Sedative-Hypnotics & the Treatment of Hypersomnia

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Glossary

Anxiolytic: decreases anxiety
Sedative: **(1)** decreases activity, **(2)** moderates excitement, **(3)** calms
Hypnotic: **(1)** produces drowsiness **(2)** facilitates onset/maintenance of sleep (based on EEG)
Sedative-Hypnotics: **(1)** general CNS depressant, **(2)** all sedative-hypnotics (except the benzodiazepines but including ethanol) produce dose-dependent CNS depression that progresses to medulla oblongata depression, coma and death.
Anesthetic: **(1)** produces state of analgesia, **(2)** absence of arousal in response to noxious stimuli
Anticonvulsant: prevents/relieves convulsions/seizures
GABA: **(1)** γ-aminobutyric acid, **(2)** main inhibitory neurotransmitter in the brain
$GABA_A$ Receptor: ionotropic receptor for GABA
$GABA_B$ Receptor: metabotropic receptor for GABA
IPSC: **(1)** inhibitory postsynaptic current, **(2)** inhibitory response in a cell resulting from binding of GABA to GABA receptors (in most cases)
Allosteric modulation: altered function achieved by binding of a drug to a site distinct from the site required for activation
Benzodiazepine (BDZ): **(1)** class of sedative-hypnotics that does not produce lethal medullary depression by itself BUT **(2)** can contribute to death in the presence of other sedative-hypnotics, **(3)** generally not analgesic except in some forms of neuropathic pain, **(4)** promotes binding of GABA to $GABA_A$ subtype of GABA receptor (allosteric modulator), **(5)** chemically speaking, *benzodiazepine* refers to the portion of the compound that is composed of a benzene ring fused to a 7-membered diazepine ring
Z compounds: **(1)** bind to benzodiazepine site on $GABA_A$ receptor, **(2)** efficacious as hypnotics, **(3)** have high affinity for $GABA_A$ receptors containing $\alpha 1$ subunits, **(4)** are structurally *unrelated* to bona fide benzodiazepines (therefore, technically they are non-benzodiazepines)
Flumazenil: **(1)** blocks benzodiazepine site on $GABA_A$ receptor, **(2)** does not alter binding of GABA to receptor
Barbiturate: **(1)** reversibly depresses the activity of all excitable tissues, **(2)** like benzodiazepines, low doses of barbiturates act as allosteric modulators (bind to β subunit) **BUT** at high doses barbiturates can open $GABA_A$ receptors and promote chloride flux even in the absence of GABA, **(3)** block AMPA receptors (a subtype of receptor for glutamate, the main excitatory receptor in the brain), **(4)** once extensively used but now largely replaced by the much safer benzodiazepines, **(5)** current uses include pre-operative sedation and emergency management of seizures
Catecholamine: group of monoamine neurotransmitters that include ephinephrine, norepinephrine and dopamine
Epinephrine: **(1)** catecholamine responsible for fight-or-flight response of sympathetic nervous system, **(2)** aka *adrenaline*
Norepinephrine: **(1)** catecholamine responsible for fight-or-flight response of sympathetic nervous system, (2) increases heart rate
Dopamine: catecholamine that plays a major role in reward-driven learning

Sympathomimetic: **(1)** Producing physiological effects resembling those caused by the activity or stimulation of the sympathetic nervous system, **(2)** drug/compound that produces such an effect

Ephedrine: **(1)** sympathomimetic amine used as a stimulant & appetite suppressant, **(2)** similar in structure to amphetamine and methamphetamine.

Amphetamine: **(1)** powerful CNS stimulant, **(2)** can be used to treat hypersomnia, **(3)** raises both systolic and diastolic blood pressure, **(4)** potent sympathomimetic amine, **(5)** α-isomer 3-4 times more potent than ℓ-isomer

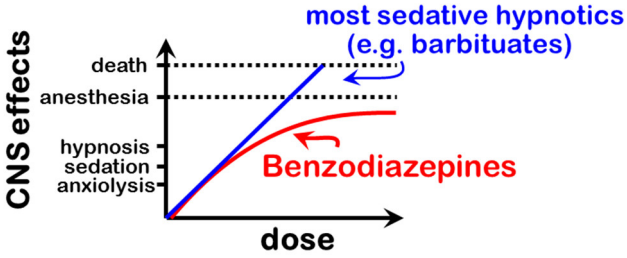
Methamphetamine: **(1)** structurally closely related to amphetamine, **(2)** small doses have prominent central stimulant effects without significant peripheral actions, **(3)** larger doses can produce sustained rise in systolic and diastolic blood pressure, **(4)** releases dopamine and other biogenic amines

Methylphenidate: **(1)** structurally related to amphetamine, **(2)** mild CNS stimulant with more prominent effects on mental than on motor activities, **(3)** e.g. Ritalin

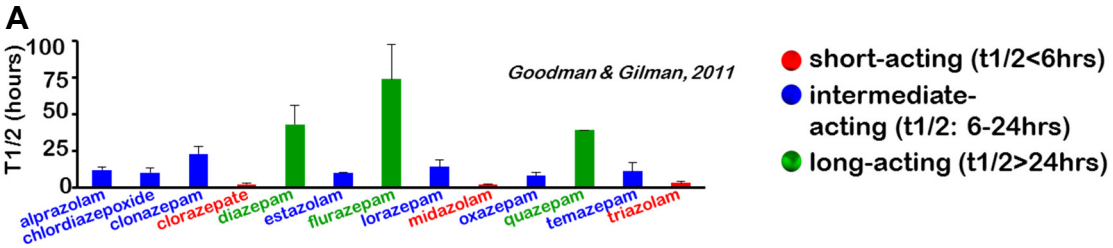
General Points

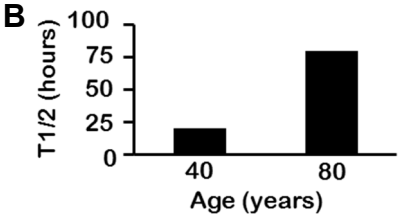
I. Benzodiazepines

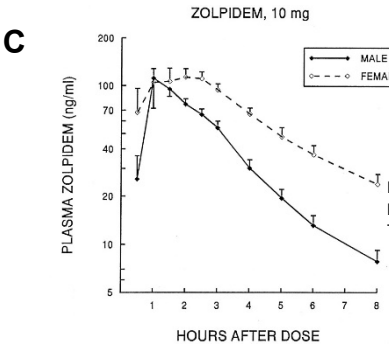
1. **General CNS depressants**: Effects are dose-dependent and do not by themselves produce anesthesia/death. Can be deadly when used in combination with other sedative-hypnotics/alcohol.



2. **Pharmacokinetics**: Pharmacokinetics are (A) highly variable, (B) age-dependent, and (C) can be sex-dependent.

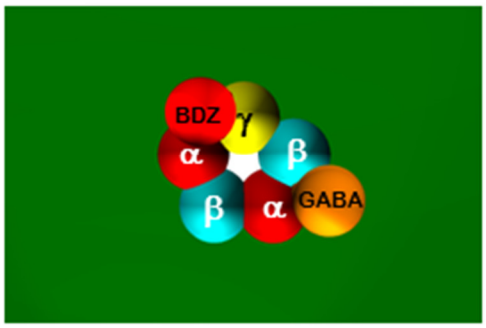


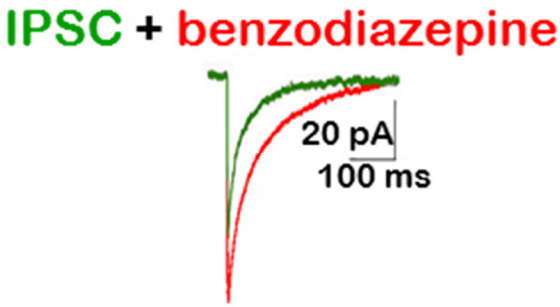




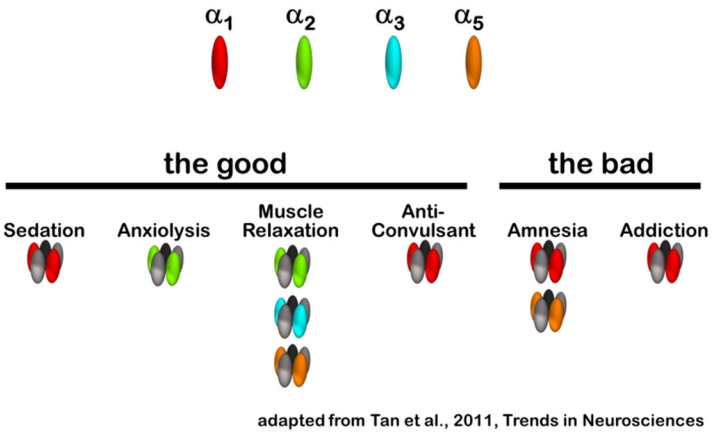
From: Greenblatt et al., 2000, Journal of Pharmacology & Experimental Therapeutics

3. **Metabolism**: All benzodiazepines are metabolized by liver before excreted. $T_{1/2}$'s can be much longer in older patients and patients with cirrhosis of the liver.
4. **Mechanism of Action**: Benzodiazepines are allosteric modulators that increase the frequency of chloride channel openings. Bind to a site on the $GABA_A$ receptor that is distinct from GABA binding site (and distinct from barbiturate binding site). Bottom line: benzodiazepines increase synaptic inhibition.





5. **Selectivity**: Effects can be α subunit-dependent



adapted from Tan et al., 2011, Trends in Neurosciences

6. **Therapeutic Uses**:
    a. **Insomnia**. Short, medium and long duration drugs can be used but shorter $T_{1/2}$ drugs are becoming popular.
        i. **Flurazepam (*Dalmane*)**: **(1)** long $T_{1/2}$ that produces little 'hangover', **(2)** can impair driving.
        ii. **Temazepam (*Restoril*)**: **(1)** intermediate $T_{1/2}$ that produces little 'hangover', **(2)** can impair driving.
        iii. **Estazolam (*Prosom*) & Triazolam (*Halcyon*)**: short $T_{1/2}$ that appears to have 'ideal' characteristics but some individuals wake up too early and/or have heightened anxiety.

iv. **Z Compounds (*Ambien*, *Sonata*, *Lunesta*): (1)** short $T_{1/2}$, **(2)** more selective for α1-containing $GABA_A$ receptors, **(3)** chemically not benzodiazepines.

b. **Anxiety**. Cardinal symptom of most psychiatric disorders, and often a normal component of many medical/surgical conditions.
   i. Generalized/non-specific anxiety syndromes: long $T_{1/2}$ benzodiazepines are used. Strategy: produce a long, low and steady level of drug that does not cause sedation.
   ii. Severe anxiety: high potency benzodiazepines (e.g. alprazolam, clonazepam, lorazepam) often used.
   iii. The non-benzodiazepine buspirone is an alternative treatment. Burspirone is non-sedative and is not hypnotic. Buspirone is a partial serotonin receptor (5HT1A) agonist.

c. **Other uses**:
   i. **Pre-anesthetic**: reduce patient's anxiety (midazolam, lorazepam)
   ii. **Alcohol withdrawal**: can suppress dangerous withdrawal symptoms
   iii. **Seizures**
      1. Absence seizures: clonazepam
      2. Status epilepticus: lorazepam

d. **Benzodiazepine overdose** (stupor)
   i. Flumazenil (benzodiazepine binding site blocker) is used to antagonize actions of benzodiazepine. Flumazenil has short $T_{1/2}$.

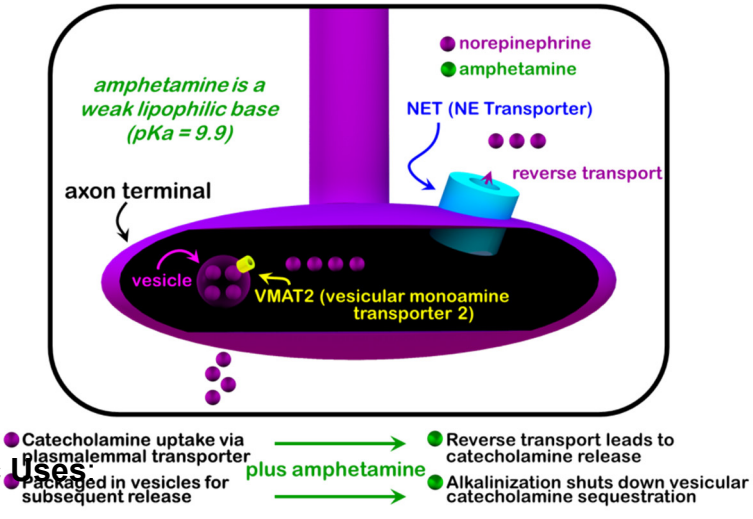
II. Non-benzodiazepine Sedative-Hypnotics (e.g. barbiturates, ethanol)

1. **General CNS depressants:** cause progressive, dose-dependent CNS depression. Begins with decreased cognitive/motor functions and proceeds to sleep, unconsciousness and coma (without notable analgesia).
2. **Physical dependence:** Can produce major physical dependence and withdrawal can be lethal. Ethanol can produce very severe dependence and very serious withdrawal symptoms (i.e. delirium tremens).
   a. Benzodiazepines can be used to treat alcohol withdrawal.
   b. Disulfiram can be used to treat alcoholism. Disulfiram inhibits aldehyde dehydrogenase, causing alcohol ingestion to produce aversive effects (i.e. 'aversive' therapy.
3. **Metabolism:** Most barbiturates have medium- to long-$T_{1/2}$s (8-48 hours). Short acting thiopental is an exception.
4. **Tolerance:** pharmacodynamic tolerance develops rapidly to all CNS effects *except* to the lethal respitory/cardiovascular depressant effects (i.e. LD_{50} only slightly changed with chronic ingestion).

5. **Mechanism of Action:** Low doses potentiate GABAergic IPSCs (like benzodiazepines) but high doses can promote chloride flux through $GABA_A$ receptors *even in the absence* of GABA.

III. Wake-promoting Drugs (e.g. amphetamines)

1. **Stimulant:** sympathomimetic amine that resembles catecholamines but is much more lipid soluble, enabling it to rapidly penetrate the blood brain barrier (unlike the bona fide catecholamines).
    a. **Peripheral effects: (1)** norepinephrine (release stimulated by amphetamine) activates α adrenergic receptors located on arterioral and venous smooth muscle cells causing vasoconstriction and elevated blood pressure, **(2)** also activates β adrenergic receptors located on heart.
    b. **CNS effects: (1)** increased alertness and delayed sleep, **(2)** norepinephrine neurons in locus coeruleus are important for maintaining waking state.
2. **Metabolism:** degraded in the liver and partly eliminated by the kidney.
3. **Mechanism of Action: (1)** rides the biogenic amine membrane transporter to gain access to inside of neuronal terminals (can also diffuse through membrane), **(2)** once inside the neuron, amphetamine diffuses into transmitter-containing vesicles and alkalinizes them (amphetamine pKa = 9.9). Alkalinization of vesicles disrupts vesicular monoamine transporter 2 (VMAT2) so less catecholamine transmitter is sequestered into vesicles. **(3)** Collectively, 1 & 2 elevates cytosolic catecholamine (and amphetamine) concentration, causing reverse transport (i.e. release) of catecholamines. **(4)** Amphetamine exerts same mechanism on dopamine, norepinephrine (and serotonergic) nerve terminals.
    a. Dopamine release primarily responsible for 'high' and addictive properties of amphetamine.
    b. Norepinephrine release primarily responsible for sleep-suppressing effect.



4. **Therapeutic Uses:**

a. **Hypersomnia/Excessive Daytime Sleepiness (EDS)**.
    i. *d*-amphetamine or methylphenidate often used.
        1. Tolerance develops so drug holidays may be required.
    ii. Amphetamines are increasingly being replaced by modafinil for EDS.
        1. Mechanism of modafinil is not clear but appears to be different than amphetamine mechanisms. Appears to activate brain's waking machinery more selectively.
b. **Attention Deficit Hyperactivity Disorder (ADHD)**
    i. Therapeutic mechanism not clear.
c. **Appetite suppression in adults**: not suggested because of adverse cardiovascular effects.

Useful Tables from Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th Edition

Benzodiazepines (Goodman & Gilman's, page 466)

Table 17–3

Trade Names, Routes of Administration, and Therapeutic Uses of Benzodiazepines

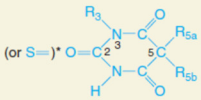
COMPOUND (TRADE NAME)	ROUTES OF ADMINISTRATION[a]	EXAMPLES OF THERAPEUTIC USES[b]	COMMENTS	$t_{1/2}$, hours[c]	USUAL SEDATIVE-HYPNOTIC DOSAGE, mg[d]
Alprazolam (XANAX)	Oral	Anxiety disorders, agoraphobia	Withdrawal symptoms may be especially severe	12±2	—
Chlordiazepoxide (LIBRIUM, others)	Oral, IM, 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[e]
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; activity due to formation of nordazepam during absorption	2.0±0.9	3.75-20, bid–qid[e]
Diazepam (VALIUM, others)	Oral, IM, IV, rectal	Anxiety disorders, status epilepticus, skeletal muscle relaxation, anesthetic premedication	Prototypical benzodiazepine	43±13	5-10, tid–qid[e]
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	—[f]
Oxazepam (SERAX)	Oral	Anxiety disorders	Metabolized solely by conjugation	8.0±2.4	15-30, tid–qid[e]
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

[a]IM, intramuscular injection; IV, intravenous administration; qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day. [b]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 $t_{1/2}$ and may not match the marketed indications. The issue is addressed more extensively in the text. [c]Half-life of active metabolite may differ. See Appendix II for additional information. [d]For additional dosage information, see Chapter 13 (anesthesia), Chapter 17 (anxiety), and Chapter 19 (seizure disorders). [e]Approved as a sedative-hypnotic only for management of alcohol withdrawal; doses in a nontolerant individual would be smaller. [f]Recommended doses vary considerably depending on specific use, condition of patient, and concomitant administration of other drugs.

Barbiturates (Goodman & Gilman's, page 470)

Table 17–4

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



COMPOUND (TRADE NAMES)	R_3	R_{5a}	R_{5b}	DOSAGE FORMS[b]	$t_{1/2}$ (hours)	THERAPEUTIC USES	COMMENTS
Amobarbital (AMYTAL)	—H	$-C_2H_5$	$-CH_2CH_2CH(CH_3)_2$	IM, IV	10-40	Insomnia, pre-op 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, pre-op sedation	Redistribution shortens duration of action of single dose to 8 hours
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[c]	Induction and maintenance of anesthesia	Only Na^+ salt available; single dose provides 5-7 min of anesthesia[c]
Pentobarbital (NEMBUTAL)	—H	$-C_2H_5$	$-CH(CH_3)CH_2CH_2CH_3$	Oral, IM, IV, rectal	15-50	Insomnia, pre-op 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 anti-convulsant; 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 available
Thiopental (PENTOTHAL)	—H	$-C_2H_5$	$-CH(CH_3)CH_2CH_2CH_3$	IV	8-10[c]	Induction/maintenance of anesthesia, pre-op sedation, emergency management of seizures	Only Na^+ salt available; single dose provides brief of anesthesia[c]

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