MUNI
MED

Introduction to Psychopharmacology

Department of Pharmacology FM MU

Lehmann classification of psychotropic substances

Affectivity	**↑ antidepressants, anxiolytics**
	↓ dysforics/antimanics
Vigility	**↑ psychostimulants/nootropics**
	↓ hypnotics/sedatives
Psychic integrity/integration	**↑ neuroleptics**
	↓ halucinogens/psychodysleptics/delirogens
memory and cognitive functions	**↑ cognitive enhancers/** nootropics
	↓ anticholinergics, dementogens, neurotoxins, amnestics

MUNI MED

SCHIZOPHRENIA

antipsychotics

DEMENTIA

cognitive enhancers

ADHD

psychostimulants

ANXIETY

anxiolytics

PSYCHIC INTEGRATION

halucinogens

psychotomimetics

MEMORY AND COGNITION

nootropics

INSOMNIA

sedatives

hypnotics

DEPRESSION

antidepressants

EPILEPSY

anticonvulsants

antiepileptics

BIPOLAR DISORDER

mood stabilizers

MUNI MED

Classification of psychotropic drugs

- a new classification of psychotropic drugs is created based on the main mechanisms of effects
- (neuroscience based nomenclature - NbN) - ECNP (European College of Neuropsychopharmacology)

- Mobile phone app !

- https://www.ecnp.eu/~/media/Files/ecnp/Projects%20and%20initiatives/Nomenclature/140214%20Nomenclature%20list.pdf

MUNI MED

Antipsychotics

Drugs used **predominantly in the therapy of psychoses** but also other indications:

pharmacoresistant depression

psychotic depression

anxiety

Huntington's disease

Tourette's syndrome

anesthesia / neuroleptanalgesia

sleep disorders

nausea, vomitus

MUNI
MED

Schizophrenia

- belong among psychoses with predominance of emotional disturbances, thinking, behavior, and personality disorder
- the most striking symptoms are delusions and hallucinations
- onset/Dg usually around 20th year of age
- genetic predisposition - gender incidence - polygenic inheritance
- affects about 1% of the population Dg. ICD 10: F20XX

MUNI
MED

Symptoms of schizophrenia

"**Positive" symptoms** - hallucinations, delusions, disintegration of thinking, speaking, catatonia, agitation, paranoia

"Negative" - absent, blunted or incongruous emotional responses, apathy, social withdrawal, anhedonia, lethargy, sexual dysfunction, impaired attention

MUNI
MED

Substances capable of causing psychosis

- levodopa (DA)
- CNS stimulants (NA, DA, 5HT)
  - cocaine
  - amphetamines
  - khat, kathinon, methkathinon, mezkalin
- hallucinogens – LSD (5HT2c agonist)
- cannabis
- apomorphine (agonism D_2)
- bupropion (NDRI)
- phencyclidin, ketamine (NMDA antag.)

MUNI
MED

Dopamine hypothesis of schizophrenia

- Antipsychotics reduce DA-activity on synapses
- Drugs increasing DA in the limbic system trigger psychosis
- Drugs that reduce DA-activity in the limbic system (DA antagonists on postsynaptic D receptors) reduce psychotic symptomatology
- Affinity of older "classical" APs to D2 rcp. correlates with their clinical effect

MUNI
MED

Classification of antipsychotics

1st. generation „typical“

Classical (basic, sedative): doses up to hundreds of milligrams

Incisive:
doses in mg to tens of milligrams

2nd. generation („atypical“)
less: EPS, tardive dyskinesias, prolactinemias, malignant neuroleptic. syndrome)

MARTA (Multi-Acting Receptor Targeted Agents)

SDA (Serotonin-Dopamine Antagonist)

D2 / D3 antagonists

DSSS (Dopamine-Serotonin System Stabilizers)

3rd. Generation ?
agonists of DA autoreceptors, partial agonists, glutamatergic, beta blockers?

Classical (typical) antipsychotics

- affects positive, less negative symptoms, can aggravate cognition. dysfunction
- mechanism of action: reduction of dopaminergic neurotransmission (blockade of postsynaptic D_2 receptors

AE

Extrapyramidal syndrome

Early (parkinsonoid, acute dyskinesia, akathisia)

Late (tardive dyskinesia and dystonia, tardive akathisia)

Neuroleptic malignant syndrome, hyperprolactinemia, anticholinergic, antihistamine, adrenolytic and others

MUNI
MED

Classical (typical) antipsychotics - basal

levomepromazine –D_2 antag. + another antag. (NA, 5HT, H, Ach)

more pronounced sedation, less EPS, adjuvant with analgesics

antiemetic, antihistaminic, anti-adrenergic and anticholinergic effects

AE: Orthostatic collapse, QTc prolongation, torsades

chlorprotixen

5HT2, D1, D2, D3, H1, M and alpha 1 receptor antagonist

In low dose for insomnia (up to 50 mg)

MUNI
MED

Classical (typical) antipsychotics - basal

melperone

Low affinity D2 antagonism

5HT2A, alpha1 antagonist, without affinity for H1, M

low risk of dyskinesia + EPS

Confusion, anxiety restlessness, especially in the elderly and alcoholics (deliria) (low doses)

tiaprid

D2, D3 antagonism

lacks affinity for H1, α1, α2, 5HTR

I: Behavioral disorders, confusion, agitation, especially in the elderly and alcoholics (deliria) (low doses

MUNI MED

Classical (typical) antipsychotics -incisive

fluphenazine

D2 antag., Highly effective (Dmax 40 mg)

AE: EPS, TD, priapism, galactorea

flupentixol - D2 antag, not so sedative, more EPS

AE: EPS - initiation of therapy, TD, insomnia, tachycardia, ↑ weight, dyslipidemia, rarely NMS

i.m.- noncompliance

haloperidol - D_2 antag. ,highly potent, better than phenothiazines, long $T_{1/2,}$ less sedation, influencing BP

better tolerability (blood count, liver injury)

MUNI MED

Comparison of basal and incisive AP

Basal AP

- Low potency
  (high doses – hundreds of milligrams)
- Sedation to hypnosis
- D2 receptor blockade
- slower PK
- Frequent anticholinergic and antihistaminic adverse effects
- ↓ EPS

Incisive AP

- High potency (lower doses)
- Little sedation
- Block D2 receptor
- faster PK
- Causes ↑ EPS

MUNI MED

Atypical antipsychotics

- higher efficacy, better tolerability
- affect positive and negative symptoms, cognition
- D_2 receptor occupancy <80%, binding to multiple neurotransmitter systems
- affect not only transport of dopamine but also other neuromediators (serotonin)
- wide range between antipsychotic effects and EPS
- selective extrastriatal (mesolimbic) blockade of dopamine D_1, D_2 receptors
- risperidone, ziprasidone, olanzapine, quetiapine ...

MUNI
MED

Atypical antipsychotics

- **selective D_2/D_3 receptor** antagonists sulpiride, amisulpride
- **selective serotonin and dopamine receptor antagonists (SDAs)**

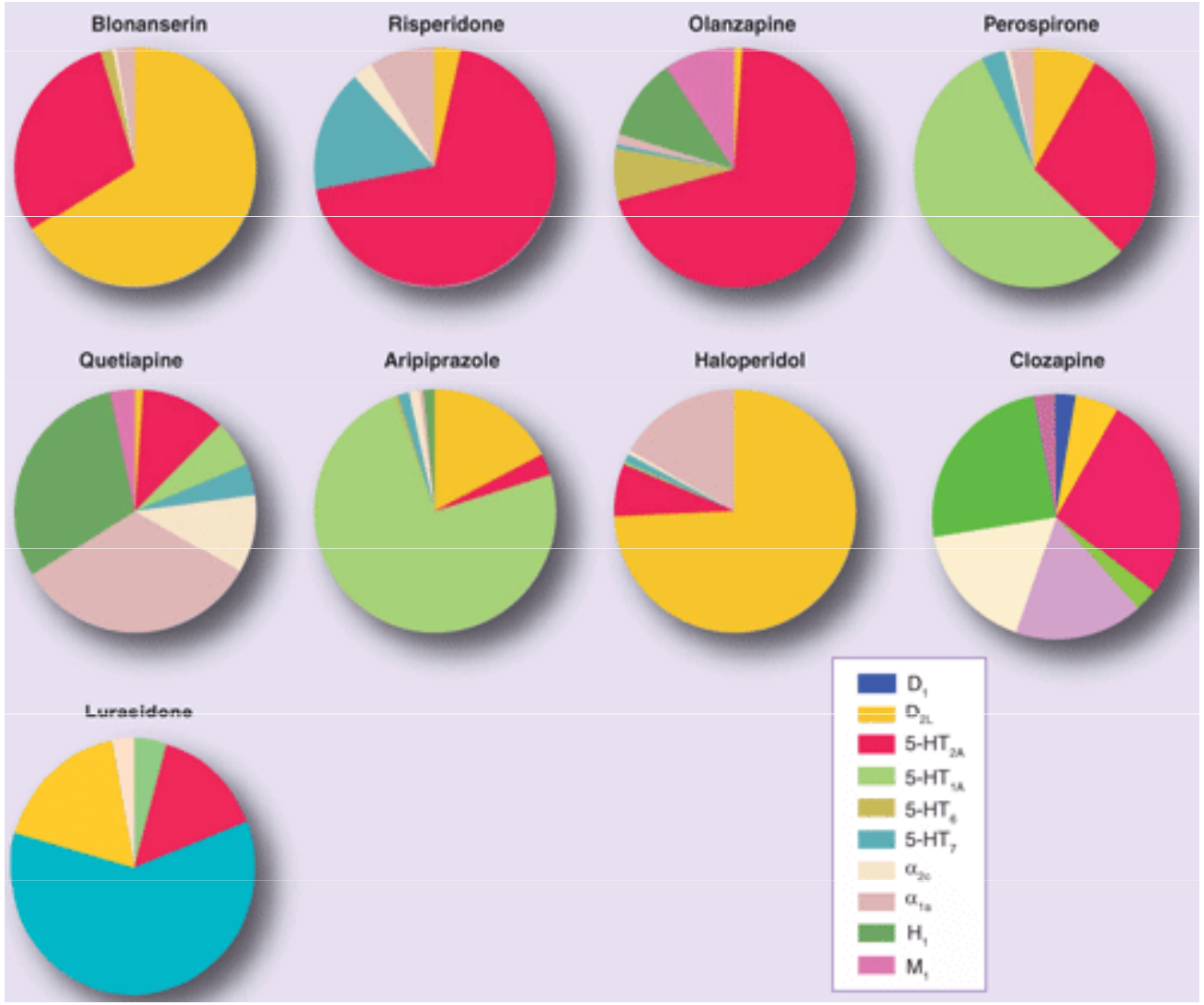
  risperidone, ziprasidone, lurasidone, iloperidone, sertindole
- **multi-receptor antagonists (MARTA:** D, 5-HT, α, H1, M)

  clozapine, olanzapine, quetiapine and zotepine
- **DSSS** (D2) **stabilizer**

  aripiprazole, cariprazine

MUNI
MED

Relative receptor profile AP2G



Sumiyoshi, Expert Rev Clin Pharmacol. 2008;1:791-802 .

Atypical antipsychotics - MARTA

clozapine

antag. D_2 , antag. $5HT_{2A}$ (↑ release DA)

$5HT_{1A}$, $5HT_{2C}$, (cognitive, affective symptoms)

minimal impact on the nigrostriatal system

Effect on alpha, 5HT2 rcp

Useful in: Pharmacoresistant psychoses - responds about 1/3

risk of suicidium, aggressive patients, EPS

AE: sedation, weight gain,

agranulocytosis - genetic test

MUNI
MED

Atypical antipsychotics - MARTA

olanzapine antag. D_2, antag. $5HT_{2A}$

$5HT_{2C}$ - improving cognitive symptoms

better efficiency

available depot injectable DDF

No/low risk of agranulocytosis

AE: sedation, weight gain, tachycardia, rarely TD

MUNI
MED

Atypical antipsychotics - SDA

risperidone

antag. D_2 , antag. 5HT2A (↑ release DA) , α1, 5HT7 (antidepresive action)

p.o. i.m. depot inj.

active metabolite 9-OH risperidon = Paliperidone

I: schizophrenia, mania, bipolar disorder, behavioral disorders in children, ADHD, resistant OCD

AE: weight gain, dyslipidemia, hyperprolactinemia

paliperidone

antag. D_2 , antag. 5HT2A, α1, less affinity 5HT7

p.o. and depot inj.

MUNI
MED

Atypical antipsychotics- SDA

lurasidone

- Risk of EPS: modest
- Relat. safe, well tolerated AP – (lacks AE: weight gain, metabolic AE, anticholinergic, sedtion, ortostatic hypotension, low risk of QTc prolongation)

cariprazine

- D2, D3, 5HT2B, 5HT1A partial agonist
- 5HT2A, 5HT2C alpha1B antagonist

MUNI
MED

Atypical antipsychotics - DSS

aripiprazole – partial agonist D_2 + 5HT1A, antag. 5HT2A (localy increases DA –improves cognitive fctions, affectivity)

blocks 5HT2C, 5HT7 –antidepresive action

¨ lacks sedation, weight gain

p.o. + depot inj.

Other Indications: augmentation of antidepressants,

MUNI MED

Adverse effects

Blockade of D_2 receptors in nigrostriatal pathway

EPS - early (acute)
- late (tardive)

Severity does not correlate with dose !

https://www.youtube.com/watch?v=FUr8ltXh1Pc&t=8s

Acute dystonia

- involuntary contraction of individual muscles or muscle groups of prolonged duration, causing abnormal movements or positioning of different body parts.
- occurs in up to 25-33% of all patients treated with typical AP

https://www.youtube.com/watch?v=2krwEbm5hBo

MUNI MED

Adverse effects

Blockade of D_2 receptors in nigrostriatal pathway

EPS

Akathisia

- intense mental discomfort, compulsive movements

restlessness

https://www.youtube.com/watch?v=W_iiy8ISvdY

MUNI
MED

Adverse effects

Blockade of D_2 receptors in nigrostriatal pathway

EPS

Parkinson's syndrome (PS)

combination of bradykinesia (movement retardation)

akinesia (inability to start movement)

hypokinesia (reduction of motion range)

stiffness/rigidity (increased muscle tone)

shaking

Typical APs : about 30-50**%.**

https://www.youtube.com/watch?v=6HKMusvSfeI

MUNI MED

Neuroleptic malignant syndrome

1. AP treatment in the previous 7 days (in depot inj. In previous 2-4 weeks)
2. Hypertermia > 38 st. C
3. Muscle rigidity
4. 5symptoms of:
   - Changes in mental state
   - Tachycardia
   - Hypertension or hypotension
   - Tachypnoea or hypoxia
   - Sweating or salivation
   - Tremor
   - Incontinence
   - Increased creatine phosphokinase or myoglobinuria
   - Leukocytosis
   - Metabolic acidosis

Excluding other neuropsychiatric or somatic disease

MUNI MED

Anxiolytic and hypnosedative drugs

MUNI
MED

Anxiety disorder

- A chronic condition characterized by an excessive and persistent sense of apprehension, with physical symptoms such as sweating, palpitations, and feelings of stress

Anxiety disorders recognised clinically include the following:

- generalised anxiety disorder (GAD)
- obsessive–compulsive disorder (OCD)
- post-traumatic stress disorder (PTSD)
- social anxiety disorder, phobias etc.

MUNI
MED

Anxiolytics

- First line: non-benzodiazepine (SSRI + others, see the AD materials)
- Second line: benzodiazepines (BZ, adjuvant therapy)

- drugs mostly acting like CNS depressants (not always sedative)
- affecting receptors in limbic system, hypothalamus, cerebellum and corpus striatum

MUNI
MED

Mechanism of action (BZD)

- **specific (via receptors)**

- selectively binding to the benzodiazepine binding site of **$GABA_A$ subunit** (coupled with Cl^- channel)
- increase affinity of binding site for GABA (positive allosteric modulation)
- increase in frequency of opening of Cl^- channel
- hyperpolarization of neuron membrane

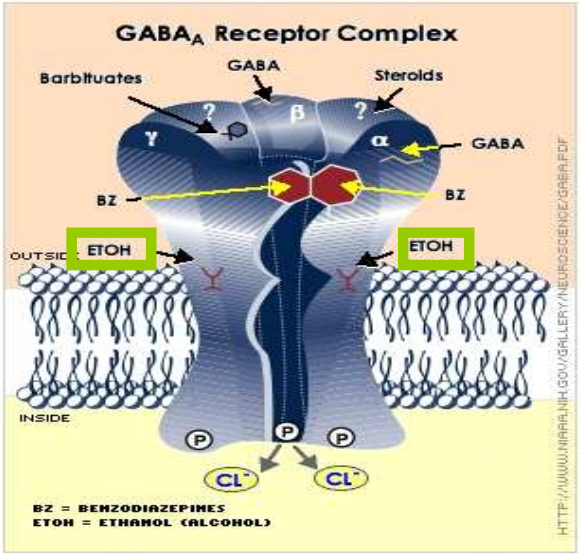
⇩

inhibition of signal transduction

Inhibition of neural activity is leading to anxiolytic effect

in higher doses to sedation and sleep

overdose can be lethal (specially if combined with ethanol)



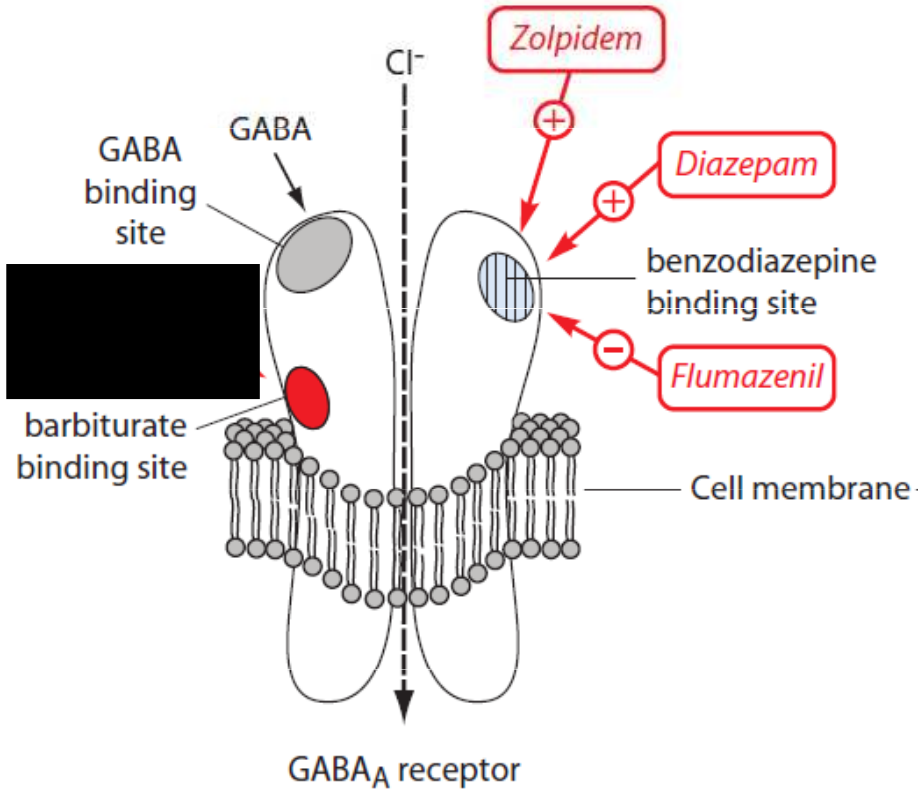


Table 44.2 GABA$_A$-receptor α-subunit selectivity of some therapeutically used benzodiazepines

Drug	Subunit selectivity
Diazepam	α1, α2, α3, α4, α5, α6
Flunitrazepam	α1, α2, α5
Midazolam	α1, α2, α3, α4, α5, α6
Zolpidem	α1
Flumazenil	Antagonist at α1, α2, α3, α4, α5, α6

GABA$_A$ subunit	effect
α_1	sedative, anterograde amnesia, partially anticonvulsive; addictive
α_2	anxiolytic, myorelaxant
α_3 α_5	contributing to myorelaxant effects
α_1 α_5	modulating temporal and spatial memory

MUNI MED

Indications

- adjuvant therapy in psychiatry (for transient period)
- acute intervention of panic attack
- treatment of acute alcohol withdrawal
- diagnostic/therapeutic procedures (gastroscopy, colonoscopy)
- commonly used together with an SSRI to provide symptomatic relief for the first few weeks before the effects of the SSRI kick in
- phobias (strong fears of specific things or situation (snakes, flying)
- psychosomatic disorders
- post-traumatic stress disorder (anxiety triggered by insistent recall of past stressful experiences
- OCD

MUNI
MED

Effects of benzodiazepines

1) hypnosedative

midazolam

2) anxiolytic

alprazolam, bromazepam, oxazepam

3) anticonvulsant

diazepam, clonazepam

4) myorelaxant

clonazepam

5) amnestic (anterograde amnesia)

most of benzodiazepines, historically typical for flunitrazepam

Pharmacokinetics of benzodiazepines

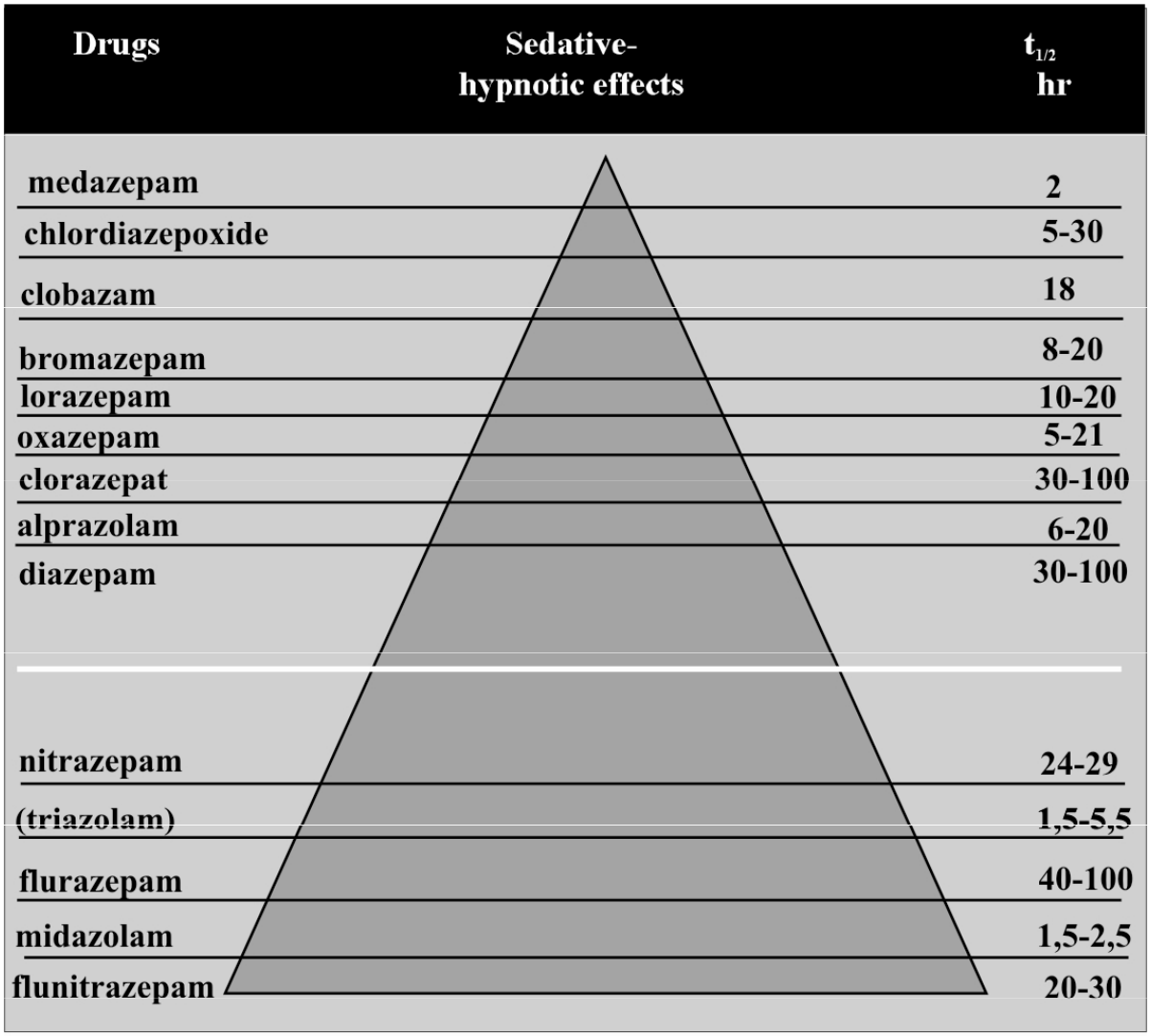
- ABSORPTION:
  - well absorbed if given orally , C_{max} reached in about 1 h
  - intramuscular injection – absorption time is mostly unpredictable
  - possible IV and per rectum application (used for pediatric febrile seizures)

- BINDING: strongly bound to plasma proteins

- DISTRIBUTION: large V_d: accumulation in body fat (high lipid solubility)

- METABOLISM: hydroxylation
- conjugation with glucuronic acid
- short-, medium- and long-acting BZ
- the role of N-desmethyldiazepam

MUNI
MED



(According to Seifertová 2004)

Clonazepam = anticonvulsant, anxiolytic use ($t_{1/2}$ = 50 hr)

MUNI
MED

Specific antagonist of benzodiazepine receptors

flumazenil

Use: in benzodiazepine overdose, antagonising the central sedative effects of benzodiazepines in anaesthesiology

- the onset of action is rapid and usually effects are seen within one to three minutes
- its action lasts for only about 1 hour, so drowsiness tends to return - repeat doses of flumazenil may be required to prevent recurrent symptoms of overdosage once the initial dose of flumazenil wears off
- can cause acute withdrawal syndrome in benzodiazepine dependent patient

MUNI
MED

Unwanted effects

- drowsiness, confusion, amnesia, impaired coordination
- paradoxical reactions (aggression, violence; see Beers list)
- 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)
- cognitive deficits (memory loss, slower psychomotor deficits)
- breath center depression
- muscle relaxation
- tolerance (gradual escalation of dose needed to produce the required effect and occurs with all BZs. Appears to represent a change at the receptor level)
- "rebound" phenomenon
- may cause „floppy baby syndrome" or neonatal abstinence syndrome when used during third trimester of gravidity (tremor, tachypnea, convulsions)

MUNI
MED

Beers list

– guidelines for healthcare professionals to help improve the safety of prescribing medications for older adults

MUNI
MED

Table 2. 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System/ Therapeutic Category/Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Benzodiazepines *Short- and intermediate-acting:* • Alprazolam • Estazolam • Lorazepam • Oxazepam • Temazepam • Triazolam *Long-acting:* • Chlorazepate • Chlordiazepoxide • Chlordiazepoxide-amitriptyline • Clidinium-chlordiazepoxide • Clonazepam • Diazepam • Flurazepam • Quazepam	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents. In general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults. May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, periprocedural anesthesia, end-of-life care.	Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium.	High	Strong	Allain 2005 Cotroneo 2007 Finkle 2011 Paterniti 2002
Nonbenzodiazepine hypnotics • Eszopiclone • Zolpidem • Zaleplon	Benzodiazepine-receptor agonists that have adverse events similar to those of benzodiazepines in older adults (e.g.,	Avoid chronic use (>90 days)	Moderate	Strong	Allain 2005 Cotroneo 2007 Finkle 2011 McCrae 2007 Orriols 2011 Rhalimi 2009

MUNI MED

Contraindications

- pregnancy and lactation
- myasthenia gravis
- ethylism, co-medication with other hypnotics
- respiratory insufficiency, sleep apnoe
- any other comorbid addiction
- patients using benzodiazepines should not donate blood or drive vehicles

MUNI
MED

Benzodiazepine withdrawal syndrome

- the cluster of symptoms that emerge when patient undergoes abrupt discontinuation of use
- more frequent with: short-acting benzodiazepines (alprazolam), higher doses, serious concurrent psychopathology
- more expressed in women and patients abusing alcohol
- 25-50 % patients are capable of consecutive discontinuation of BZ use during 6-21 months. First half of dose is discontinued easier then the other half, therefore rapid discontinuation of first half is recommended, followed by 10-20 % reduction during 3-5 days
- „plateau“ stage is recommended during discontinuation, when the dose is not reduced
- usually the morning dose is reduced in the first place, then the afternoon’s one a the evening dose is the last reduced
- long-acting benzodiazepines cause delayed withdrawal syndrome (2-4 weeks later)

MUNI
MED

Non-benzodiazepine drugs with anxiolytic effect

- SSRI: sertraline, fluvoxamine, fluoxetine (see AD materials)
- other AD: mirtazapine, trazodone, amitriptyline, dosulepin, venlafaxine
- antiepileptics: gabapentin, pregabalin (generalised anxiety disorder), tiagabine, valproic acid
- antipsychotics: quetiapine, olanzapine

MUNI
MED

Non-benzodiazepine drugs with anxiolytic effect

- partial agonist at 5-HT1A receptors: buspirone - used to treat generalised anxiety disorders and as adjuvant therapy in depression, less effective in controlling panic attacks or severe anxiety states
- H1 antihistamins: hydroxyzine
- guaifenesin (+ myorelaxant+expectorant action)
- beta-blockers: metipranolol, metoprolol

- medicinal herbs: Valerian, Hop, Saffron, Passionflower, St. Johns Wort, Rhodiola, Lavender

MUNI
MED

Hypnosedatives

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.

MUNI
MED

INDICATION

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

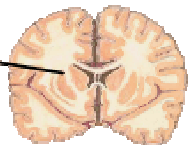
- **SEDATIVES –** in anxiety, ammeliorrate hyperactivity, aggressivity

- **No clear cut-off between HYPNOTICS and SEDATIVES „HYPNOSEDATIVES“**

MUNI
MED

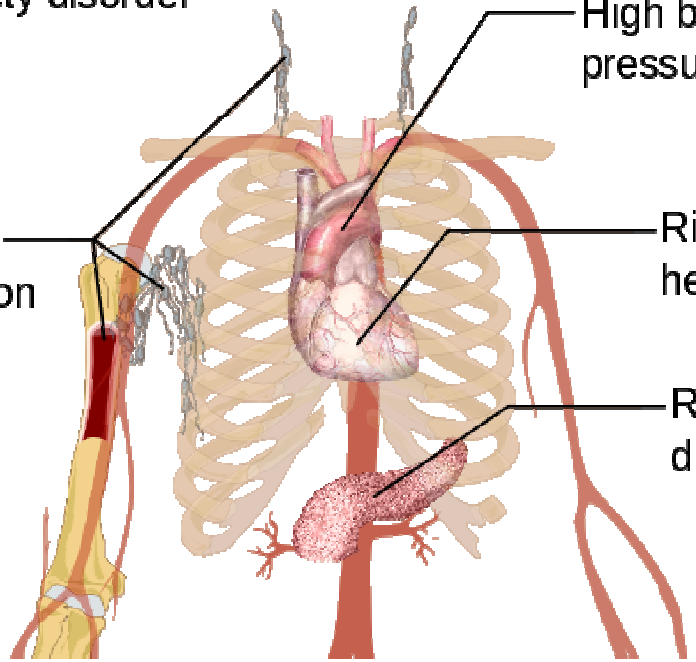
Complications of

Insomnia



Psychological
- Lower performance
- Slowed reaction time
- Risk of depression
- Risk of anxiety disorder

Other:
Overweight or obesity



High blood pressure

Poor immune system function

Risk of heart disease

Risk of diabetes

MUNI MED

Insomnia:

- **temporary** = less than week
- **short term**= less than month
- **chronic** = more than month (according to International Classification of Sleep Disorders 3 months with a frequency of 3 times a week)

MUNI
MED

Indications

Sleep disorders in case of:

- no causative treatment available
- causative treatment still not effective
- short term treatment
- severe sleep disorder (debilitating for patient, causing sick leave)

Recommended just for **short courses** of treatment of insomnia- from few days to 2 weeks (max. of 4 weeks in a row)

MUNI MED

„Ideal“ hypnotic drug

- to mimick physiological structure of sleep cycles
- broad ther. range
- optimal halflife of elimination
- rapidly absorbed after p.o. admin.
- terap. levels in blood 5-7 h, no active metabolites
- no ADE , interactions
- no risk of addiction

MUNI
MED

First generation hypnotics

clomethiazole

acts as a positive allosteric modulator at the barbiturate/picrotoxin site of the GABAA receptor

Indications: insomnia in geriatric patients, acute alcohol withdrawal syndrome, delirium tremens

Contraindicated in case of sleep apnoe and chronic respiratory insufficiency

barbiturates

- obsolete, death from respiratory and cardiovascular depression if given in large dose – flumazenil not effective
- mainly used in anaesthesia (thiopental) and as a treatment of epilepsy (phenobarbital)

MUNI MED

Second generation hypnotics

Benzodiazepines

- midazolam – also for premedication in anaesthesiology
- diazepam
- cinolazepam
- clobazam
- medazepam

unwanted effect: **dependence,** drowsiness, disturbed sleep cycle

MUNI MED

Third generation hypnotics

Selective agonists at benzodiazepine site containing α_1 subunit

- selective hypnotic effect, lacking moyrelaxant, anxiolytic and anticonvulsive effect

- non-benzodiazepine structure

- can cause dependence, not causing morning „hangover“, causing confusion, hallucinations, somnambulism and delusions in sensitive and geriatric patients

- zopiclone

- zolpidem

- zaleplon

Antidepressive drugs in treating insomnia

- **trazodone**
- **agomelatine**
- mirtazapine – see AD materials

MUNI
MED

New trends in hypnosedatives

Drugs influencing circadian rhytms

melatonin

- just weak hypnotic
- 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

MUNI
MED

New trends in hypnosedatives

Dual orexin receptor antagonist

- **suvorexant**
  - produces similar reinforcing effects to those of zolpidem and thus may have a similar abuse liability
  - unwanted effects: sleep terror, drowsiness
  - contraindicated in pregnancy

MUNI MED

Risks associated with using hypnotics

- dependence, cognitive disorders
- higher mortality (respiratory center depression caused by overdose)
- higher infection rate (weak respiratory infections, pneumonia)
- higher risk of cancer
- depression and suicide
- higher risk of dementia, fractures and injuries

MUNI
MED

Other drugs with hypnosedative effect

- antipsychotics: quetiapine
- chlorprothixen, levomepromazine
- H1 antihistamins (1. generation): hydroxyzine, promethazine, moxastine, bisulepine
- medicinal herbs

MUNI
MED

Medicinal herbs as hypnosedatives

- Melissa off. (Lemon balm)
- Valeriana off. (Valerian)
- Humulus lupulus (Hop)
- Passiflora incarnata (maypop, purple Passionflower)
- Hypericum perforatum (St. Johns Wort)

MUNI
MED