Other Sedatives-Anxiolytics

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RAMELTEON (Rozerem®)

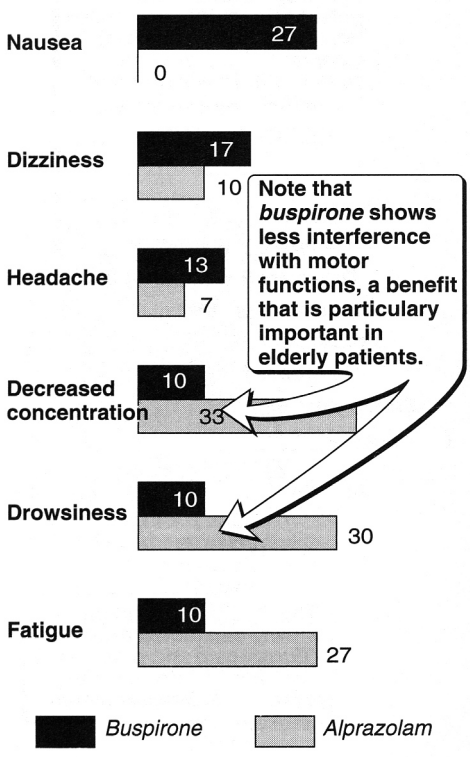
- chemically related to **MELATONIN**.

- **melatonin receptor** agonist (high affinity and selectivity for MT_1 and MT_2 receptors, vs. MT_3 receptors).
- $T_{1/2} \approx$ 1-2,6 hrs.
- metabolized by liver.
- decreases [testosterone] and increases [prolactin] in serum.
- used as **hypnotic** for SLEEP-ONSET INSOMNIA (8 mg within 30 minutes of going to bed).
- does not cause rebound insomnia.
- does not cause dependence (drug is not controlled substance!).
- adverse effects – n.y. (headache, somnolence, etc).
- should not be used with FLUVOXAMINE (ramelteon concentration↑↑↑).

BUSPIRONE (BuSpar®)

- unique chemically **AZASPIRONE** (not chemically and pharmacologically related to benzodiazepines or barbiturates or other sedatives!).

- partial agonist at **serotonin 5-HT_{1A} receptors**; some affinity for **D_2** and **5-HT_2 receptors**.
- used as **anxiolytic** in long-term therapy of generalized anxiety disorders (efficacy comparable to benzodiazepines!).
  - only ***minimal sedation***! (+ does not potentiate CNS depression of ethanol) – most useful anxiolytic in elderly patients!
  - effectively eliminates episodic outbursts of aggression and agitation in brain-damaged patients.
  - ***minimal psychomotor*** and ***cognitive dysfunction***.
  - no respiratory depression.
  - because ***higher doses cause dysphoria***, patients do not escalate dose (dependence is unlikely, ***low addiction potential***).



N.B. *buspirone is not CNS depressant* - cannot be directly substituted for benzodiazepines and does not suppress benzodiazepine withdrawal.

- at doses > 45 mg/d has **antidepressant effect** (but also at high doses may cause dysphoria).
- no anticonvulsant, hypnotic-sedating, myorelaxant properties.
- disadvantageous ***slow onset of action*** – must be given for 1 month before it is effective.
- adverse effects (rare) - headaches, nervousness, dizziness, lightheadedness.

Little potential for abuse!

CHLORAL HYDRATE

- trichlorinated derivative of acetaldehyde.

- must be metabolized by alcohol dehydrogenase to active metabolite **TRICHLOROETHANOL**.
- weak but safe **sedative-hypnotic** - induces sleep in 30 minutes and lasts 6 hours ($T_{1/2}$ = 4-10 hrs).
  - relatively safe;
  - little reduction in REM sleep;
  - has anticonvulsant properties;
  - mostly used for 1-3 nights to treat transient insomnia.
- adverse effects - unpleasant taste, GI tract irritation.
- CNS depressant effect potentiated by ethanol (combination CHLORAL ALCOHOLATE is dubbed "Mickey Finn"); addiction can occur!
- also used externally as rubefacient, anesthetic, and antiseptic.
- CHLORAL BETAINE is slowly hydrolyzed in GI tract to chloral hydrate.

PARALDEHYDE

- trimer of acetaldehyde (resembles CHLORAL HYDRATE).

- potent **sedative-hypnotic** - induces sleep in 15 minutes and lasts 4-8 hours.
- has anticonvulsant properties.
- can be administered **orally** (*strong offensive odor* and *disagreeable taste* + *GI tract irritation*!), **parenterally**, **rectally**.
- *eliminated via lungs* – does not depend on liver / kidney status!
- used exclusively for alcoholics undergoing withdrawal from alcohol.

Do not use with DISULFIRAM!

GLUTETHIMIDE

- *very narrow therapeutic index* - formerly used as **hypnotic** and as daytime **sedative**.

ETHANOL (ETHYL ALCOHOL)

- CNS depressant* with **anxiolytic & sedative** effects.

*synergizes with many other sedative agents and can produce severe CNS depression!

N.B. *toxic potential* outweighs benefits!

- shallow dose-response curve (sedation occurs over wide dosage range with ultimately hypnosis and coma).
- about **metabolism** and DISULFIRAM – see p. 702 >>

MEPROBAMATE

- propyl alcohol derivative (propanediol carbamate): hypnotic, muscle relaxant

- depresses CNS as shorter acting **barbiturates** (≈ phenobarbital).
- was widely used antianxiety agent → largely been replaced by benzodiazepines.
- well absorbed from GI tract.

DEXMEDETOMIDINE (Precedex®)

- relatively selective α_2-adrenoceptor agonist with sedative properties.

- used for sedation of intubated (mechanically ventilated) patients in ICU.
- administered by continuous IVI not to exceed 24 hours (longer use may cause withdrawal* if stopped abruptly). *similar to CLONIDINE withdrawal
- may cause bradycardia & hypotension (hypertension during loading dose may be observed).

METHOCARBAMOL (Robaxin®)

- carbamate derivative of guaifenesin (expectorant).

- CNS depressant with **musculoskeletal relaxant** properties (related to sedative properties, because drug has no direct action on contractile mechanism, motor end plate or nerve fiber).
- indication - as adjunct to rest, physical therapy, and other measures in acute painful musculoskeletal conditions.
- mode of action - not been clearly identified.
- may inhibit effect of anticholinesterase agents (pyridostigmine) - use with caution in myasthenia gravis.

NONBENZODIAZEPINE HYPNOTICS

ZOLPIDEM (Ambien®, Zolpimist®)

- **IMIDAZOPYRIDINE**.

- selective for **subtype 1 of benzodiazepine receptor** (as QUAZEPAM).
- used as **sedative-hypnotic** (advantageous over benzodiazepines!)
  - preserves sleep architecture!
  - does not cause memory disturbances (as benzodiazepines do);
  - minimal rebound insomnia;
  - no tolerance, no withdrawal effects with prolonged use.
- no anticonvulsant, no myorelaxant properties.
- rapidly absorbed from GI tract, rapid onset of action, $T_{1/2} \approx$ 1,5-3 hours.
  Zolpimist® - FDA approved oral spray for short-term treatment of difficulty with sleep initiation.
- adverse effects - nightmares, agitation, headache, GI upset, dizziness, daytime drowsiness.

ZALEPLON (Sonata®)

- **PYRAZOLOPYRIMIDINE**; ≈ ZOLPIDEM.

- rapid onset of action with ultra-short duration.

ZOPICLONE

- **CYCLOPYRROLONE**.

ESZOPICLONE (Lunesta®)

- **CYCLOPYRROLONE**.

- mechanism of action - interaction with GABA-receptor at binding domains close to (or allosterically coupled to) **benzodiazepine receptors**.
- used as **hypnotic**; likely to become first choice agent for treatment of insomnia.
  - shows continued efficacy at 12 months of continued use.
  - less addictive than benzodiazepines.
- $T_{1/2} \approx$ 6 h.
- higher doses (2-3 mg) are more effective for *sleep maintenance*, whereas lower doses (1-2 mg) are suitable for difficulty in *falling asleep*.

ANTIHISTAMINES

Nonprescription sedating antihistamines (DIPHENHYDRAMINE, DOXYLAMINE) are effective only in *mild forms of situational insomnia*.

- anticholinergic side effects make them less useful than benzodiazepines.

HYDROXYZINE - antihistamine with antiemetic activity.

- low tendency for habituation - useful for *anxiety with history of drug abuse*.
- also used for *sedation prior to dental procedures*.

BIBLIOGRAPHY for "Sedatives, Hypnotics" → follow this LINK >>