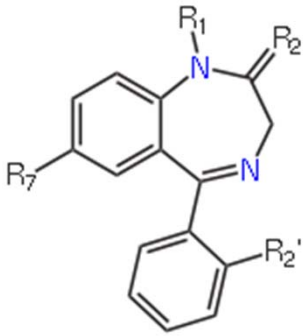
Hypnotics and sedatives

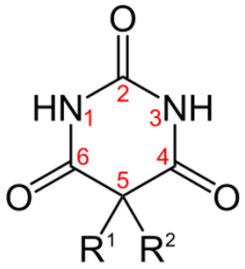
Sedative – anxiolytic – hypnotic action

Hypnotics - Sedatives

BZDs

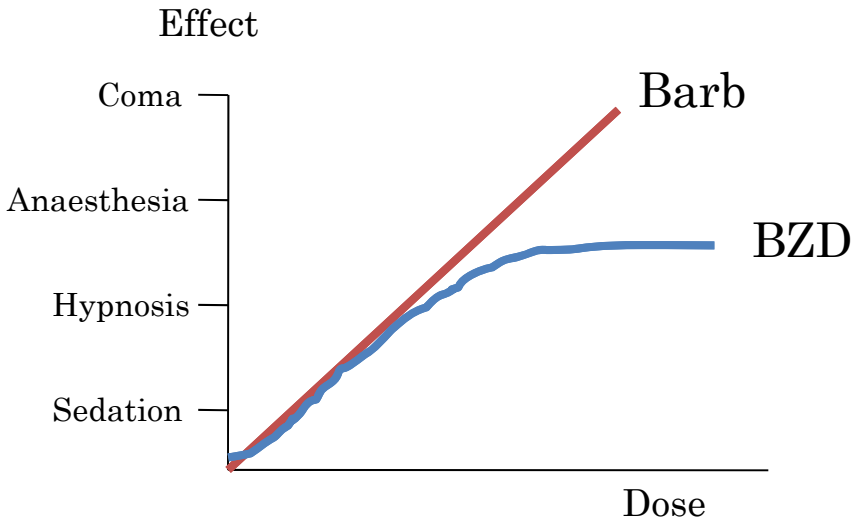


Barbiturates



Antihistamines

Big 'Z' compounds and buspirone

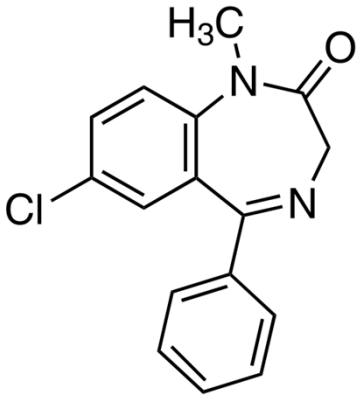


Anxiety disorders

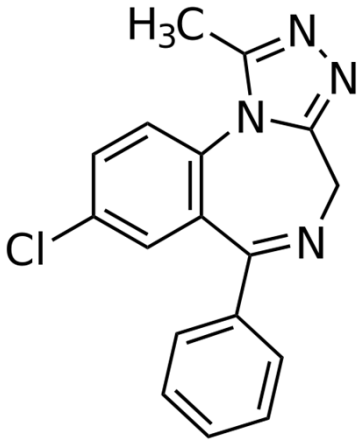
- Generalized anxiety disorder (GAD)
- Social anxiety disorder
- Panic disorder
- Phobias
- Post-traumatic stress disorder (PTSD)
- Obsessive compulsive disorder (OCD)

BZD structure

- benzene ring +
- diazepine ring (7 membered heterocyclic) +
- 5-aryl substituent ring (+ oxazole/triazole ring - alprazolam, triazolam)



diazepam

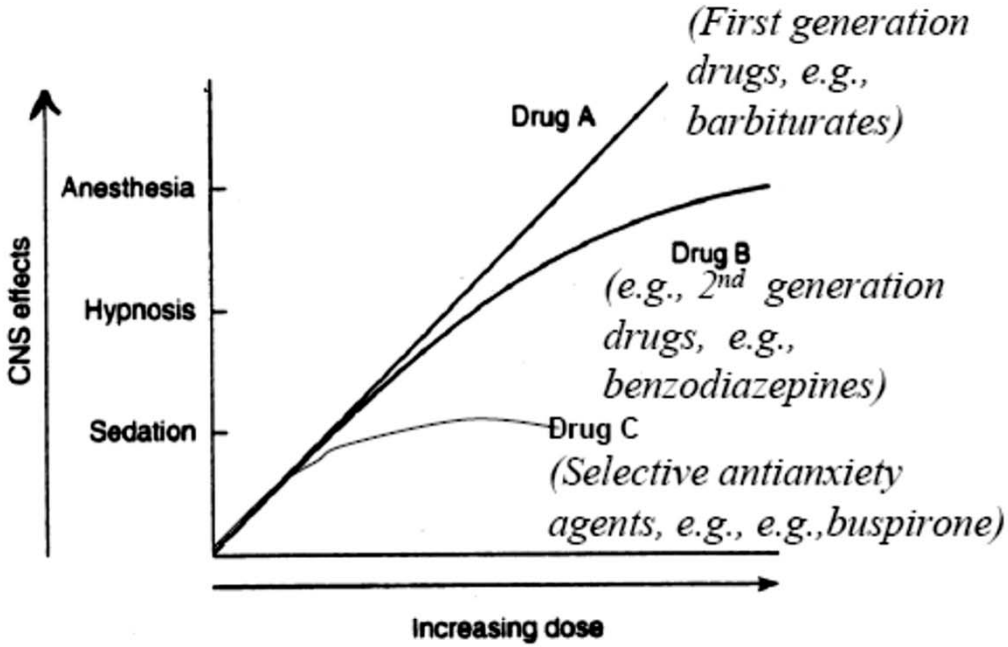


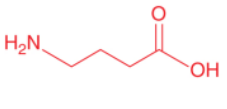
alprazolam

Basic: diazepam, chlordiazepoxide, clonazepam, midazolam
Triazole ring: triazolam
Oxazole rings: alprazolam, cloxazolam

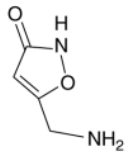
Overdose effects of an ideal antianxiety/sedative agent should not include generalized CNS depression

- Therapeutic Index (LD_{50}/ED_{50}), margin of safety : greater for 2nd generation agents than for 1st generation agents

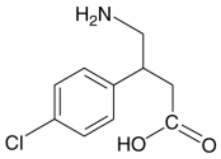




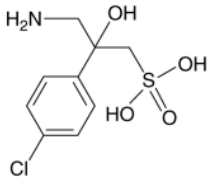
GABA
(γ-amino butyric acid)



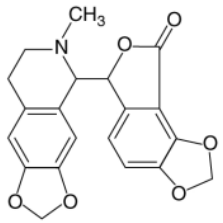
MUSCIMOL
($GABA_A$ agonist)



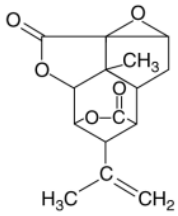
BACLOFEN
($GABA_B$ agonist)



2 – OH – SACLOFEN
($GABA_B$ antagonist)

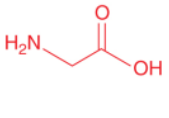


BICUCULLINE

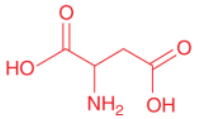


PICROTOXIN

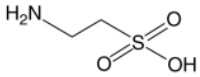
($GABA_A$ antagonists)



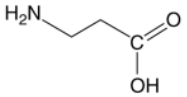
GLYCINE



ASPARTIC ACID

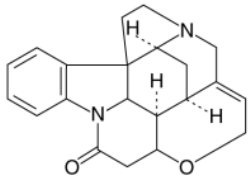


TAURINE

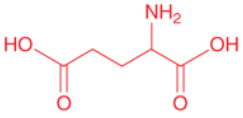


β -ALANINE

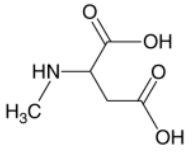
(Glycine receptor agonists)



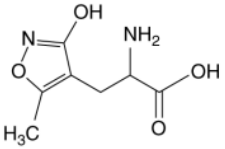
STRYCHNINE
(glycine antagonist)



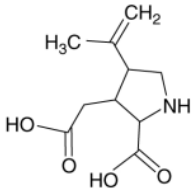
GLUTAMIC ACID



NMDA
(*N–methyl–D–aspartate*)



AMPA
(*α-amino–3–hydroxy–5–methyl–4–isoxazolepropionic acid*)

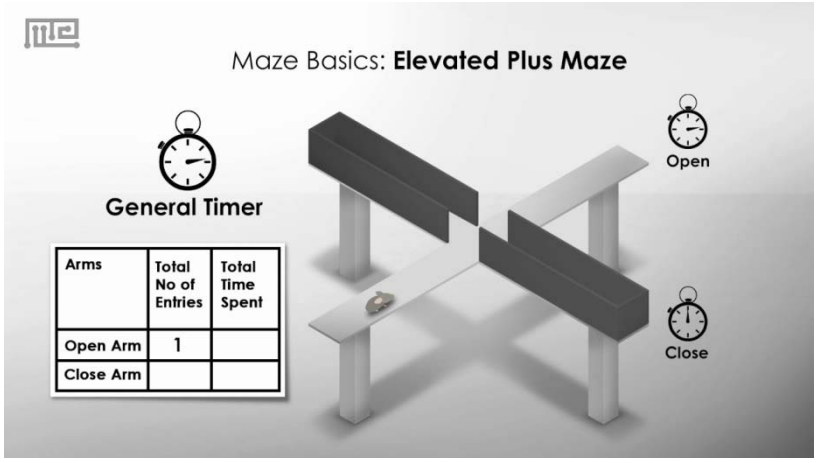


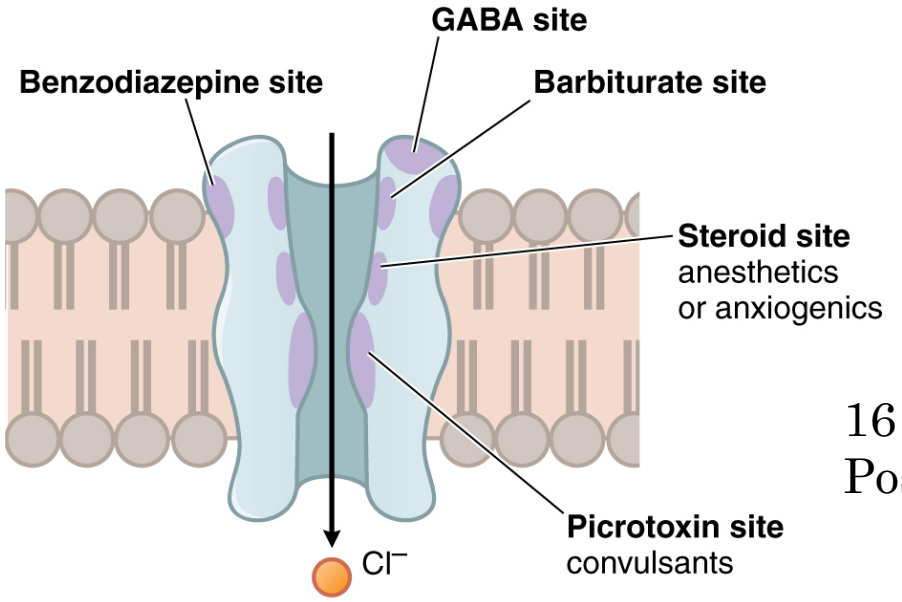
KAINIC ACID

(Glutamate receptor subtype–specific agonists)

Animal models of anxiety

- Model of bar pressing for food
- Mice in individual cage
- Placement into an unfamiliar environment
- Elevated plus maze test





Agonist
Partial agonist
Inverse agonist
Partial inverse agonist
antagonist

16 different subunits: 6α, 3β, 3γ, δ, ε, π, θ
Possible composition is over 1 M

Unlike barbiturates BZDs do not activate $GABA_A$

- γ2, α1, α2, α3, α5 subunits are necessary for BZD binding
- α1 subunit-containing $GABA_A$ receptors: sedative/hypnotic, anticonvulsant, addictive
- α2 subunit-: anxiolysis.
- α2, α3, α5: muscle relaxation
- α1, α5: amnesic effect

Pagoclone: α3 full agonist

Translocator protein: BZD receptor in mitochondrial membrane without GABA binding site

- α3 subunit-: processing of sensory motor information related to a schizophrenia endophenotype.
- α4 subunit-: sedative, hypnotic and anesthetic effects of some agents in the thalamus.
- α5 subunit- (extrasynaptic): associative temporal and spatial memory by inhibitory modulation of activities in the hippocampus.
- β3 subunit-: sedation, hypnosis and anesthesia by, e.g., pentobarbital, propofol and etomidate, but not by the neurosteroidal anesthetic alphaxalone).

Benzodiazepines

chlordiazepoxide (Librium®)
diazepam (Valium ®, Seduxen ®)
clonazepam (Rivotril ®)
triazolam
alprazolam (Xanax ®, Frontin ®)
midazolam (Dormicum ®, Midazolam Torrex ®)
flunitrazepam (Rohipnol ®)

- CNS effects
  - Sedation
  - Hypnosis
  - Decreased anxiety
  - Muscle relaxation
  - Anterograde amnesia
  - Anticonvulsant activity
- Peripheral actions
  - Coronary vasodilation
  - Muscle relaxation (clonazepam)

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: α1, α2, α3, α4, α5, α6

BZDs

PK
A: good except: clorazepate (converted to nordazepam)
D:

Ultra-short acting BZDs: midazolam
Short-acting (t1/2<6 h): triazolam
Intermediate-acting: (t1/2=6-24 h): lorazepam, estazolam, temazepam, alprazolam
Long-acting agents (t1/2>24 h): flurazepam, diazepam, quazepam

Plasma protein bounding: 70% alprazolam, 99 % diazepam

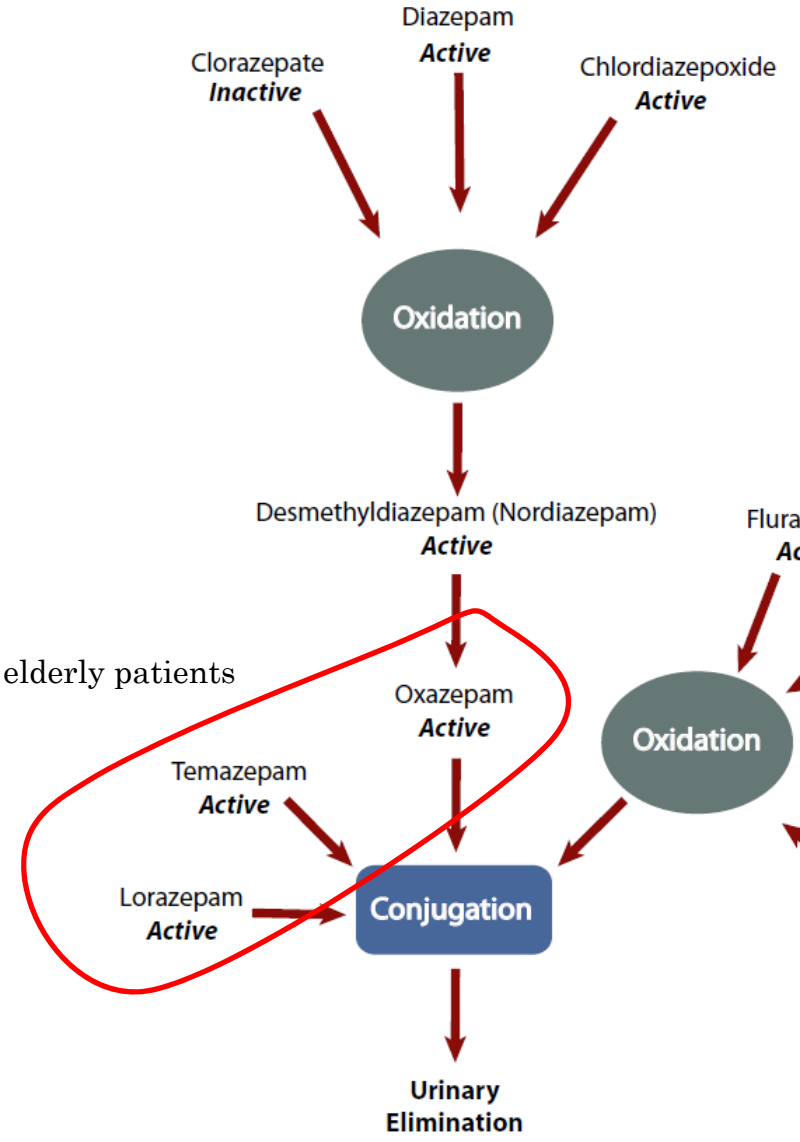
Names, Routes of Administration, and Therapeutic Uses of Benzodiazepines

Compound (Trade Name)	Routes of Administration*	Examples of Therapeutic Uses†	Comments	$t_{1/2}$, Hours‡	Usual Sedative-Hypnotic Hypnotic Dosage, mg¶
Alprazolam (XANAX)	Oral	Anxiety disorders, agoraphobia	Withdrawal symptoms may be especially severe	12±2	—
Chlordiazepoxide (LIBRIUM, others)	Oral, IM, IV	Anxiety disorders, management of alcohol withdrawal, anesthetic premedication	Long-acting and self-tapering because of active metabolites	10±3.4	50–100, qd–qid§
Clonazepam (KLONOPIN)	Oral	Seizure disorders, adjunctive treatment in acute mania and certain movement disorders	Tolerance develops to anticonvulsant effects	23±5	—
Clorazepate (TRANXENE, others)	Oral	Anxiety disorders,seizure disorders	Prodrug; nordazepam formed by decarboxylation in GI tract	2.0±0.9	3.75–20, bid–qid§
Diazepam (VALIUM, others)	Oral, IM, IV, rectal	Anxiety status epilepticus, skeletal muscle relaxation, anesthetic premed	Prototypical benzodiazepine	43±13	5–10, tid–qid§
Estazolam (PROSOM)	Oral	Insomnia	Contains triazolo ring; adverse effects may be similar to those of triazolam	10–24	1–2
Flurazepam (DALMANE)	Oral	Insomnia	Active metabolites accumulate with chronic use	74±24	15–30
Lorazepam (ATIVAN)	Oral, IM, IV	Anxiety disorders, preanesthetic medication	Metabolized solely by conjugation	14±5	2–4
Midazolam (VERSED)	IV, IM	Preanesthetic and intraoperative medication	Rapidly inactivated	1.9±0.6	—#
Oxazepam (SERAX)	Oral	Anxiety disorders	Metabolized solely by conjugation	8.0±2.4	15–30, tid–qid§
Quazepam (DORAL)	Oral	Insomnia	Active metabolites accumulate with chronic use	39	7.5–15
Temazepam (RESTORIL)	Oral	Insomnia	Metabolized mainly by conjugation	11±6	7.5–30
Triazolam (HALCION)	Oral	Insomnia	Rapidly inactivated; may cause disturbing daytime side effects	2.9±1.0	0.125–0.25

*IM, intramuscular injection; IV, intravenous administration; qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day.
†The therapeutic uses are identified as examples to emphasize that most benzodiazepines can be used interchangeably. In general, the therapeutic uses of a given benzodiazepine are related to its half-life and may not match the marketed indications. The issue is addressed more extensively in the text.
‡Half-life of active metabolite may differ. See Appendix II in the 11th edition of the parent text for additional information.
¶For additional dosage information, see Chapter 13 (Anesthesia), Chapter 17 (Anxiety), and Chapter 19 (Seizure Disorders).
§Approved as a sedative-hypnotic only for management of alcohol withdrawal; doses in a nontolerant individual would be smaller.
#Recommended doses vary considerably depending on specific use, condition of patient, and concomitant administration of other drugs.

Benzodiazepines, 1	Half-life (hrs), 2 [active metabolite]	Approximately Equivalent Oral dosages (mg), 3	Market Aim,
Alprazolam (Xanax)	**6-12**	**0.5**	**anxiolytic,**
Bromazepam (Lexotan)	**10-20**	**5-6**	**anxiolytic,**
Chlordiazepoxide (Librium)	**5-30 [36-200]**	**25**	**anxiolytic,**
Clobazam (Frisium), 5	**12-60**	**20**	**anxiolytic, anticonvulsants,**
Clonazepam (Klonopin, Rivotril), 5	**18-50**	**0.5**	**anxiolytic, anticonvulsants,**
Clorazepate (Tranxene)	**[36-200]**	**15**	**anxiolytic,**
Diazepam (Valium)	**20-100 [36-200]**	**10**	**anxiolytic,**
Estazolam (ProSom)	**10-24**	**1-2**	**hypnotic,**
Flunitrazepam (Rohypnol)	**18-26 [36-200]**	**1**	**hypnotic,**
Flurazepam (Dalmane)	**[40-250]**	**15-30**	**hypnotic,**
Halazepam (Paxipam)	**[30-100]**	**20**	**anxiolytic,**
Ketazolam (Anxon)	**30-100 [36-200]**	**15-30**	**anxiolytic,**
Loprazolam (Dormonoct)	**6-12**	**1-2**	**hypnotic,**
Lorazepam (Ativan)	**10-20**	**1**	**anxiolytic,**
Lormetazepam (Noctamid)	**10-12**	**1-2**	**hypnotic,**
Medazepam (Nobrium)	**36-200**	**10**	**anxiolytic,**
Nitrazepam (Mogadon)	**15-38**	**10**	**hypnotic,**
Oxazepam (Serax, Serenid D)	**4-15**	**20**	**anxiolytic,**
Prazepam (Centrax)	**[36-200]**	**10-20**	**anxiolytic,**
Quazepam (Doral)	**25-100**	**20**	**hypnotic,**
Temazepam (Restoril, Normison, Euhypnos)	**8-22**	**20**	**hypnotic,**
Triazolam (Halcion)	**2**	**0.5**	**hypnotic,**
"Non"-benzodiazepines with similar effects 1, 6			
Zaleplon (Sonata)	**2**	**20**	**hypnotic,**
Zolpidem (Ambien, Stilnoct)	**2**	**20**	**hypnotic,**
Zopiclone (Zimovane, Imovane)	**5-6**	**15**	**hypnotic,**
Eszopiclone (Lunesta)	6-9	3	**hypnotic,**

Metabolism of BZDs



Preferable in case of elderly patients

i.v. anesthetic

Adverse effects of BZDs

- CNS depression
  - Motor incoordination
  - Dizziness
  - Can interfere with driving, psychomotor skills
  - i.v. dose can cause respiratory depression
  - Mild euphoric effect
  - Behavioral disinhibition
  - Long term use: physical dependence (rebound: anxiety, insomnia, headache, irritability, muscle twitches) (Seizures: abrupt withrawal of alprazolam)
  - Cross tolerance development
  - Pharmacodynamic tolerance
  - Hypersensitivity reactions
  - Complex sleep-related behavior
  - FDA pregnancy category: D

Flumazenil (ANEXATE)

- BZD receptor antagonist
- competitive antagonism
- short half life (t1/2: 0,7-1,3 hours)→intoxication relapse
- diagnostic and therapeutic
- antidotum! (complex therapy of intoxication)
- 0.2-0.4 mg

BZD receptor inverse agonists

NAM: Negative Allosteric Modulators

- B-carbolines
  - Ethyl-β-carboline-3-carboxylate
  - Abecarnil
- Diazepam-binding inhibitor (10 kDa peptide)

Clinical use of BZDs

- Relief of anxiety (GAD, Phobias, OCD)
- Insomnia
- Sedation and amnesia before and during medical and surgical procedures (Anaesthesia, Preoperative phases)
- Main component of balanced anaesthesia (i.v.)
- Treatment of epilepsy and seizures
- Control of ethanol or other sedative-hypnotic withdrawal states
- Alprazolam is the only which effective in depression!
- Taper off BZDs slowly!
- Take care! Cats will be more excitable and hungry!
- Triazolam: ultra short acting, induces irritability and agression! (resembles to BZD withrawal)

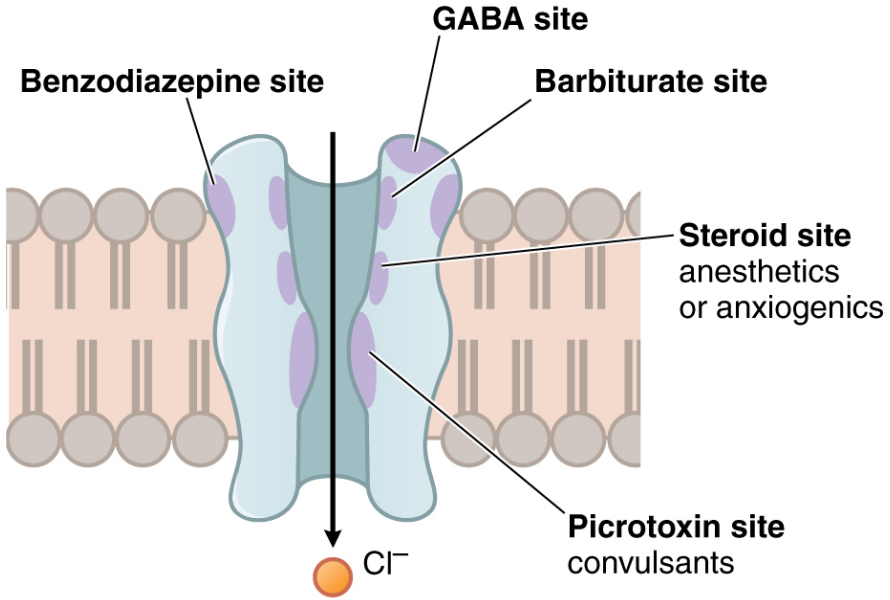
Barbiturates classification

- ultrashort: thiopental (Trapanal)
- short: cyclobarbital
- medium: secobarbital
- long: phenobarbital

Jimmy Hendrix

Barbiturates MOA

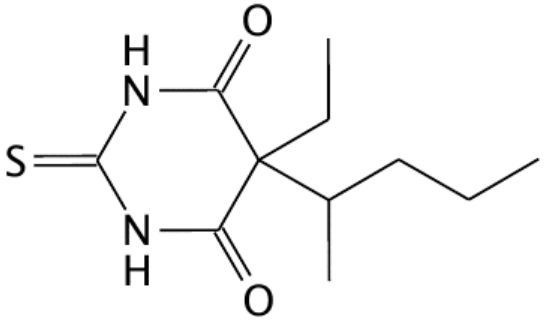
- ↑ duration of channel opening independently of the presence of GABA!!!



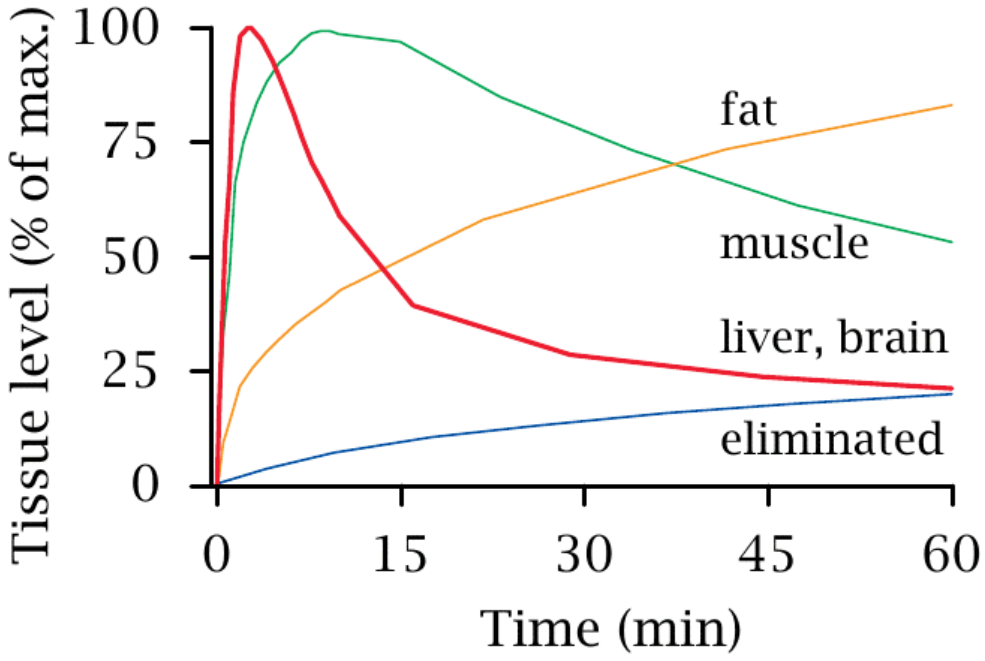
Effects of barbiturates

- similar to BDZ
- but! extremly depressant on CNS
- cardiovascular/respiratory depression
- hepatic enzyme induction (phenobarbital)
  - Induces α-aminolevulinate synthase↑ →porphyria
- Oral contraceptives, coumarin, phenytoin, digitalis (serum cc.↓)

Anesthetic effect of thiopental prolongs after the second and third i.v. administration



Thiopental

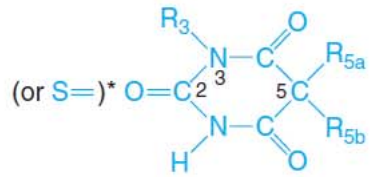


Use of barbiturates

- Thiopental has high lipid solubility, enters the CNS rapidly and can be used as an induction agent in anesthesia.
- Use:
  - Barbiturates have been used in the past to treat a variety of symptoms from **insomnia and dementia to neonatal jaundice**
  - They have largely been replaced with drugs such as benzodiazepine due to their propensity for addiction and reduced effect over extended use
  - Still widely used to treat most **seizures including neonatal seizures**
  - Used when benzo class drugs fail or in underdeveloped countries
  - **Thiopental for i.v. anesthesia**
  - Cannot be used for treatment of absence seizures

Structures, Trade Names, and Major Pharmacological Properties of Selected Barbiturates

General Formula:



Compound (Trade Names)	R_3	R_{5a}	R_{5b}	Routes of Administration†	$t_{1/2}$, Hours	Therapeutic Uses	Comments
Amobarbital (AMYTAL)	—H	$-C_2H_5$	$-CH_2CH_2CH(CH_3)_2$	IM, IV	10–40	Insomnia, preoperative sedation, emergency management of seizures	Only Na^+ salt administered parenterally
Butabarbital (BUTISOL, others)	—H	$-C_2H_5$	$-CH(CH_3)CH_2CH_3$	Oral	35–50	Insomnia, preoperative sedation	Redistribution shortens duration of action of single dose to 8 hours
Butalbital	—H	$-CH_2CH{=}CH_2$	$CH_2CH(CH_3)_2$	Oral	35–88	Marketed in combination with analgesics	Therapeutic efficacy questionable
Mephobarbital (MEBARAL)	$-CH_3$	$-C_2H_5$		Oral	10–70	Seizure disorders, daytime sedation	Second-line anticonvulsant
Methohexital (BREVITAL)	$-CH_3$	$-CH_2CH{=}CH_2$	$-CH(CH_3)C{\equiv}CCH_2CH_3$	IV	3–5‡	Induction and maintenance of anesthesia	Only Na^+ salt is available; single injection provides 5–7 minutes of anesthesia‡
Pentobarbital (NEMBUTAL)	—H	$-C_2H_5$	$-CH(CH_3)CH_2CH_2CH_3$	Oral, IM, IV, rectal	15–50	Insomnia, preoperative sedation, emergency management of seizures	Only Na^+ salt administered parenterally
Phenobarbital (LUMINAL, others)	—H	$-C_2H_5$		Oral, IM, IV	80–120	Seizure disorders, status epilepticus, daytime sedation	First-line anticonvulsant; only Na^+ salt administered parenterally
Secobarbital (SECONAL)	—H	$-CH_2CH{=}CH_2$	$-CH(CH_3)CH_2CH_2CH_3$	Oral	15–40	Insomnia, preoperative sedation	Only Na^+ salt is available
Thiopental (PENTOTHAL)	—H	$-C_2H_5$	$-CH(CH_3)CH_2CH_2CH_3$	IV	8–10‡	Induction/maintenance of anesthesia, preop sedation, emergency management of seizures	Only Na^+ salt is available; single injections provide short periods of anesthesia‡

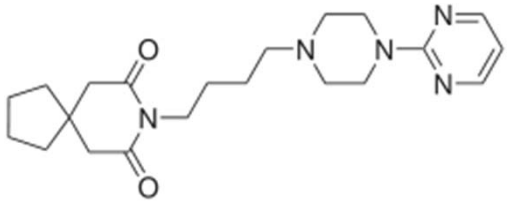
*O except in thiopental, where it is replaced by S. †IM, intramuscular injection; IV, intravenous administration.
‡Value represents terminal $t_{1/2}$ due to metabolism by the liver; redistribution following parenteral administration produces effects lasting only a few minutes.

Antihistamines

- First generation compounds: H1 receptor blockade (reduce Ach release in reticular nuclei)
  - Diphenhydramine (DAEDALON)
  - Hydroxyzine (ATARAX)
  - Doxepin

Serotonin Agonist: Buspirone

(ANXIRON, SPITOMIN)

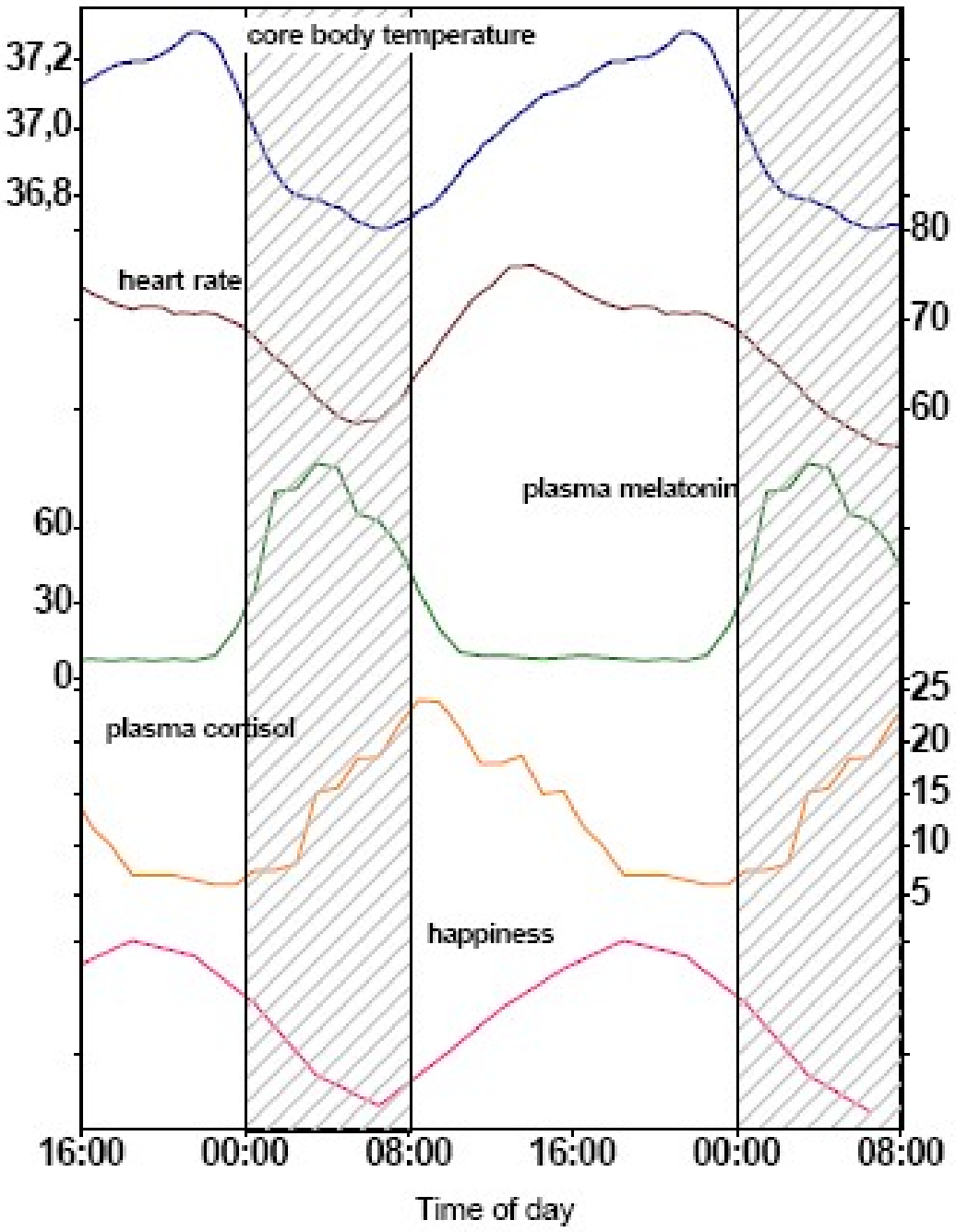


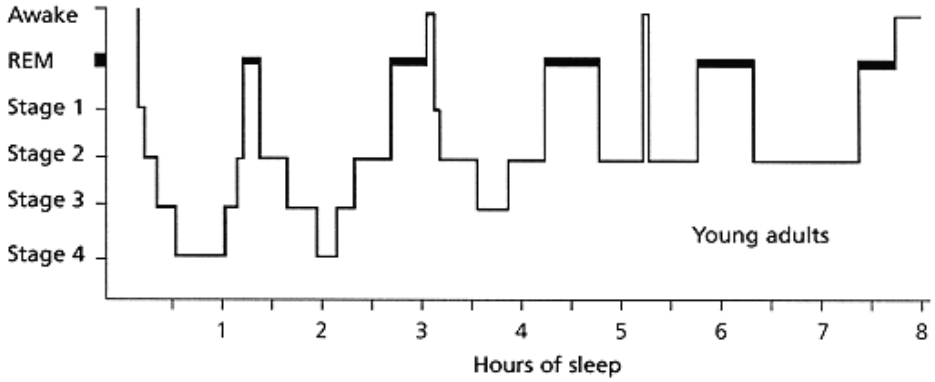
- MOA: does not interact with GABA-BZD receptor complex, has **partial agonist of serotonin type 1A receptor** (activating feedback inhibition of serotonine release) → upregulation of postsynaptic serotonine receptors (2-3 weeks)
- Act on dopamine receptors
- No anticonvulsant or muscle relaxant
- No potential for abuse, physical dependence or withdrawal symptoms
- Delayed onset of action (2-3 weeks)
- Slow onset of action, metabolized by CYP3A4
- Increase prolactin secretion and growth hormones, cause hypothermia
- SE: nausea, dizziness, headache, insomnia, agitation
- Increased risk of serotonin syndrome when co-administered with SSRI

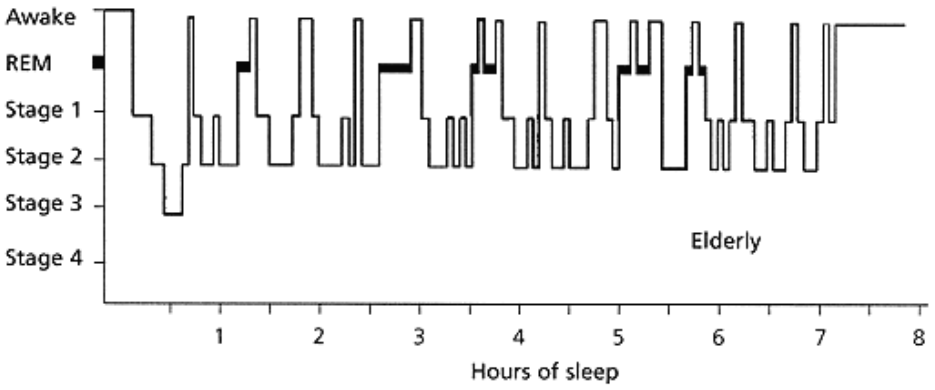
(Ipsapirone, Gepirone, Tandospirone)

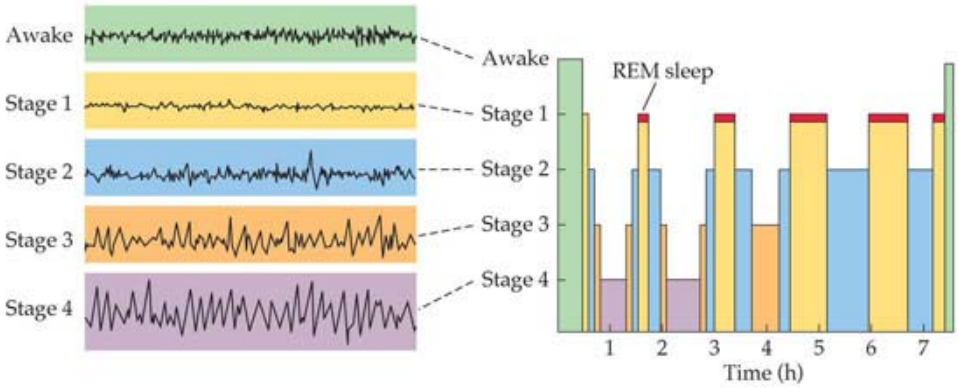
Miscellaneous sedative-hypnotic drugs

- Paraldehyde
- Chloral hydrate
- Ethchlorvynol
- Glutethimide
- Methyprylon
- Ethinamate
- Meprobamate (ANDAXIN)
- Etomidate
- Propofol (DIPRIVAN)


core body temperature
37,2
37,0
36,8
heart rate
80
70
60
plasma melatonin
60
30
0
plasma cortisol
25
20
15
10
5
happiness
16:00
00:00
08:00
16:00
00:00
08:00
Time of day







State	Effects of BZDs	Effects of Big Z
Awake	Induce sleep	Induce sleep
REM	Decrease length	Little change
Stage 1, 2	Increase length	Little change
Stage 3, 4	Decrease length	Little change

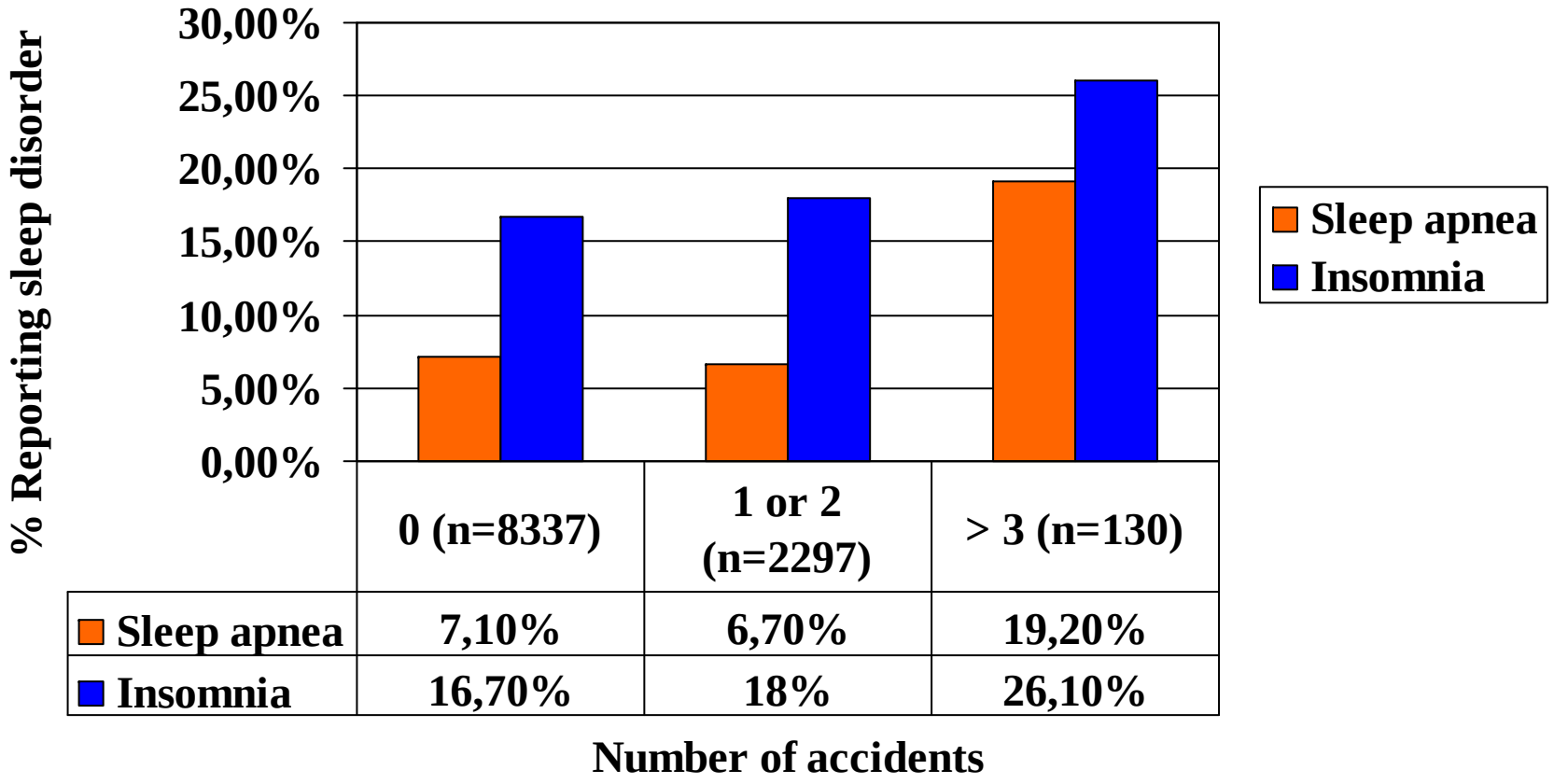
DURATION OF INSOMNIA

- Transient insomnia: episodic
  - Acute illness
  - Jet lag
  - Shift change
- Short-term insomnia: few days to 3 weeks
  - Major life event
  - Substance abuse
- Chronic insomnia : longer than 3 weeks
  - Chronic illness
  - Psychiatric illness

Insomnia

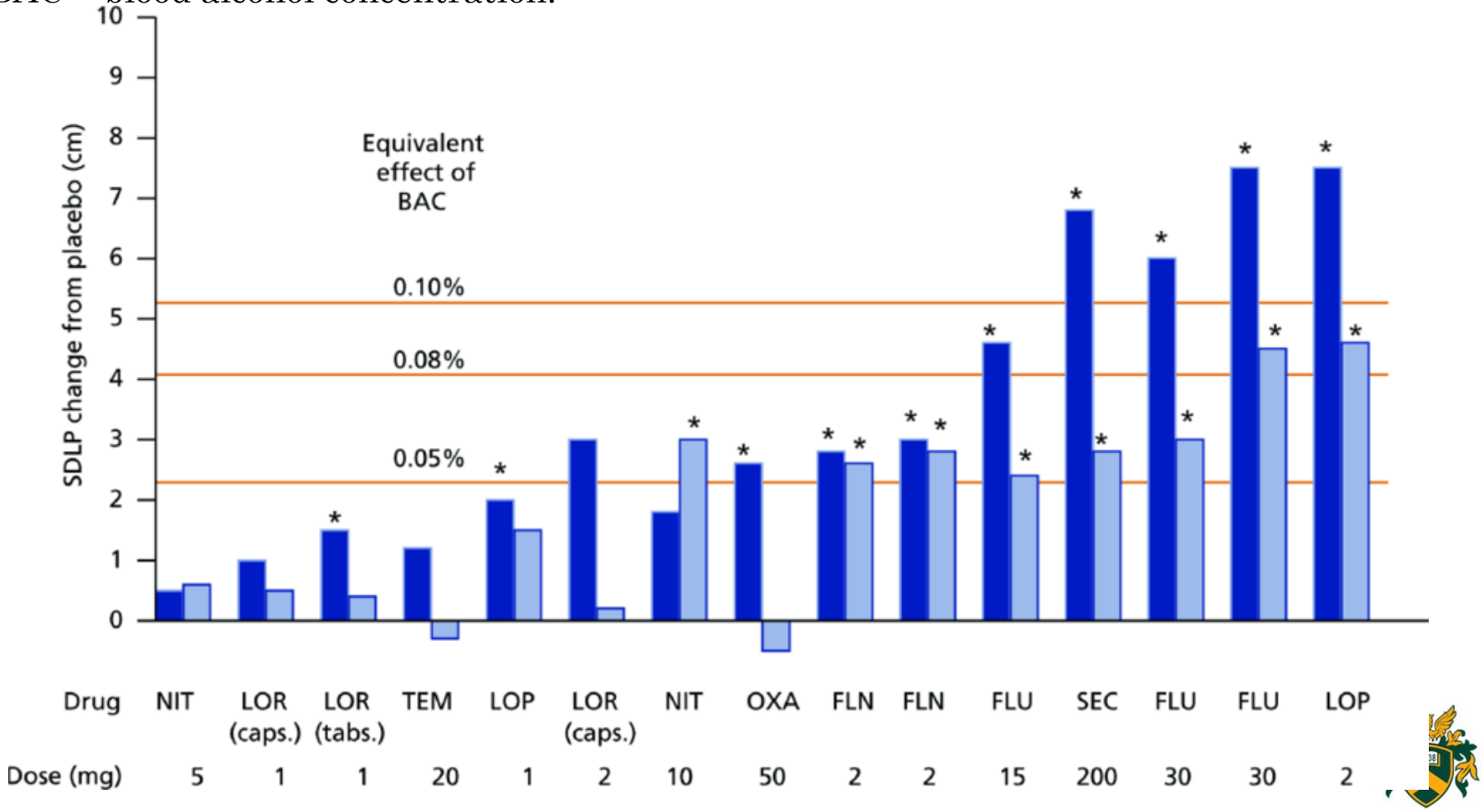
- Insomnia: difficulty initiating sleep and/or difficulty maintaining sleep
- Prevalence: estimates vary from 10% - 48%
  - Higher in women, with increasing age and in those with concurrent physical or mental health conditions
- Primary insomnia:
  - Unknown origin or arising from sleep environment, irregular sleep routine, or negative conditioning to sleep
- Secondary insomnia:
  - Underlying psychological or physical condition, prescribed/OTC medicines, caffeine or substance misuse
- Important to avoid unrealistic sleep expectations
- For all people with insomnia, offer advice on good sleep hygiene and stimulus control
  - Also consider exercise, relaxation therapies, etc.

CAR ACCIDENTS AND SLEEP DISORDERS



	0 (n=8337)	1 or 2 (n=2297)	> 3 (n=130)
Sleep apnea	7,10%	6,70%	19,20%
Insomnia	16,70%	18%	26,10%

Benzodiazepine hypnotics and driving performance. Standard Deviation of Lateral Position (SDLP) increments relative to placebo are shown. Driving tests were performed in the morning (dark blue bars) and afternoon (light blue bars) (10–11 and 16–17 h after bedtime administration, respectively). Significant differences from placebo are indicated by an asterisk, orange lines indicate levels of SDLP increment observed with most common legal blood alcohol limits for driving a car. NIT, Nitrazepam; LOR, lormetazepam; TEM, temazepam; LOP, loprazolam; FLN, flunitrazepam; FLU, flurazepam, SEC = secobarbital, caps = capsules, tabs = tablets, BAC = blood alcohol concentration.



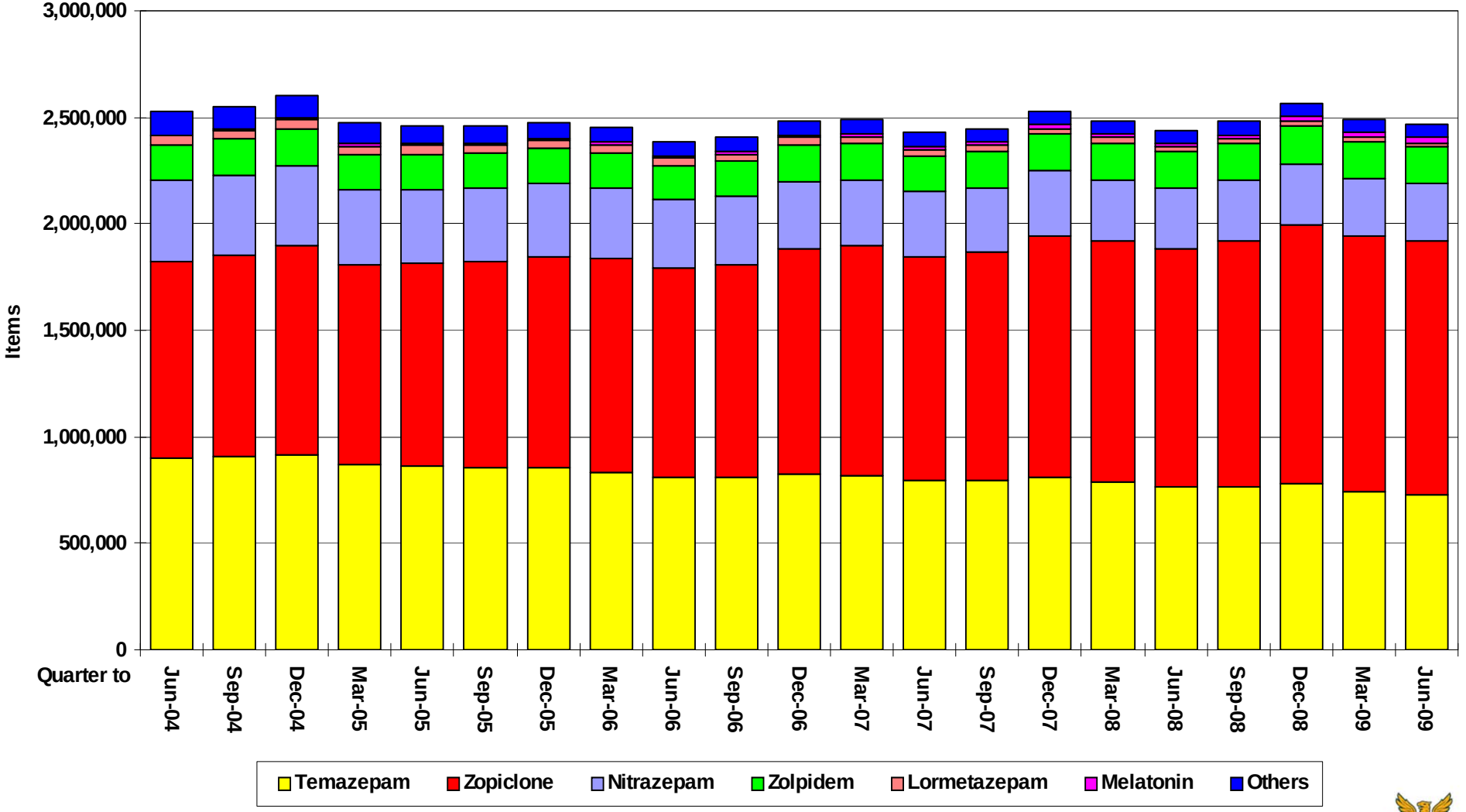
NBRAs (nonbenzodiazepine benzodiazepine-receptor agonists) the big „Z”

- Zopiclone, Zolpidem
  - Short–term treatment of insomnia…in situations where the insomnia is debilitating or is causing severe distress for the patient
  - Long–term continuous use is not recommended
  - Treatment duration: a single course of treatment should not continue for longer than 4 weeks including any tapering off

- Zaleplon
  - Treatment duration: a single course of treatment should not continue for longer than 2 weeks.

Features of big Z compounds:
selective ω1 receptor agonist (bind selectively to α1 subunit)
ω1 receptor: cortex, hippocampus
novel hypnotic effects – no CNS depression
no anxiolytic, sedative, muscle-relaxant effects
can be antagonized by flumazenil!

Trends in prescribing of hypnotics in general practice in England



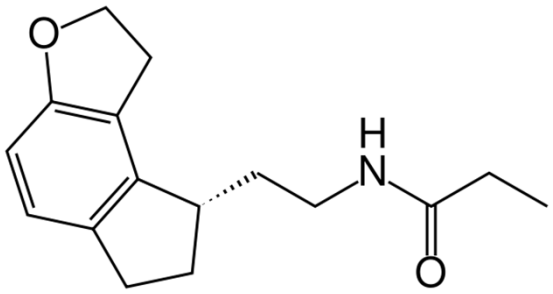
MT receptor localizations

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

Tasimelteon (HETLIOZ)
Ramelteon (ROZEREM)

Ramelteon (Rozerem)

- Synthetic melatonin agonist that acts at MT1 and MT2 receptors
- Approved for treatment of insomnia
- No potential for abuse



Melatonin itself (CIRKADIN)

Ramelteon

- agonism on MT1, MT2receptors (suprachiasm. nucl.)
- no direct effects on GABAerg neurons
- hypnotic drug
- treatment of insomnia
- oral administration
- rapid absorption, excessive first-pass metabolism
- no anxiolytic, sedative, muscle-relaxant effects
- adverse effects: dizzines, fatigue
- endocrine changes: testosterone↓ prolactin↑
- no withdrawal symptoms, no abuse
- No rebound insomnia
- Fluvoxamine (SSRI, CYP1A2 inhibitor) can increase 70-fold of ramelteon plasma cc!!!

Agomelatin: MT receptor agonist and 5-HT2C antagonist in the treatment of depression.

Tasimelteon: MT1-MT2 agonist, approved by the FDA for totally blind people with sleep disorders.

Orexin receptor antagonists

- Suvorexant
  - OX1 and OX2 antagonist
  - Orexin level is normally high in daylight and low at night
  - The drug reduces wakefulness