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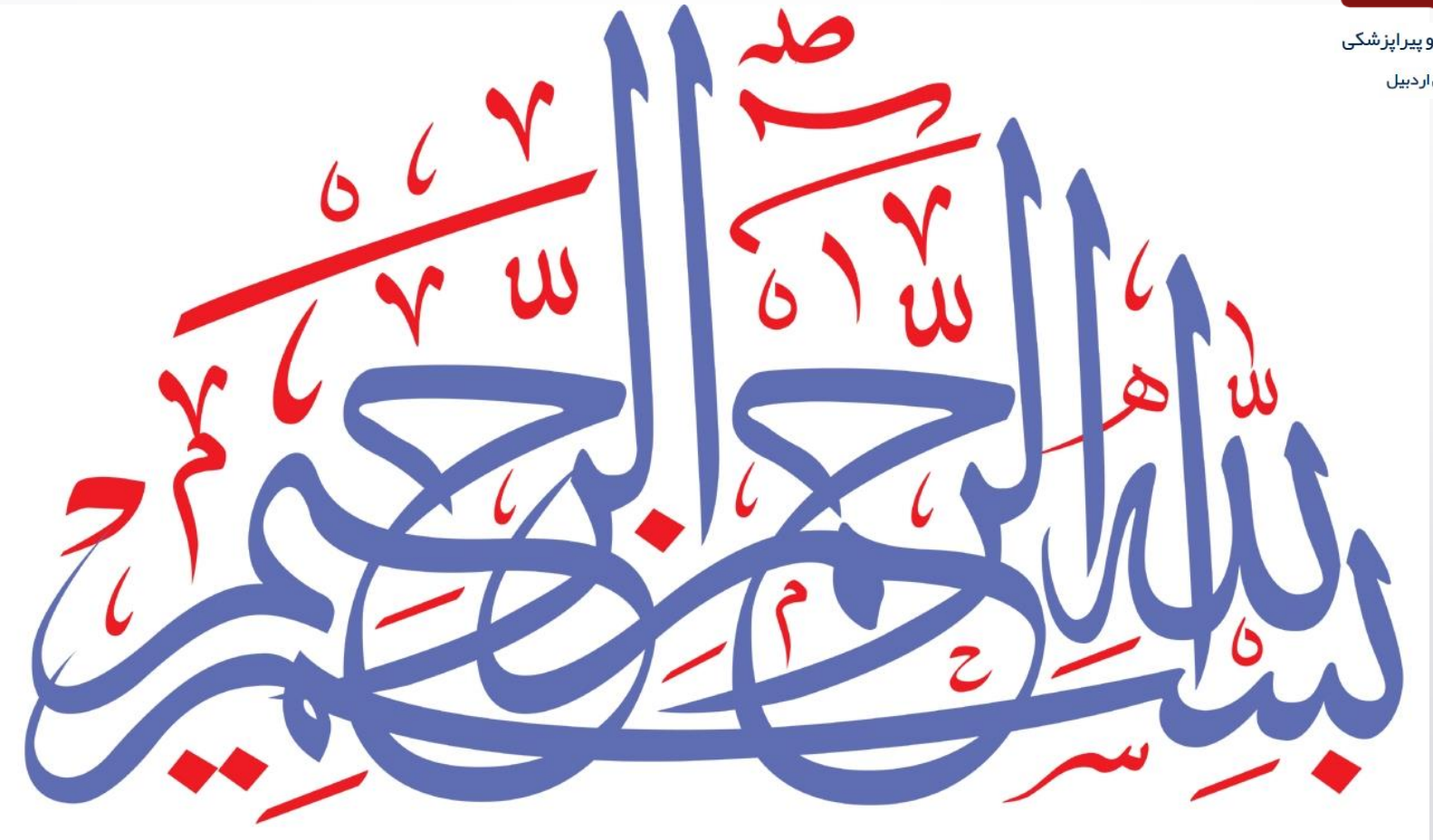

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Benzodiazepines
بنزودیازپین ها

- دکتر آنیتا آذرکلاه
- دانشگاه علوم پزشکی اردبیل، دانشکده پزشکی و پیراپزشکی
- گروه پوست و روانپزشکی

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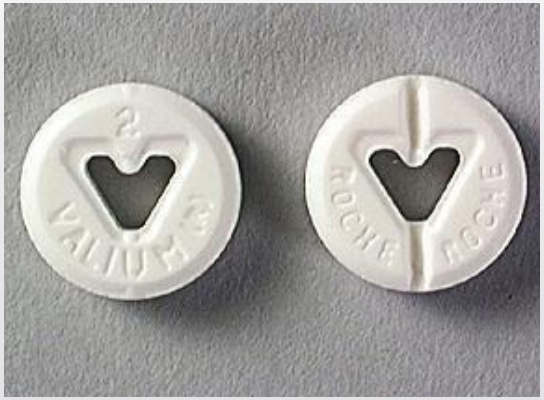
Outline

- What are Benzodiazepines
- History
- Mode of Action
- Most commonly prescribed benzodiazepines
- Indications
- Side effects
- Interactions
- pharmacokinetic
- Addictive properties
- Prescribing guidelines
- A Pharmacists perspective
- Withdrawal syndrome
- Why they should not be sold/passed on to others
- Toxicity
- CONCLUSION

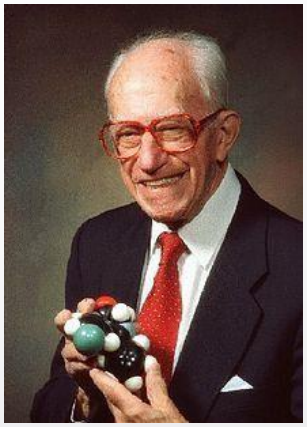


What are Benzodiazepines?

- Benzodiazepines are a group of drugs that act on the central nervous system. Used to treat anxiety, stress, sleeping problems and other disorders.

Brand	**Generic**	**Street**
Valium	Diazepam	Vallies, Roche
Xanax	Alprazolam	Xanies
Ativan	Lorazepam	Downers
Librium	Chlordiazepoxide	

History



- 1903 Barbiturates
- First discovered in 1954 by Roche scientist
- 1957 Chlordiazepoxide synthesized
- 1960 Marketed as Librium
- 1959 Diazepam synthesized
- 1963 Valium launched
- 1978 Valium – most widely prescribed drug in the world
- 1980Risk of dependence realised

Current average time from synthesis to commercial availability is 14 years

Mechanism of Action

- Benzodiazepines work by increasing the efficiency of a natural brain chemical, GABA which decreases the excitability of neurons. This reduces the communication between neurons and, therefore, has a calming effect on many of the functions of the brain.

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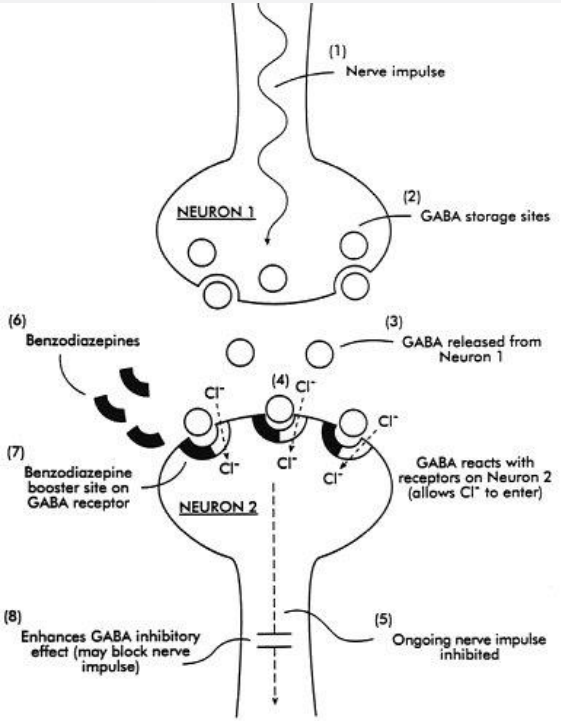
Benzodiazepines

Related Neurotransmitters

GABA



- Benzodiazepines facilitate GABA binding
- Agonistic action on GABA may account for the sedative-hypnotic and anesthetic properties.

http://nawrot.psych.ndsu.nodak.edu/Courses/465Projects06/Benzo/Page2_files/image004.jpg

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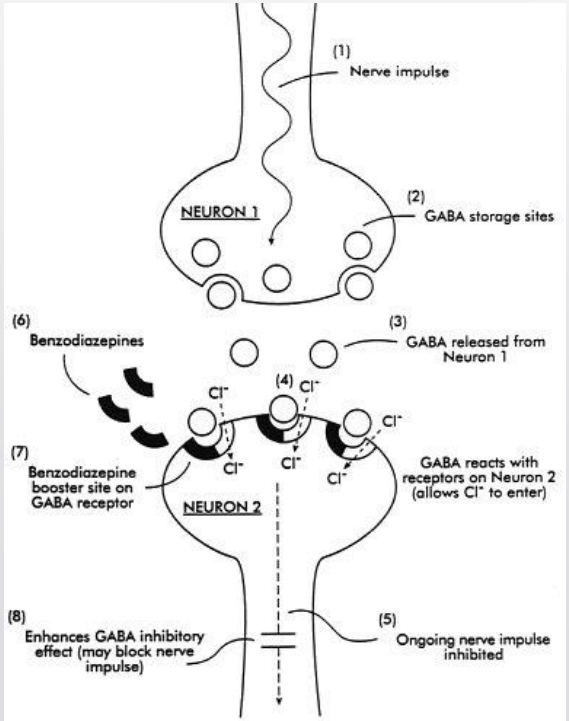
Benzodiazepines

Related Neurotransmitters

- GABA



- Benzodiazepines increase the affinity of the receptor for GABA, and thus increase Cl- conductance and hyperpolarizing current
- Therefore, benzodiazepines are indirect agonists of the GABA receptor

http://nawrot.psych.ndsu.nodak.edu/Courses/465Projects06/Benzo/Page2_files/image004.jpg

Site and Structure of Action

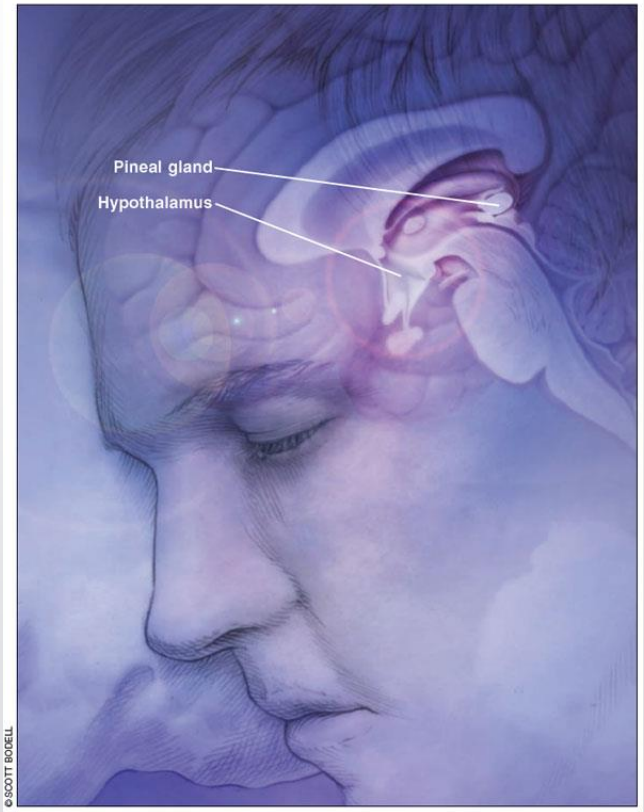
- Site of action is the $GABA_A$ receptor
- Structure of $GABA_A$ receptor
- Comprised of 5 subunits
  - 2 α subunits (to which GABA binds)
  - 2 β subunits (to which barbiturates bind)
  - 1 γ subunit (to which benzodiazepines bind)

Most commonly prescribed Benzodiazepines

- All Benzodiazepines are classified as Controlled Drugs in some countries.
- Most are CD Schedule 4
  - Diazepam (Valium,Anxicalm)
  - Alprazolam (Xanax)
  - Bromazepam (Lexotan)
  - Clobazam (Frisium)
  - Lormetazepam (Noctamid)
  - Nitrazepam (Mogadon)
  - Clonazepam
- Two are CD Schedule 3
  - Flurazepam (Rohypnol)
  - Temazepam (Nortem)

Common Benzodiazepines

- Alprazolam (Xanax)
- Cloxazolam
- Diazepam (Valium)
- Lorazepam (Ativan)
- Midazolam
- Prazepam
- Triazolam (Halcon)
- Clonazepam
- Librium
- Oxazepam



The hypothalamus and pineal gland are the areas of the brain responsible for regulating sleep function. Common treatments for insomnia enhance the activity of GABA, the primary inhibitory neurotransmitter in the CNS, by binding at the $GABA_A$ receptor sites.

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Benzodiazepines

Pharmacokinetics

- **Absorption**
  - Mostly oral, some available parenterally
- **Distribution**
  - Peak plasma concentrations are achieved in about one hour
- **Metabolism**
  - Metabolized in liver
- **Elimination**
  - Through urine

Pharmacokinetics and Dynamics

Pharmacokinetics

- Rapidly absorbed in the GI tract following oral administration (75% reaches plasma)
- Only approx. 20% is metabolized in first-pass metabolism
- Metabolized in the liver and excreted by the kidney's
- Peak plasma levels reached in approx. 1 hour

Pharmacodynamics

- Produces sedation and promotes good sleep (w/o anxiolytic, anticonvulsant, or muscle-relaxant effects)
- Memory is affected
- Flumazenil reported to reverse memory impairments and overdoses
- Flumazenil also reported to improve memory and learning, thus suggesting a possible role of endogenous benzo's in memory function

Adverse effects

- Sedation
- Lethargy
- Respiratory Depression
- Impaired motor skills
- Impaired judgment
- Cognitive dysfunction
- Delirium
- Short-term memory impairment
- Anterograde amnesia
- Ataxia
- Hypotonia
- Depressed mood
- Exacerbation of COPD, sleep apnea

Patients often do not recognize their own impairment

Tolerance and Dependence

- Tolerance to the sedative and euphoric effects are rapid, but nonexistent to anti-anxiety and antipanic effects.
- To sedative and euphoric effects in days
- To anti-epileptic effects limits use for chronic seizure control
- Incomplete tolerance to cognitive impairment
- To the anxiolytic effects "is practically nonexistent"

***Dependence can develop even following only therapeutic dosages**

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Normal

↘

ANXIOLYTIC

↘

Drowsiness/decrease reaction time

↘

HYPNOSIS

↘

Confusion, Delirium, Ataxia

↘

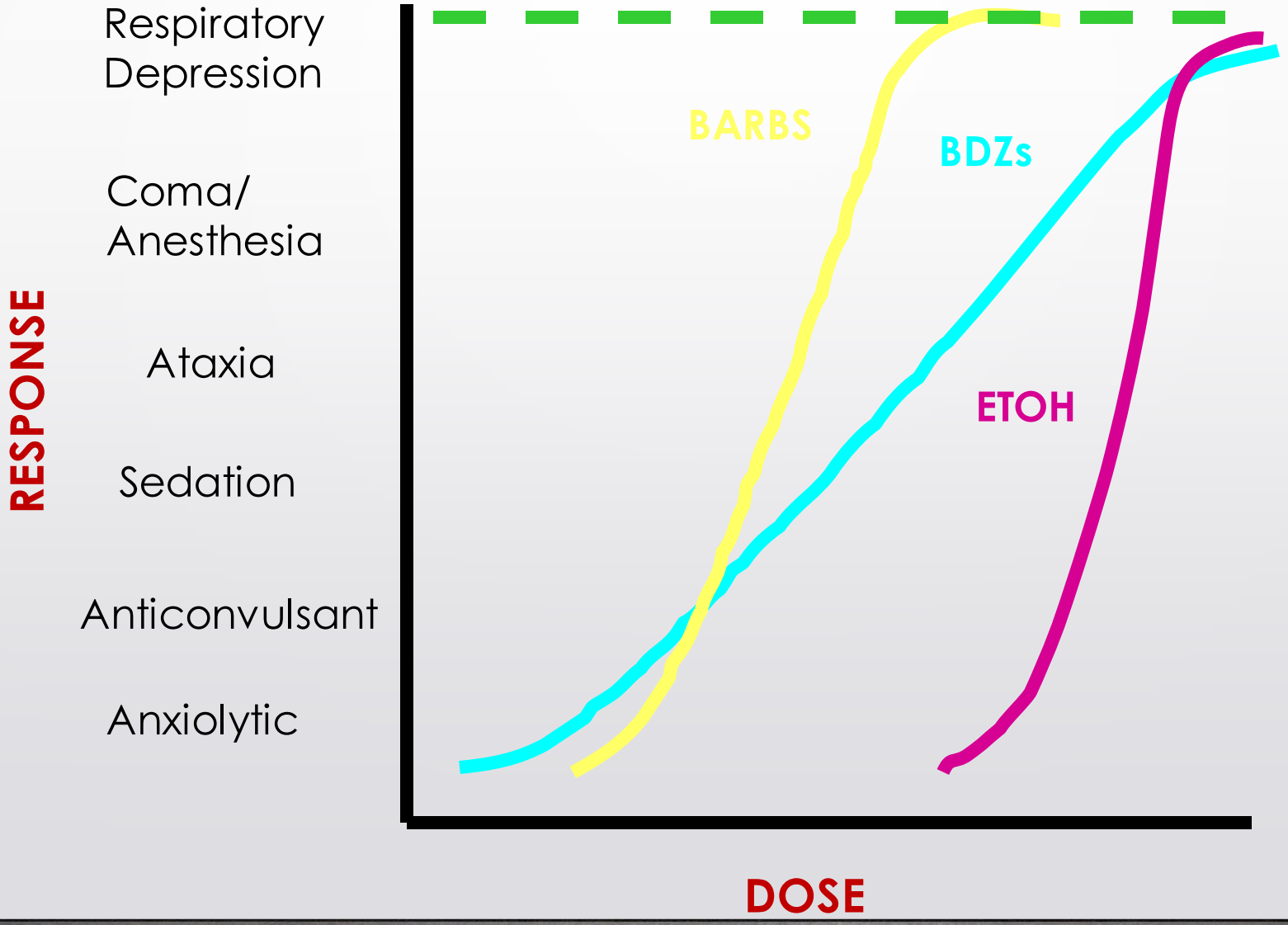
Surgical Anesthesia

↘

Coma

↘

DEATH



ANXYOLITICS

Alprazolam

Chlordiazepoxide

Diazepam

Lorazepam

Oxazepam

Triazolam

Phenobarbital

Halazepam

Prazepam

HYPNOTICS

Chloral hydrate

Estazolam

Flurazepam

Pentobarbital

Lorazepam

Quazepam

Triazolam

Secobarbital

Temazepam

Zolpidem

Indications

- Anxiety
  - Short term relief (two to four weeks only) of anxiety that is severe, disabling, or causing the patient unacceptable stress.
- Insomnia
  - Benzodiazepines should be used to treat insomnia only when it is severe, disabling or causing the patient extreme distress.

- Chronic Muscle Spasm or spasticity associated with MS
- Status epilepticus
- Febrile Convulsions
- Hypnotic (sleep inducing)
- Withdrawal treatment
- Panic disorder with anxiety

THE USE OF BENZODIAZEPINES FOR SHORT TERM MILD ANXIETY OR MINOR INJURY IS NOT APPROPRIATE.

Side Effects of Benzodiazepines

- Drowsiness & Light-headedness the next day
- Confusion & Ataxia (especially in the elderly)
- Increase in fractures -> increase in hospitalisation
- Amnesia
- Dependence, Tolerance
- Dysarthria (Slurred speech)
- Respiratory depression (more so if taken with alcohol or other CNS depressants).decr. B.P &
- Paradoxical increase in aggression
- Demotivation - Inhibition of learning behaviour, academic performance
- Coma
- Decreased libido & erection problem are common

Interactions

- Increased Effects with
  - Alcohol
  - Analgesics (Fentanyl)
  - Antibacterials (Clarithromycin, Isoniazid)
  - Antifungals (ketokonazole, itraconazole)
  - Antipsycotics
  - Antivirals
  - Muscle relaxants (baclofen)
- Decreased Effects with
  - Antibacterial (Rifampicin)
  - Probenecid
  - Theophylline
  - Neoquinolone

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Equivalent doses

Drug	BNF (1)	Maudsley (3)	Bazire (4)[a]	DoH (7)	Ashton Manual (2)[b]
Diazepam	5mg	5mg	5mg	5mg	5mg
Alprazolam	250 micrograms		500 micrograms (0.25-0.5mg)	250 micrograms	250 micrograms
Chlordiazepoxide	12.5mg	12.5mg	15mg (10-25mg)	12.5 - 15mg	12.5mg
Clobazam	10mg		10mg	10mg	10mg
Clonazepam*	250 micrograms	0.5-1mg	500 micrograms (0.25-4mg)	250 micrograms	250 micrograms
Flurazepam	7.5-15mg		7.5-15mg	7.5 – 15mg	7.5-15mg
Loprazolam	0.5-1mg		0.5-1mg	0.5 – 1mg	0.5-1mg
Lorazepam	500 micrograms	500 micrograms	500 micrograms	500 micrograms	500 micrograms
Lormetazepam	0.5-1mg	500 micrograms	0.5-1mg	0.5mg – 1mg	0.5-1mg
Nitrazepam	5mg	5mg	5mg (2.5-20mg)	5mg	5mg
Oxazepam	10mg	15mg	15mg (10-40mg)	10 - 15mg	10mg
Temazepam	10mg	10mg	10mg	10mg	10mg

منبع NHS PPT-PGN-21

IN PREGNANCY:

- Is subject to controversy
- Not major teratogen
- Cleft plate reported
- W.D. symptoms in newborns

Effects on Pregnancy

- Benzodiazepines (and their metabolites) can freely cross the placental barrier and accumulate in fetal circulation
- Administration during the first trimester can result in fetal abnormalities
- Administration in third trimester (close to the time of birth) can result in fetal dependence, or "floppy-infant syndrome"
- Benzodiazepines are also excreted in the breast milk

Short Acting and the Elderly

- Short-lasting benzo's are *not* converted to active intermediates; they are metabolized directly into inactive products
- The elderly have a reduced ability to metabolize long-acting benzo's (and their active metabolites)
- Pharmacokinetics are not drastically altered with the short-acting benzo's
- Short to intermediate acting BDZ (oxazepam & temazepam) are safer than the other in elderly.

Caution with Benzodiazepines Reduce dose with:

- Elderly or debilitated.
- Acute alcohol intoxication.
- Acute angle glaucoma - midazolam (Versed®).
- COPD.

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Prescribing Recommendations

- Address the cause of symptoms
- Psychotherapeutic guidance required – Listen to the patient
- Has the patient tendency to misuse drugs/alcohol?
- Ensure dose is correct
- Prescribed for as long as necessary, aiming for shortest time – but not > 4/52
- Rebound anxiety, tapering dose, support
- Reduction/Discontinuation – Careful medical supervision & appropriate psychological interventions

Before prescription

- Take a full history including an alcohol and licit and illicit drug history.
- Inform the patient of the side-effect profile of benzodiazepines and offer an information leaflet.
- Consider and treat, if possible, any underlying causes.
- Consider referral to other services.
- Consider alternative therapies.
- Consider delaying prescribing until a subsequent visit

When prescribing for the 1st time

- Initiate with the lowest recommended dose, but this may need to be adjusted depending on patient's response.
- Do not prescribe for longer than 4 weeks.
- Use phased dispensing where possible.
- Ensure that agreements between doctor and patient are documented.
- Record all details of medication prescribed and duration of treatment.
- Clear, effective and speedy communication concerning benzodiazepine usage should always take place between the prescribing professionals both within and between services.

Benzodiazepine dependent patients or pts in receipt of continuing prescribing

- Issue small quantities at a time Review regularly – monthly
- Use a long acting benzodiazepine in dosages no higher than diazepam 5 mg three times daily (or equivalent)
- Make patients aware of the risks of long term benzodiazepine use and document this communication.
- Signed consent forms should be used where appropriate.
- Encourage dependent pts to withdraw, offer them a detoxification programme at regular intervals (at least annually) and document
- A significant number of requests for repeat benzodiazepine prescribing are associated with addiction problems, primarily alcohol, or in urban areas, opiate misuse. A doctor who suspects this is the case should seek specialist advice

Methods for withdrawal of B's

- Any Benzodiazepine withdrawal programme should be carefully planned and structured, the aim being to gradually reduce to zero the amount of drug being taken.
- Gradual Dose Reduction
- Substitution
- Dose reduction then immediate substitution
  - Greater flexibility in dosing of longer acting Diazepam
- Adjuvant pharmacotherapy
  - Reduce the physical symptoms of withdrawal
    - Tremor, Sweating, Insomnia. Convulsions
- BENZODIAZEPINES ARE HIGHLY ADDICTIVE

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Sedative Hypnotics

- Withdrawal:
  - Minor: tremors; insomnia (REM rebound); high fever; clonic blink.
  - 12-16hrs: minor symptoms plus abdominal cramps; nausea and vomiting, hypertension; ⇑ deep tendon reflexes.
  - 24hrs: pronounced weakness, course tremors ("the shakes"), hyperactive reflexes, early illusions and hallucinations.
  - 48-72hrs: convulsive seizures ; vivid auditory and visual hallucinations agitation, disorientation, delirium, paranoid delusions.

Sedative/ Hypnotics

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Withdrawal (con't)

- Hyperthermia, dehydration, electrolyte imbalance, exhaustion, cardiovascular collapse => **Threat to life.**
- Time of onset and symptoms experienced vary with CNS depressant use, similar to alcohol withdrawal.
- Additive effect of sedative/hypnotics.

Benzodiazepines

Withdrawal

- **Rebound** anxiety
- **Rebound** insomnia, restlessness, agitation, irritability, and unpleasant dreams

*Rarely, hallucinations, psychosis, and seizures have been reported

Treatment of Withdrawal

- Stabilization: diazepam, chlordiazepoxide, phenobarbital (cross-dependence).
- Drug tapered off slowly => prevention of onset of withdrawal (reversible only early in its course).
- Propranolol or clonidine for tremors and twitching.
- No use antipsychotic.
- No use alcohol (toxicity).

Why Benzodiazepines should not be sold or passed on

- The National Drug-Related Death Index
  - Benzodiazepines were implicated in 31% of drug related deaths
  - Huge increase in number of cases seeking treatment for misuse
  - Age profile of under 18 yr olds seeking help had risen
- They are a Controlled Drug requiring GP management
- Are highly addictive
- Withdrawal effects are very unpleasant
- Should only be taken by the patient they are prescribed for as drug choice and dose are specific to pts needs
- Should not be sold or passed on even if symptoms are similar.
- You are not helping anybody by sharing this medication with them.

Sedative Hypnotics

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Club Drugs

Alcohol
Rohypnol
GHB
LSD
MDMA (Ecstasy)

Ketamine (Special-K)
Amphetamines
Methamphetamine.

Sedative Hypnotics

E. Acute Intoxication

Pupils are normal; BP and respiration are depressed; nystagmus on lateral gaze; tendon reflexes depressed; ataxia; slurred speech; confusion; coma; shock

=> Risk of Death, particularly with BARBs.

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Management of overdose and poisoning

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General- evaluation

- recognition of poisoning
- identification of agents involved
- assessment of severity
- prediction of toxicity

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General- management

- provision of supportive care
- prevention of poison absorption
- enhancement of elimination of poison
- administration of antidotes

Supportive care

- ABCD
- Vital signs, mental status, and pupil size
- Pulse oximetry, cardiac monitoring, ECG
- Protect airway
- Intravenous access
- cervical immobilization if suspect trauma
- Rule out hypoglycaemia
- Naloxone for suspected opiate poisoning

History

- Pill bottles
- Alcohol
- Drug history including access
- Remember OTC drugs
- Suicide note
- National Poisons Information Centre *or toxicologist consultant

Examination

- Physiologic excitation –

  anticholinergic, sympathomimetic, or central hallucinogenic agents, drug withdrawal

- Physiologic depression –

  cholinergic (parasympathomimetic), sympatholytic, opiate, or sedative-hypnotic agents, or alcohols

- Mixed state –

  polydrugs, hypoglycemic agents, tricyclic antidepressants, salicylates, cyanide

Preventing absorption

Gastric lavage

- Not in unconscious patient unless intubated (risk aspiration)
- Flexible tube is inserted through the nose into the stomach
- Stomach contents are then suctioned via the tube
- A solution of saline is injected into the tube
- Recommended for up to 2 hrs in TCA & up to 4hrs in Salicylate OD

Induced Vomiting

- Ipecac - Not routinely recommended
- Risk of aspiration

Preventing absorption

Activated charcoal

- Adsorbs toxic substances or irritants, thus inhibiting GI absorption
- Addition of sorbitol →laxative effect
- Oral: 25-100 g as a single dose
- repetitive doses useful to enhance the elimination of certain drugs (eg, theophylline, phenobarbital, carbamazepine, aspirin, sustained-release products)
- not effective for cyanide, mineral acids, caustic alkalis, organic solvents, iron, ethanol, methanol poisoning, lithium

Elimination of poisons

Renal elimination

- Medication to stimulate urination or defecation may be given to try to flush th excess drug out of the body faster.

Forced alkaline diuresis

- Infusion of large amount of NS+NAHCO3
- Used to eliminate acidic drug that mainly excreted by the kidney eg salicylat
- Serious fluid and electrolytes disturbance may occur
- Need expert monitoring

Hemodialysis or haemoperfusion:

- Reserved for severe poisoning
- Drug should be dialyzable i.e. protein bound with low volume of distribution
- may also be used temporarily or as long term if the kidneys are damaged due to the overdose.

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Antidotes

- Does an antidote exist?
- Does actual or predicted severity of poisoning warrant its use?
- Do expected benefits of therapy outweigh its associated risk?
- Are there contraindications?

Reversal Agent for Benzodiazepines
Flumazenil (Romazicon®)

- Inhibits the action of the benzodiazepine
- **Does not necessarily correct respiratory depression**
- Use cautiously in patients at high risk for seizure or arrhythmia
- Monitor for *re-sedation*
- Observe for dizziness, nausea, vomiting
- Drug-drug interaction includes anti-depressants

Flumazenil contraindication

A. Co-ingestion (TCA)

B. Recent CNC surgery

C. Known case of convulsion

D. Chronic user of BDZ

Guidance on the use of Benzodiazepines

Prior to initiation:

Consider non-pharmacological methods before using BZD/ZDs e.g. Talk 1st techniques, sleep hygiene etc.

On initiation:

- Discuss the use of BZD/ZDs with the patient i.e. side-effects, risk of tolerance/ dependence, cognitive impairment and/or sedation
- Use lowest dose for the shortest time possible
- Consider setting a review/stop date at time of prescribing.
- Indication, intended duration of treatment & plans for review & discontinuation MUST be documented on RiO.

During treatment:

Frequently review and document the continued need for BZD/ZDs, with a view to stopping them.

Review quantity of medication supplied during leave periods to minimize risk.

Discharge:

Review the BDZ/ZD & stopped before discharge if appropriate.

A treatment plan should be made for BDZ/ZDs that continue post-discharge.

This plan should be communicated with the GP via the MHDS.

The treatment plan should include:

- Indication for use
- Expected duration of treatment
- When treatment will be reviewed and by whom
- Advice about discontinuation (if indicated)
- Who to contact within Secondary Care if problems arise
- Rationale for any unlicensed prescribing.

Conclusion

- Benzodiazepines are safe when used within the guidelines
- They are highly addictive even when used for short periods
- Cause many road traffic accidents due to driving under the influence of drugs
- They can be fatal when used with other drugs/alcohol
- Are Controlled drugs and require medical supervision
- Should be taken only by the pt they are prescribed for.
- Directions for use should be followed exactly
- Withdrawal from long term use of Benzodiazepines is difficult but with motivation & support is possible

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با تشکر از توجه و حوصله شما

Thank you for your attention