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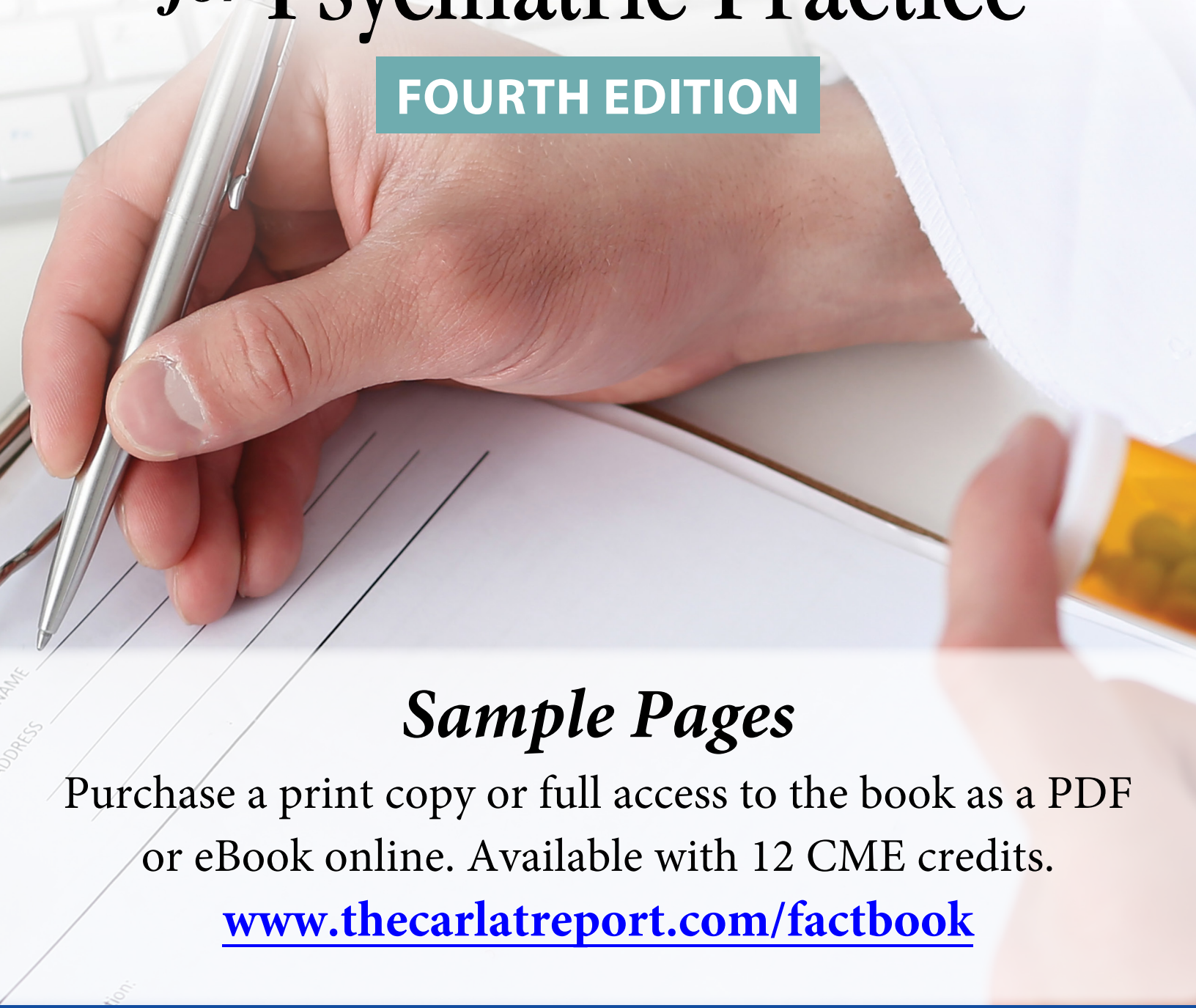
Medication Fact Book *for* Psychiatric Practice

FOURTH EDITION



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TALIA PUZANTIAN, PharmD, BCPP
DANIEL J. CARLAT, MD

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Talia Puzantian, PharmD, BCPP
Associate Professor, Keck Graduate Institute School of Pharmacy, Claremont, CA

Daniel J. Carlat, MD
Publisher and Editor-in-Chief, The Carlat Psychiatry Report
Associate Clinical Professor, Tufts University School of Medicine, Boston, MA

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Publisher and Editor-in-Chief: Daniel J. Carlat, MD

Deputy Editor: Talia Puzantian, PharmD, BCPP
Executive Editor: Janice Jutras

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Anxiolytic Medications

GENERAL PRESCRIBING TIPS

Although antidepressants are arguably the most effective medications for anxiety, in this chapter we focus on benzodiazepines and other drugs used specifically for anxiety disorders.

Psychiatry has long had a love/hate relationship with benzos. They work quickly and predictably, but they often lead to dependence and sometimes to outright addiction.

Assuming you've done a good enough diagnostic evaluation to identify malingerers and drug abusers, here's a reasonable approach to deciding on which anxiolytic medication to prescribe.

1. Start with a long-acting medication such as clonazepam. It's less likely to lead to addiction, because its onset and offset are more gradual.
2. Reserve short-acting benzos, like alprazolam or lorazepam, for patients who have occasional anxiety, and prescribe these on an as-needed basis.
3. When treating anxiety disorders that are responsive to antidepressants (and which ones aren't?), do the following: Start patients on an SSRI/SNRI plus a benzo. Tell them that in 2 weeks they will be able to stop taking the benzo because the antidepressant will have kicked in.
4. Give buspirone a chance, especially for generalized anxiety disorder. It may not work as reliably as benzos, but it is non-addictive.
5. Don't forget propranolol, which can be really effective for patients who have strong somatic symptoms of anxiety, such as pounding heart and shortness of breath.
6. Finally, prazosin, another blood pressure medication, is effective for PTSD, especially for insomnia and nightmares.

Class Warnings

Combining benzodiazepines with opiates

The FDA has issued a black box warning about the dangers of combining benzodiazepines with opiates due to the risks of profound sedation, respiratory depression, coma, and death. The FDA stipulates that the benzo/opioid combination should be reserved for patients when alternative options have not worked, that you should minimize the dosage and duration of treatment, and that patients should be monitored closely for sedation and respiratory depression.

Sleep architecture

Benzodiazepines affect sleep architecture; thus, long-term use is discouraged.

TABLE 8: Anxiolytic Medications

Generic Name (Brand Name) Year FDA Approved *[G] denotes generic availability*	Relevant FDA Indication(s)	Available Strengths (mg)	Onset of Action (oral)	Half-Life (hours)	Duration of Action (hours)	Usual Dosage Range (starting–max) (mg)
Alprazolam (Xanax, Xanax XR, Niravam) [G] 1981	GAD Panic disorder	Tablets: 0.25, 0.5, 1, 2 ER tablets: 0.5, 1, 2, 3 ODT: 0.25, 0.5, 1, 2 Liquid: 1 mg/mL	30 min (IR, ODT) 1–2 hrs (XR)	11–16	3–4 (IR) 10 (XR)	0.25 mg TID–2 mg TID 0.5 mg–3 mg QD (XR)
Buspirone (BuSpar[1]) [G] 1986	GAD	Tablets: 5, 7.5, 10, 15, 30	1–2 weeks+	2–3	N/A	5 mg TID–20 mg TID
Clonazepam (Klonopin, Klonopin Wafers[1]) [G] 1975	Panic disorder	Tablets: 0.5, 1, 2 ODT: 0.125, 0.25, 0.5, 1, 2	1 hr	20–80	4–8	0.5 mg BID–2 mg TID
Diazepam (Valium) [G] 1963	GAD Alcohol withdrawal	Tablets: 2, 5, 10 Liquid: 5 mg/5 mL, 5 mg/mL Injection: 5 mg/mL	30 min	>100	4–6	2 mg BID–10 mg QID
Lorazepam (Ativan) [G] 1977	GAD	Tablets: 0.5, 1, 2 Liquid: 2 mg/mL Injection: 2 mg/mL, 4 mg/mL	30–60 min	10–20	4–6	1 mg BID–5 mg BID
Prazosin (Minipress) [G] 1976	PTSD (off-label)	Capsules: 1, 2, 5	1–2 hrs	2–3	4–6	1 mg/day–10 mg/day QHS or divided BID
Propranolol (Inderal) [G] 1973	Performance anxiety (off-label)	Tablets: 10, 20, 40, 60, 80	60 min	3–6	4–6	10–40 mg PRN

[1]Brand discontinued; available as generic only

TABLE 8.1: Benzodiazepine Dosage Equivalencies

Benzodiazepine	Approximate Equivalent Dosage (mg)
Alprazolam (Xanax)	0.5
Chlordiazepoxide (Librium)	25
Clonazepam (Klonopin)	0.25–0.5
Clorazepate (Tranxene)	7.5
Diazepam (Valium)	5
Estazolam (ProSom)	1
Flurazepam (Dalmane)	15
Lorazepam (Ativan)	1
Oxazepam (Serax)	15
Quazepam (Doral)	15
Temazepam (Restoril)	15
Triazolam (Halcion)	0.25

ALPRAZOLAM (Xanax) Fact Sheet [G]

FDA Indications:

Generalized anxiety disorder (GAD); panic disorder.

Off-Label Uses:

Other anxiety disorders; insomnia; acute mania or psychosis; catatonia.

Dosage Forms:

- **Tablets (G):** 0.25, 0.5 mg, 1 mg, 2 mg.
- **ER tablets (Xanax XR, G):** 0.5 mg, 1 mg, 2 mg, 3 mg.
- **Orally disintegrating tablets (Niravam, G):** 0.25 mg, 0.5 mg, 1 mg, 2 mg.
- **Oral concentrate (G):** 1 mg/mL.

Dosage Guidance:

- GAD: Start 0.25 mg–0.5 mg TID; increase by 0.25 mg–0.5 mg/day increments every 3–4 days as needed and tolerated to max dose 4 mg/day divided TID–QID.
- Panic disorder: Start 0.5 mg TID; increase by increments of no more than 1 mg/day every 3–4 days as needed to a target dose 4 mg–6 mg/day divided TID–QID. Max dose 10 mg/day.
- For panic disorder using XR: Start 0.5 mg–1 mg QD; increase by increments of no more than 1 mg/day at intervals of 3–4 days to target dose 3 mg–6 mg QD.

Monitoring: No routine monitoring recommended unless clinical picture warrants.

Cost: $; ODT: $$

Side Effects:

- Most common: Sedation, somnolence, memory impairment, slurred speech, incoordination, dependence.
- Serious but rare: Anterograde amnesia, increased fall risk, paradoxical reaction (irritability, agitation), respiratory depression (avoid in patients with sleep apnea).

Mechanism, Pharmacokinetics, and Drug Interactions:

- Binds to benzodiazepine receptors to enhance GABA effects.
- Metabolized primarily through CYP3A4; t ½: 11–16 hours.
- Avoid use with other CNS depressants, including alcohol and opioids (additive effects). Potent CYP3A4 inhibitors (eg, fluvoxamine, erythromycin) may increase alprazolam levels; CYP3A4 inducers (eg, carbamazepine) may decrease alprazolam levels.

Clinical Pearls:

- Schedule IV controlled substance.
- Benzodiazepines are very effective immediately for GAD and panic disorder, particularly in the early weeks of SSRI therapy while awaiting onset of therapeutic effect.
- Paradoxical reaction of aggression, agitation, and combativeness is more likely to occur in the elderly or those with brain injury.
- While benzodiazepines are highly abusable, patients with panic disorder rarely self-increase their dose when treated adequately, indicating that tolerance to anxiolytic effects does not occur.

Fun Fact:

There are many slang terms for alprazolam; some of the more common ones are Bars, Z-bars, Zannies, Footballs, Blues, or Blue Footballs.

Bottom Line:

Fast-acting and effective for GAD and panic disorder, but short duration of action may contribute to breakthrough symptoms between doses and make withdrawal more difficult.

BUSPIRONE (BuSpar) Fact Sheet [G]

FDA Indications:
Generalized anxiety disorder (GAD).

Off-Label Uses:
Treatment-resistant depression; anxiety symptoms in depression.

Dosage Forms:
Tablets (G): 5 mg, 7.5 mg, 10 mg, 15 mg, 30 mg (scored).

Dosage Guidance:
Start 7.5 mg BID or 5 mg TID; increase by increments of 5 mg/day every 2–3 days to target dose 20 mg–30 mg/day divided BID–TID; max 20 mg TID.

Monitoring: No routine monitoring recommended unless clinical picture warrants.

Cost: $

Side Effects:
Most common: Dizziness, nervousness, nausea, headache, jitteriness.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Serotonin 5HT1A receptor partial agonist.
- Metabolized primarily through CYP3A4; t ½: 2–3 hours.
- Avoid use with MAOIs; caution with serotonergic agents due to additive effects and risk for serotonin syndrome. Caution with 3A4 inhibitors or inducers as they may affect buspirone serum levels; adjust dose.

Clinical Pearls:
- Similar to antidepressants, buspirone requires 1–2 weeks for onset of therapeutic effects, with full effects occurring over several weeks, and offers no "as-needed" benefits.
- Non-sedating, non-habit-forming alternative to benzodiazepines for anxiety. May be less effective or ineffective in patients who have previously responded to benzos.
- Has only shown efficacy in GAD, not in other anxiety disorders (PTSD, OCD, panic disorder).
- May potentiate antidepressant effects when used in combination with SSRIs in refractory depression.

Fun Fact:
Other psychotropic agents with 5HT1A partial agonist effects include aripiprazole, ziprasidone, and vilazodone.

Bottom Line:
An alternative to benzodiazepine in patients for whom benzos are not appropriate. Don't expect as robust a response, though.

CLONAZEPAM (Klonopin) Fact Sheet [G]

FDA Indications:

Seizure disorders; panic disorder.

Off-Label Uses:

Other anxiety disorders; insomnia; acute mania or psychosis; catatonia.

Dosage Forms:

- **Tablets (G):** 0.5 mg, 1 mg, 2 mg.
- **Orally disintegrating tablets (G):** 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg.

Dosage Guidance:

- Dose varies based on patient characteristics (eg, age) and tolerance to benzodiazepines.
- Anxiety: Start 0.5 mg BID; increase by 0.5 mg–1 mg/day increments every 2–4 days to max 6 mg/day divided BID–TID.
- Insomnia (off-label use): Start 0.25 mg–0.5 mg QHS as needed for insomnia. Max 2 mg at bedtime.
- Use lower doses for elderly.

Monitoring: No routine monitoring recommended unless clinical picture warrants.

Cost: $

Side Effects:

- Most common: Somnolence, daytime grogginess, confusion, ataxia.
- Serious but rare: Anterograde amnesia, increased fall risk, paradoxical reaction (irritability, agitation), respiratory depression (avoid in patients with sleep apnea).

Mechanism, Pharmacokinetics, and Drug Interactions:

- Binds to benzodiazepine receptors to enhance GABA effects.
- Metabolized primarily through CYP3A4; t ½: 20–80 hours.
- Avoid concomitant use with other CNS depressants, including alcohol and opioids (additive effects). Potent CYP3A4 inhibitors (eg, fluvoxamine, erythromycin) may increase clonazepam levels; CYP3A4 inducers (eg, carbamazepine) may decrease clonazepam levels.

Clinical Pearls:

- Schedule IV controlled substance.
- High potency, long-acting benzodiazepine with active metabolites that may accumulate.
- Withdrawal effects may not be seen until 3–5 days after abrupt discontinuation and may last 10–14 days due to long half-life and active metabolites of clonazepam.
- Full effects of a particular dose may not be evident for a few days since active metabolites will accumulate with continual use (versus PRN use). Wait several days before increasing dose if patient is taking clonazepam regularly.

Fun Fact:

Klonopin tablets (or "K-pins") have a street value of $2–$5 per tablet, depending on dose and geographic region.

Bottom Line:

Fewer breakthrough symptoms compared to alprazolam when used for anxiety due to longer half-life. May work as a good hypnotic for the short term, although dependence and long half-life limit this use.

DIAZEPAM (Valium) Fact Sheet [G]

FDA Indications:
Generalized anxiety disorder (GAD); alcohol withdrawal; seizures; muscle spasms.

Off-Label Uses:
Other anxiety disorders; insomnia; acute mania or psychosis; catatonia.

Dosage Forms:
- **Tablets (G):** 2 mg, 5 mg, 10 mg (scored).
- **Oral liquid (G):** 5 mg/5 mL, 5 mg/1 mL.
- **Injection (G):** 5 mg/1 mL.

Dosage Guidance:
Anxiety: Start 2 mg BID–5 mg BID; increase by 2 mg–5 mg/day increments every 2–4 days to max 40 mg/day divided BID–QID.

Monitoring: No routine monitoring recommended unless clinical picture warrants.

Cost: $

Side Effects:
- Most common: Somnolence, daytime grogginess, confusion, ataxia.
- Serious but rare: Anterograde amnesia, increased fall risk, paradoxical reaction (irritability, agitation), respiratory depression (avoid in patients with sleep apnea).

Mechanism, Pharmacokinetics, and Drug Interactions:
- Binds to benzodiazepine receptors to enhance GABA effects.
- Metabolized primarily through CYP3A4 and 2C19; t ½: >100 hours.
- Avoid concomitant use with other CNS depressants, including alcohol and opioids (additive effects).

Clinical Pearls:
- Schedule IV controlled substance.
- Long-acting benzodiazepine with active metabolites that may accumulate.
- Tolerance to sedative effect may develop more rapidly (within 2–4 weeks of use) than tolerance to anti-anxiety effect.
- Withdrawal effects may not be seen until 3–5 days after abrupt discontinuation and may last 10–14 days due to long half-life and active metabolites of diazepam.
- Diazepam has the highest lipid solubility of all benzos, which means very rapid distribution into and out of the CNS, resulting in the greatest "rush" felt by patients using in a single-dose manner. This feature makes diazepam the most abusable benzo.

Fun Fact:
Valium has been glorified in music more than once. The Rolling Stones' "little yellow pill" in "Mother's Little Helper" and Lou Reed's "Walk on the Wild Side" ("Jackie is just speeding away/Thought she was James Dean for a day/Then I guess she had to crash/Valium would have helped that bash") are two good examples.

Bottom Line:
Diazepam has a long history of use with good efficacy for anxiety. Its long half-life makes it a particularly effective anxiolytic for some patients.

LORAZEPAM (Ativan) Fact Sheet [G]

FDA Indications:

Generalized anxiety disorder (GAD); status epilepticus (IV route).

Off-Label Uses:

Other anxiety disorders; insomnia; acute mania or psychosis; catatonia.

Dosage Forms:

- **Tablets (G):** 0.5 mg, 1 mg, 2 mg.
- **Oral concentrate (G):** 2 mg/mL.
- **Injection (G):** 2 mg/mL, 4 mg/mL.

Dosage Guidance:

- Anxiety: Start 1 mg BID; increase by 0.5 mg–1 mg/day increments every 2–4 days up to 6 mg/day divided BID–TID. Max 10 mg/day divided BID–TID.
- Insomnia (off-label use): Start 0.5 mg–1 mg QHS, 20–30 minutes before bedtime; max 4 mg nightly.
- Use lower doses in elderly.

Monitoring: No routine monitoring recommended unless clinical picture warrants.

Cost: $

Side Effects:

- Most common: Somnolence, dizziness, weakness, ataxia.
- Serious but rare: Anterograde amnesia, increased fall risk, paradoxical reaction (irritability, agitation), respiratory depression (avoid in patients with sleep apnea).

Mechanism, Pharmacokinetics, and Drug Interactions:

- Binds to benzodiazepine receptors to enhance GABA effects.
- Metabolism primarily hepatic (non-CYP450) to inactive compounds; t ½: 10–20 hours.
- Avoid concomitant use with other CNS depressants, including alcohol and opioids (additive effects). No risk for CYP450 drug interactions.

Clinical Pearls:

- Schedule IV controlled substance.
- Lorazepam does not have a long half-life or active metabolites that could accumulate, and poses no CYP450 drug interaction risk.
- Withdrawal symptoms usually seen on the first day after abrupt discontinuation and last 5–7 days in patients receiving short–intermediate half-life benzodiazepines such as lorazepam. A gradual taper is highly recommended, particularly if the patient is receiving prolonged treatment on a high dose.
- Tolerance to sedative effect may develop within 2–4 weeks of use, and benzodiazepines affect sleep architecture; thus, long-term use is discouraged.

Fun Fact:

Early Ativan marketing efforts included clever direct-to-consumer advertising campaigns. These included "Now it can be yours—The Ativan experience" in 1977 and "In a world where certainties are few . . . no wonder Ativan is prescribed by so many caring clinicians" in 1987.

Bottom Line:

When a benzodiazepine is appropriate for use (short-term; minimal risk of abuse), we consider lorazepam to be a first-line agent.

PRAZOSIN (Minipress) Fact Sheet [G]

FDA Indications:
Hypertension.

Off-Label Uses:
PTSD.

Dosage Forms:
Capsules (G): 1 mg, 2 mg, 5 mg.

Dosage Guidance:
- PTSD (off-label): Titrate dose slowly to minimize possibility of "first-dose" orthostatic hypotension. Start 1 mg QHS x 3 days, then 2 mg QHS x 4 days. If tolerating but still symptomatic, increase to 3 mg QHS x 7 days. Dose can be increased further, based on response, to 4 mg QHS x 7 days. Target 1 mg–5 mg/day.
- May dose-divide BID to target daytime PTSD-associated arousal symptoms.

Monitoring: Periodic blood pressure.

Cost: $

Side Effects:
- Most common: Somnolence, dizziness, headache, weakness.
- Serious but rare: Orthostasis and syncope; prolonged erections and priapism have been reported.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Alpha-1 adrenergic receptor antagonist.
- Metabolism primarily hepatic (non-CYP450); t ½: 2–3 hours.
- Caution with other antihypertensive agents, diuretics, and PDE5 inhibitors (eg, Viagra) that may have additive hypotensive effects.

Clinical Pearl:
Initial studies showed improvement in trauma-related nightmares and sleep quality when dosed at bedtime. Subsequent randomized controlled trials have shown positive effects on daytime PTSD symptoms also when dosed BID.

Fun Fact:
Prazosin is an older drug, which is now rarely used for its original indication (hypertension). It's now used as a second-line agent for urinary hesitancy in benign prostatic hyperplasia. It is also being investigated for alcohol dependence.

Bottom Line:
Use prazosin for PTSD, especially for PTSD-associated nightmares.

PROPRANOLOL (Inderal) Fact Sheet [G]

FDA Indications:
Hypertension; angina; post-MI cardioprotection; atrial fibrillation; migraine prophylaxis; essential tremor.

Off-Label Uses:
Performance anxiety, tremor due to medication side effects (especially lithium).

Dosage Forms:
Tablets (G): 10 mg, 20 mg, 40 mg, 60 mg, 80 mg (scored).

Dosage Guidance:
- Performance anxiety (off-label use): Give 10 mg about 60 minutes prior to performance; usual effective dose is 10 mg–40 mg.
- Medication-induced tremor: Start 10 mg BID as needed; can go up to 30 mg–120 mg daily in two or three divided doses. Can also use Inderal LA, long-acting version of propranolol, 60 mg–80 mg once a day.

Monitoring: Periodic blood pressure/pulse.

Cost: $

Side Effects:
Most common: Dizziness, fatigue, bradycardia, and hypotension.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Non-selective beta-1 and beta-2 adrenergic receptor antagonist.
- Metabolized primarily through CYP2D6, also 1A2 and 2C19; t ½: 3–6 hours.
- Caution with other antihypertensives (additive effects). CYP2D6 inhibitors, as well as inhibitors or inducers of 1A2 and 2C19, may affect propranolol levels.

Clinical Pearl:
With beta blockade, propranolol reduces some of the somatic symptoms of anxiety (tremor, sweating, flushing, tachycardia).

Fun Fact:
The list of notable people who suffer or have suffered from performance anxiety or stage fright is long. It includes Barbra Streisand, Carly Simon, Van Morrison, Frédéric Chopin, Renee Fleming, Jay Mohr, Hugh Grant, Laurence Olivier, Mahatma Gandhi, and Thomas Jefferson, among others.

Bottom Line:
Effective and safe for use in performance anxiety, particularly when the sedating or cognitive side effects of benzos could interfere with an individual's performance.

Weight Gain

Characteristics: Typically, patients will report food craving and binging. Weight gain rapid in first 3 months, more gradual over following year, then often plateaus. Rapid initial weight gain is correlated with greater eventual cumulative weight gain. FDA definition of weight gain is ≥7% increase in weight from baseline.

Meds That Cause It: Antipsychotics, especially clozapine, olanzapine, and quetiapine. Somewhat less weight gain with risperidone and paliperidone. Least weight gain with aripiprazole, haloperidol, ziprasidone, and lurasidone. Antidepressants: Mirtazapine, tricyclics, paroxetine. Mood stabilizers: Lithium, valproic acid.

Mechanism: Blockade of histamine and serotonin 2A receptors, leading to increased hunger.

General Management:

- Monitoring: Weight, BMI, waist circumference every 4 weeks for 3 months, then every 3 months.
- Lifestyle modification, including exercise and dietary changes, is helpful for patients who are motivated; several studies have shown some benefit, but in actual clinical settings it may be difficult to match their results.
- Switch to a medication that is more weight neutral.

First-Line Medications: (some evidence specifically for reducing psychotropic-induced weight gain)

- Topiramate 100 mg–300 mg/day; SE: Cognitive dulling.
- Metformin XR 500 mg–2000 mg: Take with largest meal, split into 2 doses if needed (based on GI side effects).
- Orlistat 120 mg 3 times daily after meals. Interferes with fat absorption; SE: Diarrhea.
- Aripiprazole 15 mg/day. Antipsychotic. May be useful for olanzapine-induced weight gain as adjunct.

Second-Line Medications: (effective for weight loss, but little or no evidence specifically for psychotropic-induced weight gain)

- Bupropion SR 300 mg–400 mg daily.
- Any psychostimulant either methylphenidate or amphetamine class.
- Naltrexone/bupropion (Contrave) 8 mg/90 mg up to 2 tabs twice daily. Anti-obesity drug.
- Phentermine (Suprenza) 15 mg–37.5 mg daily. Anti-obesity drug.
- Phentermine/topiramate (Qsymia) 7.5 mg/46 mg up to 2 tabs daily. Anti-obesity drug.
- Zonisamide (Zonegran) 100 mg–600 mg/day. Anticonvulsant.
- Nizatidine (Axid) 150 mg–300 mg daily. Antacid, H-2 blocker, available OTC.
- Amantadine (Symmetrel) 100 mg–300 mg/day.

Clinical Pearls:

- Weight gain is most likely in the first 6 weeks of taking an antipsychotic, and it's difficult for patients to ever lose this weight. As such, you should monitor weekly initially, and switch to a more weight-neutral agent at the first sign of weight gain.
- If patient gains 5% or more of body weight, switch to a different drug.
- Ziprasidone and aripiprazole are probably the most weight-neutral antipsychotics and may even cause weight loss, especially if switching from another agent.
- Weight gain tends to be most severe in patients who are taking an antipsychotic for the first time.
- Ask weight-gaining patients about dry mouth; many psychotropics cause this, and such patients may gain weight from drinking sugary beverages to deal with this side effect.

Fun Fact:

Some researchers have hypothesized that treatment-emergent weight gain is related to and predictive of clinical response, but others argue it may be a marker for medication adherence instead.