Psychotropic (Psychoactive) drugs - classification (Anxiolytics, Hypnosedatives)

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This study material is exclusively for students of general medicine and stomatology in Pharmacology II course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for neither tests in practicals nor the final exam.
Psychoactive drugs

Definition:
Any medication which has the capability to alter mood, anxiety, behavior or cognitive processes;
### Classification according to influence on the basic psychic function

<table>
<thead>
<tr>
<th>Category</th>
<th>Influence</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>I. Vigility</td>
<td>+</td>
<td>Psychostimulants</td>
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<tr>
<td></td>
<td>-</td>
<td>Hypnosedatives, General anaesthetics</td>
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<td>II. Affectivity</td>
<td>+</td>
<td>Antidepressants, Anxiolytics, Antimanic drugs</td>
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<tr>
<td></td>
<td>-</td>
<td>Dysphoric drugs (depressants)</td>
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<td>III. Psych. Integration</td>
<td>+</td>
<td>Antipsychotics (Major tranquilizers), (neuroleptics)</td>
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<tr>
<td></td>
<td>-</td>
<td>Hallucinogens, Deliriogens</td>
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<tr>
<td>IV. Memory</td>
<td>+</td>
<td>Nootropics, cognitive enhancers</td>
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<tr>
<td>(and cognitive functions)</td>
<td>-</td>
<td>Anticholinergic drugs</td>
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Classification according to the MAIN THERAPEUTIC effect on the basic psychic disorders

Examples:

- **Drugs of affective disorders**
  (antidepressants, thymoprophylactics)

- **Drugs of anxiety disorders**
  (anxiolytics)

- **Drugs of sleeping disorders**
  (hypnotics, sedatives, hypnosedatives)

- **Drugs of movement disorders**
- etc.
ANXIOLYTICS

• Syn. „minor tranquilizers“, ataractics, antiphobic drugs, antineurotics/

• Drugs mostly depressant effe. on CNS (not always sedative effect)

• Influencing subcortical structures in the brain, limbic system, F.R.
ANXIOLYTICS

- benzodiazepines

- risk of psychic + somatic dependence
Indications

- generalised anxiety disorder (an ongoing state of excessive anxiety lacking any clear reason)
- panic disorder (attacks of overwhelming fear occurring in association with somatic symptoms (sweating, tachycardia, chest pain)
- phobias (strong fears of specific things or situation (snakes, flying)
- postraumatic stress disorder (anxiety triggered by insistent recall of past stressful experiences
- psychosomatic disorders
- diagnostic/therapeutic procedures (gastroscopy, colonoscopy)
- restless legs syndrome, treatment of acute alcohol withdrawal, OCD
- commonly used together with an SSRI to provide symptomatic relief for the first few weeks before the effects of the SSRI kick in
Effects of BZDs

1) hypnosedative
   flunitrazepam, midazolam

2) anxiolytic
   alprazolam, bromazepam, oxazepam

3) anticonvulsive
   diazepam, klonazepam

4) myorelaxant
   klonazepam

(5) amnestic
   most of BZ
MECHANISM OF ACTION OF BZ

- specific (via receptors)

- selectively binding to the specific binding site ("benzodiazepine receptor") of $\text{GABA}_A$ subunit (coupled with $\text{Cl}^-$ channel)

- increase affinity of binding site for GABA (positive allosteric modulation)
increase in frequency of opening
Cl⁻ channel

hyperpolarization of neuron membrane

inhibition of signal transduction
Unwanted effects

- unwanted effects occurring during therapeutic use
  --- Influence on 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)
  --- breath center depression

- tolerance, dependence
  Tolerance (gradual escalation of dose needed to produce the required effect) occurs with all BZs. T.appears to represent a change at the receptor level.
  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.
  • rebound phenomenon !!
  • may cause „floppy baby syndrome“ when used during third trimester of gravidity
BZ contraindications

- Pregnancy, lactation
- Myasthenia gravis
- Ethylism, hypnotics comedication
- Sleep apnoe
- Any addiction suspected
- Patients using BZs should not donate blood or drive vehicles
Pharmacokinetics of BZ:

- **absorption**: well absorbed if given orally, Cmax reached in about 1 h
- **binding**: strongly bound to plasma proteins
- **distribution**: large Vd: accumulation in body fat (high lipid solubility)
- **metabolism**:
  - hydroxylation
  - conjugation with glucuronic acid
  - short-, medium- and long-acting BZ
  - the role of N-desmethyldiazepam
Anxiolytic and hypnotic drugs - benzodiazepines (BZ)

*Triazolam withdrawn in UK
Specific antagonist of BZ receptors

flumazenil

USE: in benzodiazepine overdose
dg. coma of unknown aetiology
Acts quickly and effectively when given by injection, but its action lasts for only about 2 hours, so drowsiness tends to return
Can cause acute withdrawal syndrome in BZ dependent patient
Febrile seizures

- Febrile seizures are convulsions brought on by a fever in infants or small children.
- The majority of children with febrile seizures have rectal temperatures greater than 38°C.
- Usually occur in children between the ages of 3 months and 6 years and are particularly common in toddlers, risk of recurrence in 1/5 of them.
- Idiopathic syndrome.
- Treatment: diazepam rectally + antipyretics.
  - Dose of 5 mg for children with weight less than 15 kg.
  - Dose of 15 mg for children with weight more than 15 kg.
Barbiturates
similar mech. of action as BZD, obsolete for more than 15 yrs) as anxiolytics

- dependance
- high risk of serious advers effects
- high interaction potential
Other anxiolytics

- Partial agonists of 5-HT$_{1A}$ rec. buspirone

- Low dose of antidepress. fluvoxamine, fluoxetine (SSRI), venlafaxin, amitriptylin, dosulepine,…

- Low doses of neuroleptics (levomepromazine, thioridazin, …)

- H$_1$ - antiHis.: hydroxyzine

- Beta-blockers: metipranolol, metoprolol,…

- Derivatives of propan: guaifenesin (+myorelaxant+expectorant action), (meprobamate, mephenoxolon)

- Antiepileptics: gabapentin, pregabalin

Influencing serotonergic system
A sedative-hypnotic drug (terminology)

Sedation can be defined as a suppression of responsiveness to a constant level of stimulation, with decreased spontaneous activity and ideation.

A hypnotic drug should produce drowsiness and encourage the onset and maintenance of a state of „sleep“ that as far as possible resembles the natural state of sleep.

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

• **HYPNOTICS**: are used for treating sleep disturbances and disorders
  – insomnia

• **SEDATIVES** – in anxiety, ammeliorrate hyperactivity, aggresivity

• No clear cut-off between HYPNOTICS and SEDATIVES

„**HYPNOSEDATIVES““
Sleep disorders

• 1. Parasomnia
• 2. Hypersomnia
• 3. Insomnia: Difficulty initiating sleep
  Difficulty maintaining sleep
  Early-morning awakening with inability to return to sleep
Insomnia:

- **temporary** = less than week
- **short term** = less than month
- **chronic** = more than month
Stages of Sleep
Measured by EEG

Alpha activity:
A smooth electrical activity of 8 – 12 Hz recorded from the brain; generally associated with a state of relaxation or meditation.

Beta activity:
Irregular electrical activity of 13 – 30 Hz recorded from the brain; generally associated with a state of arousal.

Theta activity:
EEG activity of 3.5 – 7.5 Hz that occurs intermittently during early stages of slow wave sleep and REM sleep.

Delta activity:
Regular, synchronous electrical activity of less than 4 Hz recorded from the brain; occurs during the deepest stages of slow-wave sleep.
REM sleep:
A period of desynchronized EEG activity during sleep, at which time dreaming, rapid eye movements, and muscular paralysis occur.
Decreased blood flow to inferior frontal lobe associated with distortions of time.

Non-REM sleep:
All stages of sleep except REM sleep.
INDICATIONS

Sleep disorders in case of:

• No causative treatment available

* Causative treatment still not effective
* Short term treatment
* Severe sleep disorder

• Recommended just for short courses of treatment of insomnia (2-3 weeks)
„IDEAL“ HYPNOTIC drug

- To mimick physiological structure of sleep cycles
- Broad ther. range
- Optimal halflife of elimination
- Rapidly absorbed after p.o. admin.
- Therapeutic levels in blood 5-7 h, no active metabolites
- No ADE, interactions
- No risk of addiction
HYPNOTICS

I. generation
prolong 2 NREM, shorten 3 and 4 NREM and REM

II. generation
prolong 2 NREM, just slightly suppress 3 and 4 NREM, do not suppress REM

III. generation
prolong 2 NREM, shorten 3 and 4 NREM and REM
HYPNOTICS

I. generation  barbiturates – obsolete

• if given in a large dose — death from respiratory and cardiovascular depression (flumazenil not effective)
• a high degree of tolerance: BA strongly induce the synthesis and activity of hepatic CYP450 and conjugating enzymes thus increasing the rate of metabolic degradation of many other drugs

--- drug-drug interactions

• dependence
barbiturates are no longer used as anxiolytic and hypnotic drugs
  (are mainly used in anaesthesia - thiopental (i.v.) and treatment of epilepsy – phenobarbital)

Non-barbiturates (ob-solete or less freq. used)
e.g. clomethiazol (insomnia in geriatric patients, acute alcohol withdrawal syndrome, delirium tremens)
HYPNOTICS

II. generation benzodiazepines

midazolam
diazepam
nitrazepam
cinolazepam
clobazam
medazepam

unwanted effect: dependence, drowsiness, disturbed sleep cycle
HYPNOTICS

III. generation selective agonists of $\Omega_1$ benzodiazepine receptors ($\Omega_1 \text{rec.}=\text{BZD}_1 \text{rec.}$)

- Selective hypnotic effect, lacking myorelaxant effect, lacking anxiolytic + anticonvulsive effect.

non-benzodiazepine structure
Anxiolytic and hypnotic drugs – zolpidem, zaleplon

zolpidem  pharmacodynamics
• binds selectively to the BZ$_1$ 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 hypnotic BZs

pharmacokinetics
rapidly metabolized to inactive metabolites by the liver, T1/2 1.5-3.5 h. Dosage reduction in hepatic dysfunction, elderly.
Anxiolytic and hypnotic drugs – zolpidem, zaleplon

Ind- short-term treatment of insomnia

zaleplon resembles zolpidem, $t_{1/2} = 1\text{h}$
Rapid onset and short duration of action are favorable properties for those patients who have difficulty falling asleep.
NEW trends in hypnosedatives

I. Drugs influencing circadian rhythms
   - melatonin
     (just WEAK hypnotic !!)
   - syntetic drugs acting on melatonin receptor

II. Orexin receptor antagonist
   - Suvorexant (Belsomra© in USA)
Melatonin

- Universal signal molecule which gives estimate about light/dark cycle to the brain
- Is synthetised in epiphysis, retina, GIT
- Sleep do not affect synthesis, peak levels between 11PM and 3AM
- In GIT = ROS scavenger
Where Melatonin Binds

- Works by binding 3 receptors
- MT1 = Found in the SCN of hypothalamus, pituitary gland, cardiac blood vessels
- MT2 = Retina and hippocampus
- MT3 = Kidney, brain, other organs
Melatonin hypnotics

- melatonin (CIRCADIN)
- agomelatin (THYMANAX, VALDOXAN - antidepressant)
- ramelteon, tasimelteon
Medicinal herbs as hypnosedatives

• - Melissa off. (Lemon balm)

• - Valeriana off. (Valerian)

• - Humulus lupulus (Hop)

• - Crataegus monogyna (single-seeded Hawthorn)

• - Passiflora incarnata (maypop, purple Passionflower)

• - Hypericum perforatum (St. Johns Wort)