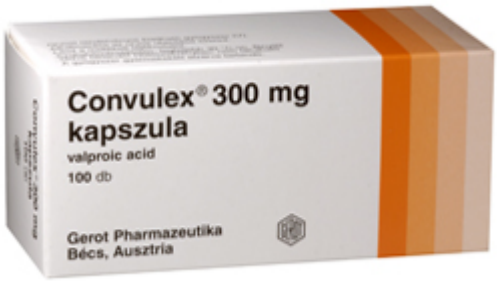
Antiseizure drugs – Fatty acids

Valproic acid (Convulex®)

Valproate-pivoxil (pro-drug), Valpromide, Valnoctamide



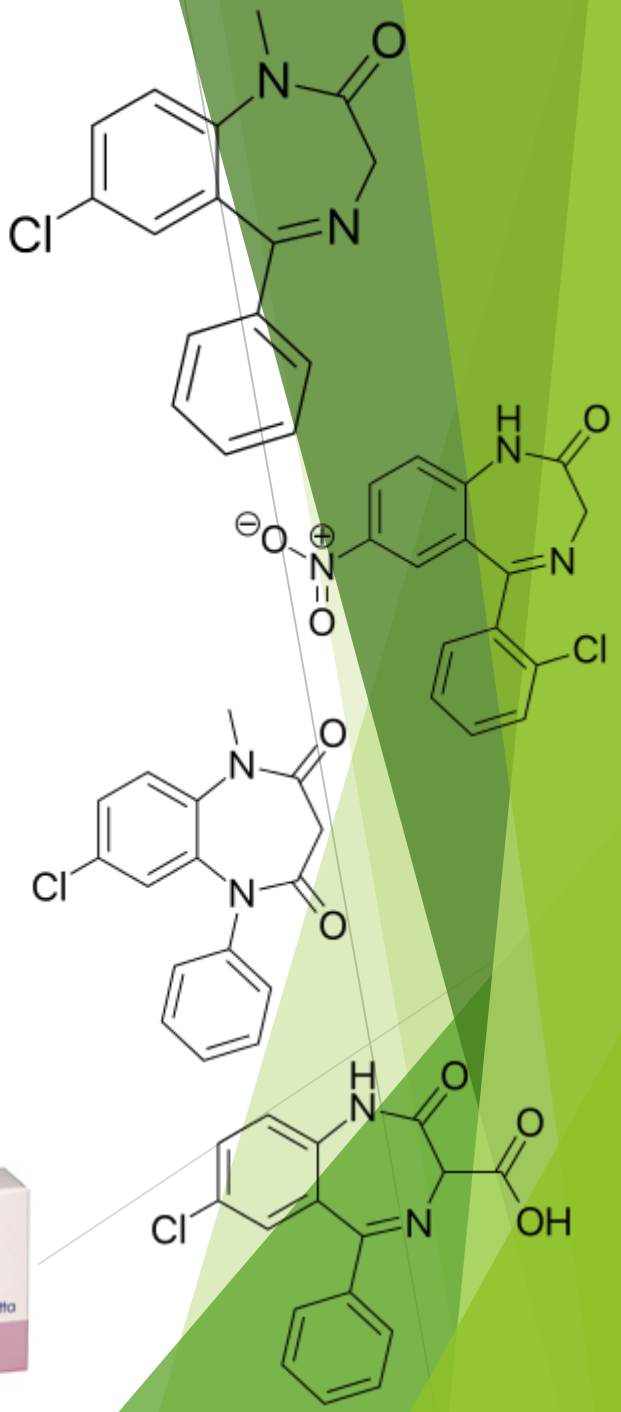
- pharmacodynamic features
  - blocking VG Na^+ channels
  - Also blocks T-type Ca^{++} channels
  - facilitating GAD
  - inhibiting GAT-1
  - inhibiting GABA-T - at high concentrations
- pharmacokinetic features
  - well absorbed
  - plasma protein binding ≈90%
- adverse effects
  - nausea, vomitus
  - hepatitis
  - embriopathy (spina bifida)
- clinical use
  - Wide range anti-epileptic:
  - absence seizures
  - GTCS



Antiseizure drugs – BZDs

<u>Benzodiazepines</u>

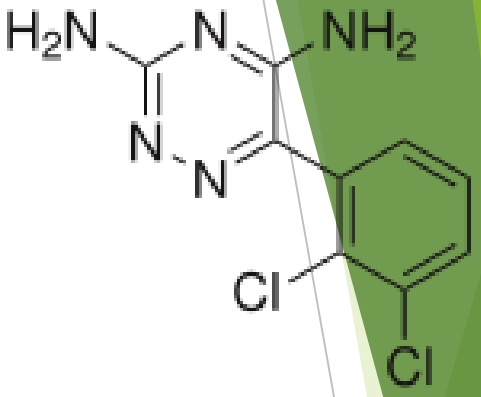
Diazepam, clonazepam, clobazam, clorazepate



- pharmacodynamic features
  - $GABA_AR$ PAM
- pharmacokinetic features
  - well absorbed
- adverse effects
  - sedation
  - cardiovascular/respiratory depression
- clinical use
  - continuous seizure activity
  - repeated epileptiform attack
  - status epilepticus

Antiseizure drugs – Other derivatives

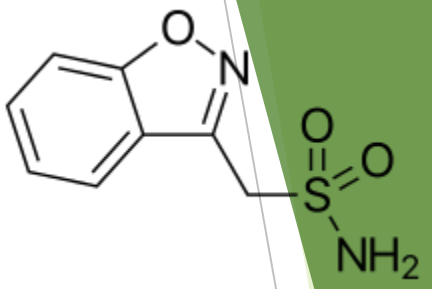
Lamotrigine (Lamictal®)



- pharmacodynamic features
  - blocking N-type (neural) Ca^{2+} channels
  - blocking Na^{+} channel
- pharmacokinetic features
  - rapidly absorbed
  - half life: 24 hours
- adverse effects
  - headache
  - diplopia
  - somnolence
  - skin rash
- clinical use
  - Wide spectrum anti-epiletic:
  - Lennox-Gastaut syndrome (in childhood, multiple seizure types, mental retardation)
  - 100-300mg/ day

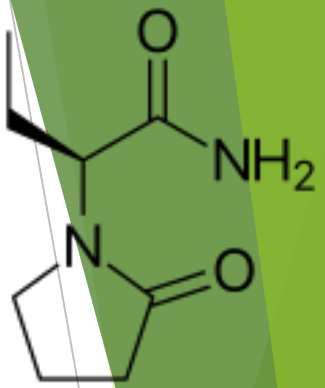
Antiseizure drugs – Other derivatives

Zonisamide (Zonegran®)



- pharmacodynamic features
  - blocking N-type (neural) Ca^{2+} channels
  - blocking Na^{+} channel
- pharmacokinetic features
  - Metabolized by CYP3A4
- adverse effects
  - Sedation
  - Dizziness
  - calculus
- clinical use
  - Wide spectrum anti-epiletic:
  - Partial, GTCS, myoclonic seizures etc.
  - 100-300mg/ day

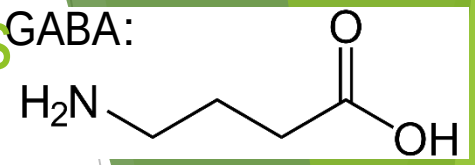
Antiseizure drugs – Other derivatives



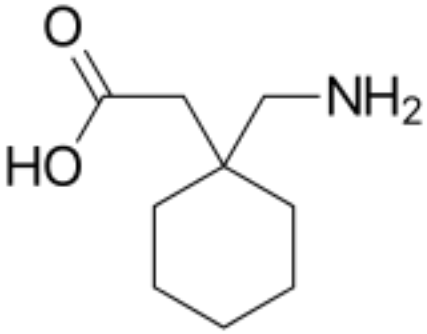
Levetiracetam (Keppra®)

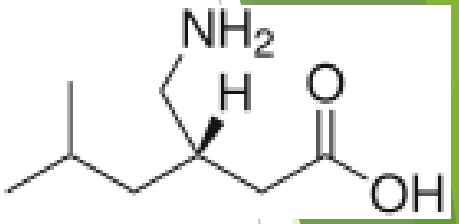
- pharmacodynamic features
  - Specifically binds to „synaptic vesicular protein” thus modifies the neurotransmitter release
- pharmacokinetic features
  - Partly excreted unchanged through kidneys
  - The rest is metabolized NOT by CYP
- adverse effects
  - Sedation
  - Dizziness
- clinical use
  - Wide spectrum anti-epiletic:
  - Partial, GTCS, especially in myoclonic seizures etc.
  - 1000-3000mg/ day

Antiseizure drugs – Other derivatives



Gabapentin, Pregabalin

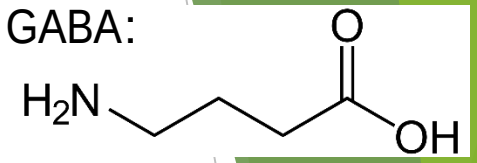


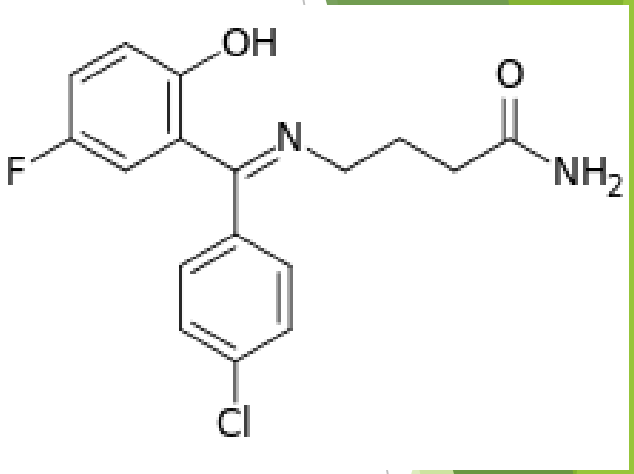


GABA analogs

- pharmacodynamic features
  - structural analog of GABA however
  - not agonist on $GABA_A$ R (in spite of structural resemblence to GABA)
  - blocking VG-Ca^{2+} channels (N-type)
- pharmacokinetic features
  - not bound to plasma proteins
- adverse effects
  - sedation
- clinical use
  - partial seizures
  - Neuropathic pain syndromes
  - 900-1800-3600 mg/day

Antiseizure drugs – Other derivatives





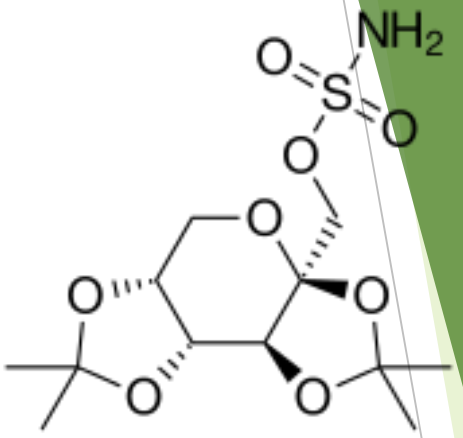
Progabide (Gabrene)

GABA analog and prodrug

- pharmacodynamic features
  - structural analog of GABA and
  - It is conversed into GABA ➔
  - agonist on $GABA_A$ R
- pharmacokinetic features
  - bound to plasma proteins in 95%
- adverse effects
  - Sedation
  - Elevates corticosterone level
- clinical use
  - Wide spectrum anti-epiletic:
  - Partial, GTCS, myoclonic seizures etc.
  - Lennox-Gastaut syndrome (in childhood, multiple seizure types, mental retardation)

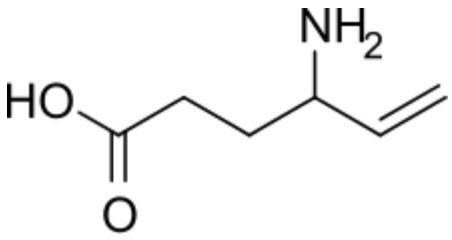
Antiseizure drugs – Other derivatives

Topiramate (Topamax®, Etopro®, Topepsil®)



- pharmacodynamic features
  - blocking VG Na^+ channels,
  - Inhibiting AMPA-rec.
  - enhancing $GABA_A$ mediated Cl^- currents
- pharmacokinetic features
  - rapidly absorbed
- adverse effects
  - fatigue,
  - cognitive slowing
  - paraesthesias
- clinical use
  - partial seizures
  - Lennox-Gastaut syndrome
  - Migraine prevention, headache
  - 200-600 mg/day

Antiseizure drugs – Other derivatives

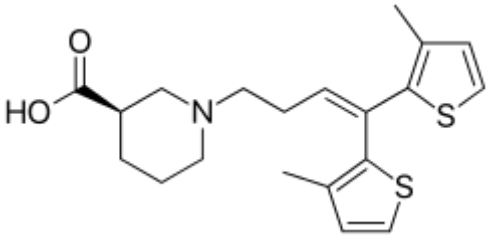


Vigabatrine (Sabril®)

- pharmacodynamic features
  - structural analog of GABA: gamma-vinyl-GABA
  - irreversible inhibitor of GABA-T (GABA transaminase)
- pharmacokinetic features
  - well absorbed
- adverse effects
  - drowsiness, dizziness, weight gain
  - bilateral vision loss
  - intramyelinic oedema (infants)
- clinical use
  - refractory partial seizures

Antiseizure drugs – Other derivatives

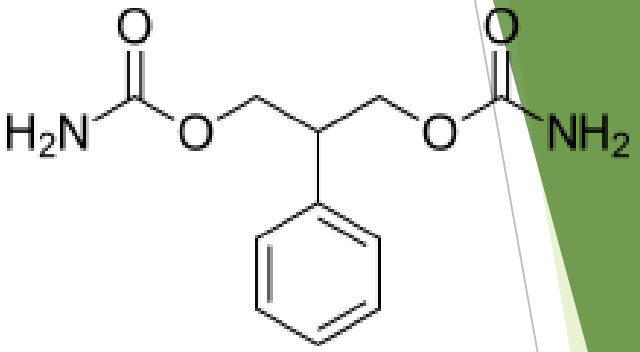
Tiagabine



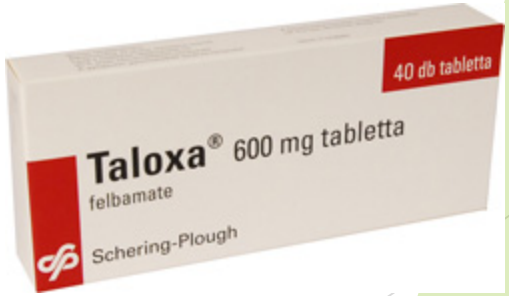
- pharmacodynamic features
  - inhibitor of GABA re-uptake mechanism
  - blocking GAT-1> GAT-2> GAT-3→e.c. GABA↑
  - modulating VG-Ca++ channels (N-type)→glutamate release↓
- pharmacokinetic features
  - total absorption: 90-100%
  - Metabolized by CYP3A4
- adverse effects
  - nervousness,
  - dizziness,
  - tremor
  - somnolence,
  - ataxia
- clinical use
  - refractory partial seizures
  - partial seizure secondarily generalized

Antiseizure drugs – Other derivatives

Felbamate (Taloxa®)



- pharmacodynamic features
  - blocking NMDA R
  - modulating $GABA_A$ R
- pharmacokinetic features
  - well absorbed
  - excreted in urine
- adverse effects
  - hepatitis
  - aplastic anaemia, agranulocytosis
- clinical use
  - partial seizures



Therapeutic indications

simple/complex partial seizures
- carbamazepine
- phenytoin
- valproic acid

absence seizures
- ethosuximide
- valproic acid

GTCS
- carbamazepin/oxcarbazepine
- phenytoin
- levetiracetam

status epilepticus
- benzodiazepine
  - diazepam (10-20 mg i.v.), clonazepam (2 mg i.v.)
- O2, glucose i.v., tiamine
- phenytoin (15-20 mg/kg-ECG controll)
- phenobarbital (15-20 mg/kg, 100mg/min i.v.)
- thiopental, muscle relaxation, resp. support