



Introduction to Psychopharmacology

Lehmann classification of psychotropic substances



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

SCHIZOPHRENIA

antipsychotics

DEMENTIA

cognitive
enhancers

ADHD

psychostimulants

ANXIETY

anxiolytics

PSYCHIC INTEGRATION

hallucinogens
psychotomimetics



MEMORY AND COGNITION

nootropics

INSOMNIA

sedatives
hypnotics

DEPRESSION

antidepressants

EPILEPSY

anticonvulsants
antiepileptics

BIPOLAR DISORDER

mood stabilizers

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>



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

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

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

Substances capable of causing psychosis



- levodopa (DA)
- CNS stimulants (NA, DA, 5HT)
 - cocaine
 - amphetamines
 - khat, kathinon, methkathinon, mezkalin
- hallucinogens – LSD (5HT_{2c} agonist)
- cannabis
- apomorphine (agonism D₂)
- bupropion (NDRI)
- phencyclidin, ketamine (NMDA antag.)

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

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 D₂ 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

Classical (typical) antipsychotics - basal

levomepromazine –D₂ 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)

Classical (typical) antipsychotics - basal

melperone

Low affinity D2 antagonism

5HT_{2A}, α ₁ 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, α ₁, α ₂, 5HTR

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

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 - D₂ antag. ,highly potent, better than phenothiazines, long

T_{1/2}, less sedation, influencing BP

better tolerability (blood count, liver injury)

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

Atypical antipsychotics



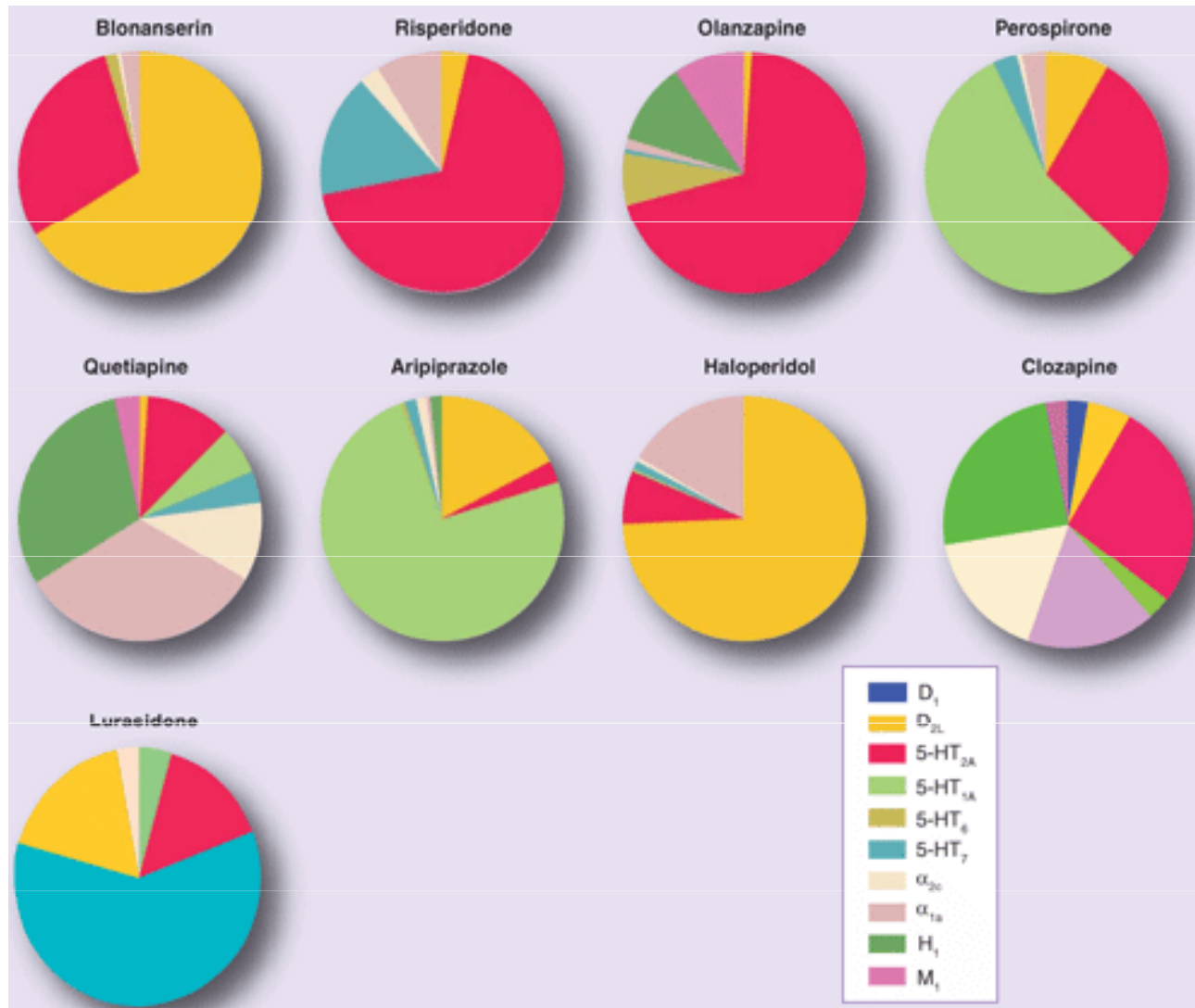
- higher efficacy, better tolerability
- affect positive and negative symptoms, cognition
- D₂ receptor occupancy <80%, binding to multiple neurotransmitter systems
- affect not only transport of dopamine but also other neuromediators (serotonin)
- wide range between antipsychotic effects and EPS
- selective extrastriatal (mesolimbic) blockade of dopamine D₁, D₂ receptors
- risperidone, ziprasidone, olanzapine, quetiapine ...

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

Relative receptor profile AP2G



Atypical antipsychotics - MARTA

clozapine

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

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

minimal impact on the nigrostriatal system

Effect on alpha, $5HT_2$ rcp

Useful in: Pharmacoresistant psychoses - responds about 1/3

risk of suicidium, aggressive patients, EPS

AE: sedation, weight gain,

agranulocytosis - genetic test

Atypical antipsychotics - MARTA

olanzapine antag. D₂, 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

Atypical antipsychotics - SDA

risperidone

antag. D_2 , antag. 5HT_{2A} (↑ release DA) , α_1 , 5HT₇ (antidepressive 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. 5HT_{2A}, α_1 , less affinity 5HT₇

p.o. and depot inj.

Atypical antipsychotics- SDA

lurasidone

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

cariprazine

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

Atypical antipsychotics - DSS

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

blocks 5HT2C, 5HT7 –antidepressive action

“ lacks sedation, weight gain

p.o. + depot inj.

Other Indications: augmentation of antidepressants,

Adverse effects



Blockade of D₂ 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>

Adverse effects

Blockade of D₂ receptors in nigrostriatal pathway

EPS

Akathisia

**- intense mental discomfort, compulsive movements
restlessness**

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

Adverse effects

Blockade of D₂ 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=6HKMusvSfel>

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



Anxiolytic and hypnotosedative drugs

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.

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

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

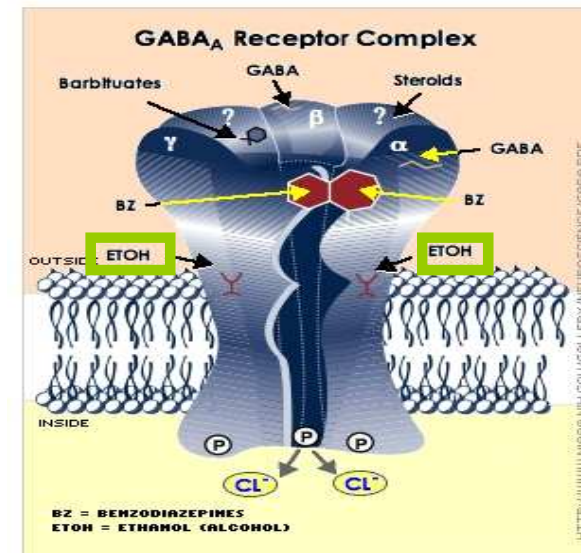


inhibition of signal transduction

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)



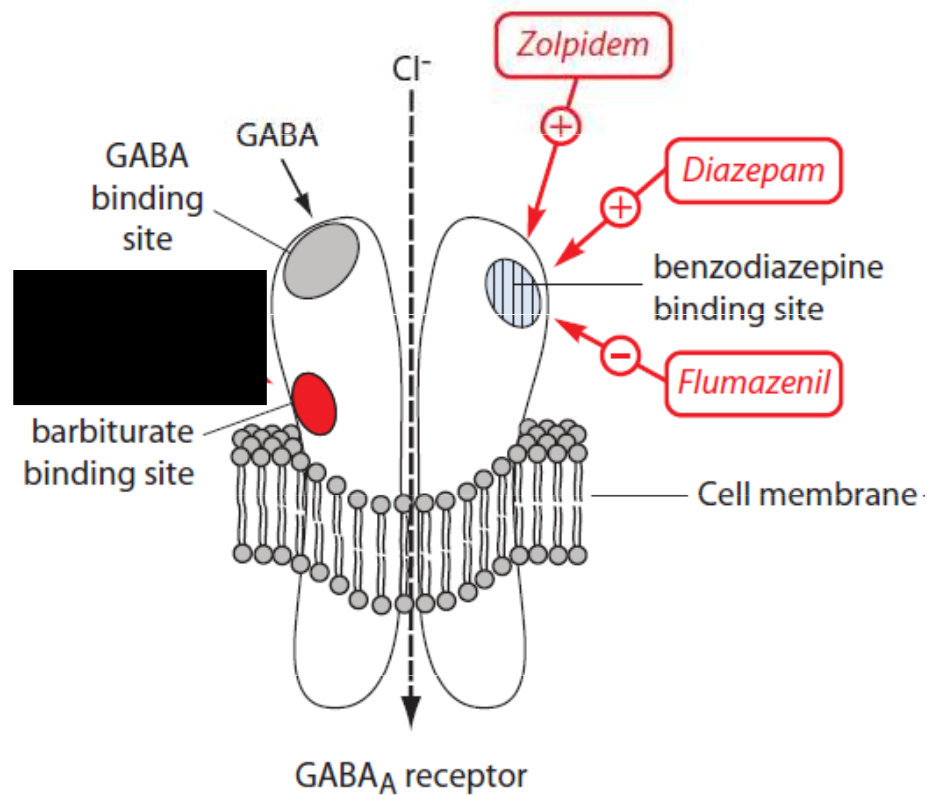


Table 44.2 GABA_A-receptor α -subunit selectivity of some therapeutically used benzodiazepines

Drug	Subunit selectivity
Diazepam	$\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6$
Flunitrazepam	$\alpha_1, \alpha_2, \alpha_5$
Midazolam	$\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6$
Zolpidem	α_1
Flumazenil	Antagonist at $\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6$

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



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

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

Drugs	Sedative- hypnotic effects	t_{1/2} hr
medazepam		2
chlordiazepoxide		5-30
clobazam		18
bromazepam		8-20
lorazepam		10-20
oxazepam		5-21
clorazepat		30-100
alprazolam		6-20
diazepam		30-100
nitrazepam		24-29
(triazolam)		1,5-5,5
flurazepam		40-100
midazolam		1,5-2,5
flunitrazepam		20-30

(According to Seifertová 2004)

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

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

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)

Beers list



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



Organ System/ Therapeutic Category/Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Benzodiazepines <i>Short- and intermediate-acting:</i> <ul style="list-style-type: none"> • Alprazolam • Estazolam • Lorazepam • Oxazepam • Temazepam • Triazolam <i>Long-acting:</i> <ul style="list-style-type: none"> • Chlorazepate • Chlordiazepoxide • Chlordiazepoxide-amitriptyline • Clidinium-chlordiazepoxide • Clonazepam • Diazepam • Flurazepam • Quazepam 	<p>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.</p> <p>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.</p>	Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium.	High	Strong	Allain 2005 Cotroneo 2007 Finkle 2011 Paterniti 2002
Nonbenzodiazepine hypnotics <ul style="list-style-type: none"> • 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

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

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 than 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 and the evening dose is the last reduced
- long-acting benzodiazepines cause delayed withdrawal syndrome (2-4 weeks later)

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

Non-benzodiazepine drugs with anxiolytic effect



- partial agonist at 5-HT_{1A} 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

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.

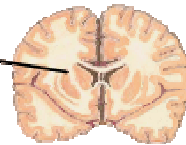
INDICATION

- **HYPNOTICS:** are used for treating sleep disturbances and disorders
 - insomnia
- **SEDATIVES** – in anxiety, ameliorate hyperactivity, aggressivity
- **No clear cut-off between HYPNOTICS and SEDATIVES**
„HYPNOSEDATIVES“

Complications of Insomnia

Psychological

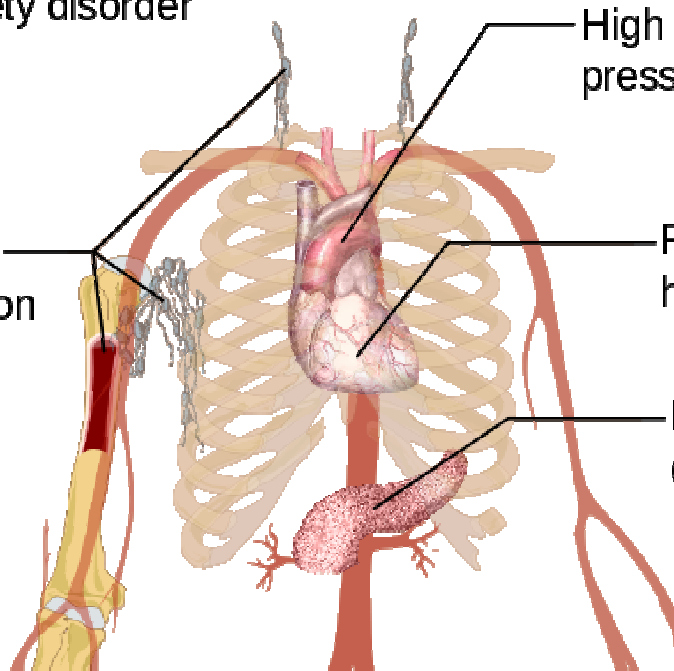
- Lower performance
- Slowed reaction time
- Risk of depression
- Risk of anxiety disorder



Other:

Overweight or obesity

Poor immune system function



High blood pressure

Risk of heart disease

Risk of diabetes

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)

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)

„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

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)

Second generation hypnotics



Benzodiazepines

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

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

Third generation hypnotics



Selective agonists at benzodiazepine site containing α_1 subunit

- selective hypnotic effect, lacking myorelaxant, 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

New trends in hypnotosedatives



Drugs influencing circadian rhythms

melatonin

- just weak hypnotic
- universal signal molecule which gives estimate about light/dark cycle to the brain
- is synthesised in epiphysis, retina, GIT
- sleep do not affect synthesis, peak levels between 11PM and 3AM

New trends in hypnotosedatives



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

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

Other drugs with hypnosedative effect



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

Medicinal herbs as hypnosedatives

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