Minor Tranquilizers

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Introduction

Definitions

sedative: a medication which ⇓ activity, moderates excitement, calms recipient

hypnotic: produces drowsiness & facilitates onset & maintenance of a state of sleep which resembles natural sleep (in EEG characteristics) & from which recipient is easily aroused.

History

earliest	potions of laudanum, alcohol, herbals
1853	bromides
prior to 1900	chloral hydrate, paraldehyde, urethan, sulfonal
1903	barbital
1912	phenobarbital
1961	chlordiazepoxide

Usage in North America

1977 study of prescriptions in Saskatchewan[1]:

- 20% of population received an Rx for a mood-altering drug; half (ie 10%) for minor tranquilizers;
- 4% of population received 5 or more Rx's in one year for the same mood-altering drug;
- women:men 2:1;
- elderly significantly more than others.

[1] Cooperstock R, Hill J. The effects of tranquillization: BDZ use in Canada. Ministry of National Health & Welfare, Canada 1982

Usage in the United States[2]

- 1974 peak for BDZ: 105 million prescriptions;
- 1986: 68 millionprescriptions;
- percentages by doctor type (1981):

50% GP's & osteopaths
19% internists
18% psychiatrists (down to 9% in 1988)
10% surgeons

- only one-third of Rx's for psychiatric disorders; the rest for musculoskeletal, presurgery, & geriatrics;
- 50% of inappropriate Rx's for BDZ are written by 5% of prescribers.

Benzodiazepines

Mechanism of Action

- BDZ potentiate GABA-ergic neurotransmission throughout the CNS (including spinal cord). (GABA is an inhibitory neurotransmitter);
- BDZ receptors interact with GABA post-synaptic receptors to enhance GABA effectiveness at increasing conductance of the chloride channel associated with the GABA receptor.

Effects

CNS: sedation, hypnosis, ⇓ anxiety, muscle relaxation, anticonvulsant activity (prevent subcortical spread of seizure activity);
- depressant effect on spinal reflexes;
- ⇓ duration of electrical afterdischarge in limbic system;

EEG: blocks EEG arousal 2° stimulation of brainstem reticular formation; ⇑ fast β activity with ⇑ amplitude;

[2] Nemeroff CB. Use and abuse of benzodiazepines: what are the facts? Audio-Digest Psychiatry 1990 Jun 18; 19(12)

CVS & respiratory: minimal effects; diazepam 5-10mg iv gives slight ⇓ in respiration, BP, & left ventricular stroke work; may get ⇑ HR & ⇓ cardiac output;

peripheral: coronary vasodilatation, neuromuscular blockade (only in v. high doses);

- do not get general anesthesia (awareness usually persists, insufficient relaxation for surgery);
- get anterograde amnesia (ie for events occurring while drug is present).

Pharmacokinetics

Absorption

oral: since most BDZ are weakly basic, they are absorbed most effectively in duodenum (where Ph is high);

- diazepam and desmethyldiazepam are the most rapidly absorbed;

im: diazepam & chlordiazepoxide are unreliably absorbed im; lorazepam im is well absorbed;

sublingual: very rapid (lorazepam).

Distribution

- most BDZ are 85-95% bound to plasma protein (thus dialysis useless for OD);
- high apparent volumes of distribution (1-3 litres/kg);
- get 2° plasma concentration peaks, eg 6-12 hrs for diazepam; prob. 2° enterohepatic circulation;
- lipid solubility determines rate at which drug enters CNS. Diazepam is highly lipid soluble, therefore a fast onset of action;
- higher lipid solubility also results in a shorter duration of clinical activity because of increased drug distribution to peripheral adipose tissue, leading to rapid exit from the blood & brain.

Elimination

- via transformation into water-soluble metabolites which are excreted by kidneys;
- some BDZ (chlordiazepoxide, diazepam, clorazepate, prazepam, halazepam) are initially oxidized in the hepatic microsomal enzyme system), then conjugated by glucuronyl transferases into glucuronides;
- oxazepam, lorazepam, temazepam,alprazolam, triazolam are conjugated only (1-step metabolism);
- for elderly pts, premature neonates, or pts with liver disease, half-lives for BDZ requiring oxidation may ⇑ by 3-4 times;
- half-life values are usually given for single-dose administration; half-lives can increase (2x) for repeated dosing[3].

Uses

General considerations

- rapid absorption & high lipid solubility lead to rapid entry into the CNS, thus more likely to cause euphoria, disinhibition, & abuse;
- short half-life compounds have more rebound withdrawal symptoms;
- long half-lives may produce unwanted daytime sedation & drowsiness.

Anxiety

Physical signs and symptoms of anxiety[4]

anorexia
"butterflies" in stomach
chest pain or tightness
diaphoresis
diarrhea
dizziness
dyspnea
dry mouth
faintness
flushing
headache
hyperventilation
lightheadedness
muscle tension
nausea
pallor
palpitations
paresthesias
sexual dysfunction
shortness of breath
stomach pain
tachycardia
tremulousness
urinary frequency
vomiting

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3 Bernstein JG. Handbook of drug therapy in psychiatry. Chicago: Year Book Medical Publishers, 1988: 59-60

4 Rosenbaum JF. The drug treatment of anxiety. NEJM 1982 Feb 18;306(7): 401-4

Physical causes of anxiety-like symptoms[5]

Up to 42% of patients referred for treatment of psychiatric symptoms (eg depression, anxiety, psychosis) were found to have underlying medical illnesses that were responsible for their distress.

cardiovascular	angina, arrhythmias, CHF, hypertension, hypovolemia, MI, syncope, valvular disease, shock
dietary	caffeinism, MSG, vitamin-deficiency
drug-related	akathisia, anticholinergic toxicity, digitalis, hallucinogens, hypotensive agents, stimulants (amphetamines, cocaine, etc.), withdrawal from alcohol or sedative-hypnotics
hematologic	anemias
immunologic	anaphylaxis, SLE
metabolic	Cushing's, hyperkalemia, hyperthermia, hyperthyroidism, hypocalcemia, hypoglycemia, hyponatremia, hypothyroidism, menopause, acute intermittent porphyria
neurologic	encephalopathies, essential tremor, intracranial mass lesions, post-concussion syndrome, seizure disorders, vertigo
respiratory	asthma, COPD, pneumonia, pneumothorax, pulmonary edema or embolism
secreting tumours	carcinoid, insulinoma, pheochromocytoma

- BDZ are treatment of choice for generalized anxiety disorder[6];

tolerance: does develop to some unwanted effects, eg sedation; but may not develop to anxiolytic effects;

abuse: anxious patients without Hx of alcohol or substance abuse are not more likely to abuse BDZ[7].

5 Rosenbaum JF. The drug treatment of anxiety. NEJM 1982 Feb 18;306(7): 401-4

6 Lydiard RB, Roy-Byrne PP, Ballenger JC. Recent advances in the psychopharmacological treatment of anxiety disorders. Hosp Comm Psychiatry 199 Nov; 39(11): 1157-65

7 Garvey MJ, Tollefson GD. Prevalence of misuse of prescribed benzodiazepines in patients with primary anxiety disorder or major depression. Am J Psychiatry 1986; 143: 1601-2

Other Approaches

- Self-regulatory therapies such as relaxation, biofeedback, or meditation[8].

Sleep disorders

Insomnia

- some c/o insomnia may be simply a dissatisfaction with sleep pattern; medication may not help here;
- elderly require less sleep;
- difficulty falling asleep followed by persistent period of adequate sleep may require no therapy;
- sedating antihistamines or L-tryptophan may help by reducing sleep latency;
- frequent night-time awakening, with or without early AM awakening, should suggest depression, and may benefit from antidepressants even if a depression is not clinically obvious;

BDZ: ⇓ sleep latency, ⇓ no. of awakenings; ⇓ stage 1 sleep, ⇑ stage 2 sleep, ⇓ slow-wave sleep (stages 3 & 4) leads to ⇓ terrors & nightmares; may ⇓ REM sleep but ⇑ number of REM cycles. Tolerance develops to these effects.

Sleep Apnea

- contraindication to use of BDZ;
- Occurs in ~ 25% of elderly: 17% obstructive; 6% central sleep apnea, 1% mixed;

OSA: c/o excessive daytime sleepiness, reduced energy level, insomnia;

- number of apneic events correlates with rating on depression scales;
- depressed patients with OSA treated with TCA's report ⇓ daytime sleepiness, ⇓ snoring, +/- fewer apneic events;

Rx: eliminate alcohol, lose weight.

Depression

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Panic disorder[9]

- phenelzine (an MAOI) is probably most effective, followed by imipramine;
- alprazolam is as effective as imipramine, and may have faster onset of action;

8 Goldberg RJ. Anxiety reduction by self-regulation: theory, practice, and evaluation. Ann Int Med 1982 Apr; 96(4): 483-7

9 Lydiard RB, Roy-Byrne PP, Ballenger JC. Recent advances in the psychopharmacological treatment of anxiety disorders. Hosp Comm Psychiatry 199 Nov; 39(11): 1157-65

- alprazolam and other BDZ, eg diazepam, lorazepam, clonazepam, are probably equally effective, but depressive symptoms may emerge (treat with antidepressants);
- combination of behavioural and drug treatments is superior to either one alone.

Post-traumatic stress disorder[10]

- these individuals often abuse sedative-hypnotics & other substances in attempts to self-medicate;
- tricyclics, MAOI's, carbamazepine may help;
- clonidine may reduce agitation & autonomic overactivity;
- propranolol up to 640mg/day may reduce autonomic activitation.

Alcohol withdrawal[11]

Alcohol withdrawal seizures
incidence:
- essentially unknown; one study reported 2.5% (no anticonvulsant Rx);
- prob. ⇑ with ⇑ duration of alcohol abuse;
- of 472 seizure admissions, 59% were in alcohol withdrawal.

characteristics:
- occur 12-48 hours after stop drinking;
- grand mal, non-focal, typically single (or bursts of 2-4);
- seldom progress to status epilepticus;
- normal interictal EEG;
- 30% go on to delirium.

Standard detox drugs
diazepam: po for mild to moderate withdrawal; 5-50 mg iv for severe withdrawal;
chlordiazepoxide: 25mg qid for moderate anxiety & tremor; 500mg/day or more for severe withdrawal & DT's;
phenobarbital: 15mg for each 30 ml of 80-100 proof alcohol on first day, then ⇓ by 10-25% on each subsequent day;
hydroxyzine: inferior to BDZ (ie more seizures & DT's);
neuropeptics: avoid, since ⇓ seizure threshold, exc. haldol;
carbamazepine: used in Scandinavia; ⇓ anxiety & distress; 800mg/day first day, divided doses, ⇓ to 0 in one week.

personal recommendations
clonazepam for mild/moderate symptoms, or prophylactically - less abuse potential, fewer probs on withdrawal;
lorazepam to control severe symptoms/DT's (can be given im, iv, or sublingually).

Delirium

The combination of IV haloperidol and lorazepam has been found helpful in treating delirious states in the ICU[12]. These patients can be sedated quickly and safely and behavioral calm maintained while the search for reversible causes proceeds. Adams, at the U. of Texas System Cancer Center, reported[13] on 20 patients who receiv ed total 24-hour doses ranging from 100 to 240 mg of haloperidol and 36 to 240 mg of lorazepam (ie up to 10 mg IV each, q1h for up to 15 days). Start with 3mg halop & l5-1mg loraz; if insuff response after 30min, 5mg halop/.5-2mg loraz; if still insuff resp after 30 min, 10mg halop/.5-10mg loraz q1h until adequate sedation; stop & observe; if restlessness begins in 4 hrs, continue meds q4h for 12-18hrs; then D/C loraz & increase duration between halop doses.

Miscellaneous

Seizures
status epilepticus: diazepam 10mg iv; give over 1 minute; watch for respiratory arrest
absence seizures: clonazepam suppresses the spike and wave discharges
infantile spasm, myclonic seizures: nitrazepam is used

Musculoskeletal disorders
cerebral palsy, tetanus: diazepam helps control spasticity

Adverse effects

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10 Lydiard RB, Roy-Byrne PP, Ballenger JC. Recent advances in the psychopharmacological treatment of anxiety disorders. Hosp Comm Psychiatry 199 Nov; 39(11): 1157-65

11 Wilbur R, Kulik FA. Am J Hosp Pharm 1981; 38: 1138-43

12 Ayd FJ Jr, ed. Intravenous haloperidol-lorazepam therapy for delirium. Int Drug Therapy Newsletter 1984 Nov; 19(9): 33-5

13 Adams F. Neuropsychiatric evaluation and treatment of delirium in the critically ill cancer patient. Cancer Bull 1984; 36: 156-60

Withdrawal

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Behavioral toxicity

- patients receiving BDZ or other minor tranquilizers were nearly 5 times more likely to experience a severe MVA than non-users[14];
- BDZ users utilize more health-care services as a consequence of accidents and injuries than do non-users[15];
- about 30% of the elderly who fracture their hip never walk again[16].

Medication Abuse

Substance Abuse: culturally determined.
Addiction: behaviours associated with abuse; refers to the compulsive involvement with drug use and the obtaining of supplies.
Dependence: a physiological state such that if you give the person a medication and then stop it, they go into a physiological withdrawal.

- 40% of patients chronically treated with BDZ will have withdrawal symptoms if medication suddenly stopped - they are dependent.
- however, dependence is not evil in itself - eg insulin dependence; dependence on anti-epileptic drugs.
- it seems that only the people most likely to abuse BDZ are people who abuse other substances (including alcohol). Family members of alcoholics may also be at risk[17].

14 Skegg DCG, Richards SM, Doll R. Minor tranquillisers and road accidents. Br Med J 1979: 1: 917-9

15 Oster G, et al. Accident- and injury-related health-care utilization among benzodiazepine users and nonusers. J Clin Psychiat 1987 Dec; 48(12) Suppl.: 17-21

16 Nemeroff CB. Use and abuse of benzodiazepines: what are the facts? Audio-Digest Psychiatry 1990 Jun 18; 19(12)

17 Nemeroff CB. Use and abuse of benzodiazepines: what are the facts? Audio-Digest Psychiatry 1990 Jun 18; 19(12)

Drug interactions[18]

Benzodiazepines interacting with:	Effects	Mechanism
disulfiram	⇑ BDZ effect	⇓ BDZ metabolism
antacids	⇓ BDZ effect	impaired GI absorption
isoniazid	⇑ BDZ effect	enzyme inhibition
estrogens	⇑ BDZ effect	enzyme inhibition
tobacco smoking	⇓ BDZ effect	enzyme induction
rifampin	⇓ BDZ effect	enzyme induction
digoxin	⇑ digoxin half-life	unknown

cimetidine gives ⇑ BDZ effect (exc. for those BDZ which are only conjugated) through ⇓ BDZ metabolism.
succinylcholine + diazepam gives prolonged neuromuscular blockade (mechanism uncertain).
erythromycin + triazolam gives ⇑ triazolam plasma level (triaz metabolism ⇓).

Barbiturates

pentobarbital
secobarbital
amobarbital
phenobarbital

should <u>not</u> be used as sedative/hypnotics:

- lack specificity of effect in CNS;
- poor therapeutic index;
- tolerance develops, thus severe withdrawal problems;
- high abuse potential;
- lots of drug interactions;

however, still useful as:

- anticonvulsants;
- general anesthetics;
- management of acute maniacal states;
- management of delirium;
- for sodium amytal interviews;

18 Bernstein JG. Handbook of drug therapy in psychiatry. Chicago: Year Book Medical Publishers, 1988: 348-9

- to reduce cerebral edema;
- to treat hyperbilirubinemia in neonates (liver enzyme induction).

Barbiturate overdose:

- resembles alcohol intoxication if amounts moderate;
- **severe OD**: coma; ⇓ reflexes; ⇑ Babinski;
- **EEG**: burst-suppression type;
- **pupils**: constricted, reactive to light (later, hypoxic paralytic dilatation);
- **breathing**: either slow, or rapid & shallow, or Cheyne-Stokes (measure arterial PO_2, PCO_2);
- **shock**: 2° blood vessel dilatation, ⇓ cardiac contractility;
- **pulmonary**: atelectasis, edema, pneumonia;
- renal failure.

treatment:
- supportive measures for respiration, shock, hypothermia;
- drug elimination via: emesis, gastric lavage, hemodialysis, hemoperfusion, forced diuresis, alkalinization.

Chloral Hydrate

- Chloral hydrate [$CCl_3CH(OH)_2$] is reduced to trichloroethanol [CCl_3CH_2OH] (also a hypnotic & CNS depressant) by alcohol dehydrogenase within several minutes;
- in first week: ⇓ sleep latency; ⇓ # of awakenings; ? ⇓ total sleep time, ⇓ slow wave sleep, ? ⇓ REM sleep;
- effects on sleep negligible after 2 wks continuous use;
- no REM rebound when D/C'd;
- little effect on respiration, BP w/ therapeutic doses.

Untoward Effects
- unpleasant taste, epigastric distress, nausea, occ. vomiting, flatulence;
- CNS: lightheadedness, malaise, ataxia, nightmares, "hangover" (but less than barbiturates & some BDZ's);
- in elderly: fewer persistent effects cf agents metabolized by hepatic microsomal enzyme system;
- idiosyncratic rxns: somnambulism, disorientation, incoherence, paranoia
- allergic rxns;
- displaces acidic protein-bound drugs - possible problem if taken w/ furosemide;
- synergistic effect with alcohol: the "Mickey Finn";

Overdose: ~10g is toxic dose: Sx & Rx like for barbiturates;

Abuse: may get abuse, addiction with tolerance; sudden withdrawal leads to delirium, seizures, high death risk; also see death with a sudden "break in tolerance".

Dosage:
- 0.5 - 1g recommended, but has only slight effect; many people need 2g;
- give well diluted with water or milk;
- can be given w/ olive oil in a retention enema.

Other Medications

Non-barbiturate sedatives

ethchlorvynol	Placidyl
gletethimide	Doriden
methyprylon	Noludar
meprobamate	Equanil, Miltown
methaqualone	Quaalude

- these meds should <u>not</u> be used - they have a low therapeutic index, induce tolerance & dependence, & are drugs of abuse;
- sudden withdrawal can be dangerous (eg convulsions);

overdose: treat as for barbiturates.

Paraldehyde

Sometimes used to treat DT's - can then become a drug of addiction - its withdrawal results in DT's.

L-tryptophan

- doses 1 - 5 g;
- ⇑ stage 2 sleep, ? ⇓ sleep latency;
- 5-HT (100 - 200mg) similar effect; ? ⇓ REM sleep;
- β-blockers, eg oxprenolol, alprenolol, may enhance effect of l-tryptophan.

Buspirone[19,20]

Pharmacology

- acts at serotonin autoinhibitory receptors (partial serotonin agonist-antagonist);
- modest dopaminergic & noradrenergic activity;
- does not bind to BDZ-GABA receptor complex.

Anxiolytic Profile

- effective in anticonflict, conditioned avoidance, and antiaggression animal avoidance models;
- no anticonvulsant or muscle relaxant effects.

Abuse/Dependence Characteristics

- no significant euphoria;
- dysphoria with single 40-mg dose;
- no self-administration by laboratory animals;
- not preferred over placebo by recreational drug users;
- no interaction with CNS depressants (eg no cross-tolerance with BDZ's);
- patients on long-term treatment do not require dose increases;
- no withdrawal syndrome with doses of 15 to 60 mg per day.

Side Effects

- incidence of sedative-type SE (eg drowsiness, incoordination, fatigue, depression, and weakness) not sign. different between buspirone & placebo;
- dizziness (9%), headache (7%), nervousness (4%), light-headedness (4%), diarrhea (3%), paresthesia (2%), excitement (2%), sweating/clamminess (1%), occurred in buspirone patients at significantly greater incidence than for placebo;
- significantly less drowsiness for buspirone cf. BDZ.

19 Feighner JP. Buspirone in the long-term treatment of generalized anxiety disorder. J Clin Psychiat 1987 Dec; 48(12) Suppl.: 3-11

20 Lader M. Long-term anxiolytic therapy: the issue of drug withdrawal. J Clin Psychiat 1987 Dec; 48(12) Suppl.: 12-6

Drug Interactions[21]

- side-effect profiles of buspirone did not differ significantly for patients receiving buspirone alone (N= about 400), compared to those (N= about 300) taking it with concomitant medication (eg analgesics, antihistamines/vasoconstrictors, contraceptives, diuretics/antihypertensives, hormones, and sedative/hypnotics);
- buspirone did not interfere with or potentiate the hypnotic effects of either triazolam or flurazepam;
- no potentiation of alcohol-induced impairment of performance (eg in driving simulator tests).

Therapeutic Considerations

- patients with history of prior BDZ use have less improvement than BDZ-naive patients on buspirone;
- BDZ withdrawal symptoms are not suppressed by buspirone;
- optimum dose 15-30 mg/day;
- not immediately effective; takes 2 weeks to work;
- when switching from a BDZ: add buspirone to BDZ, then begin to taper the BDZ 2 weeks later;
- caution patients about absence of euphoric effect;
- ask them to remain on drug for two weeks before telling you their assessment;
- ask them to keep a diary of anxiety;
- must be taken regularly, 3 times/day; PRN's ineffective;
- ineffective in panic disorder.

21 Schnabel T Jr. Evaluation of the safety and side effects of antianxiety agents. Am J Med 1987 May 22; 82(suppl 5A): 7-13