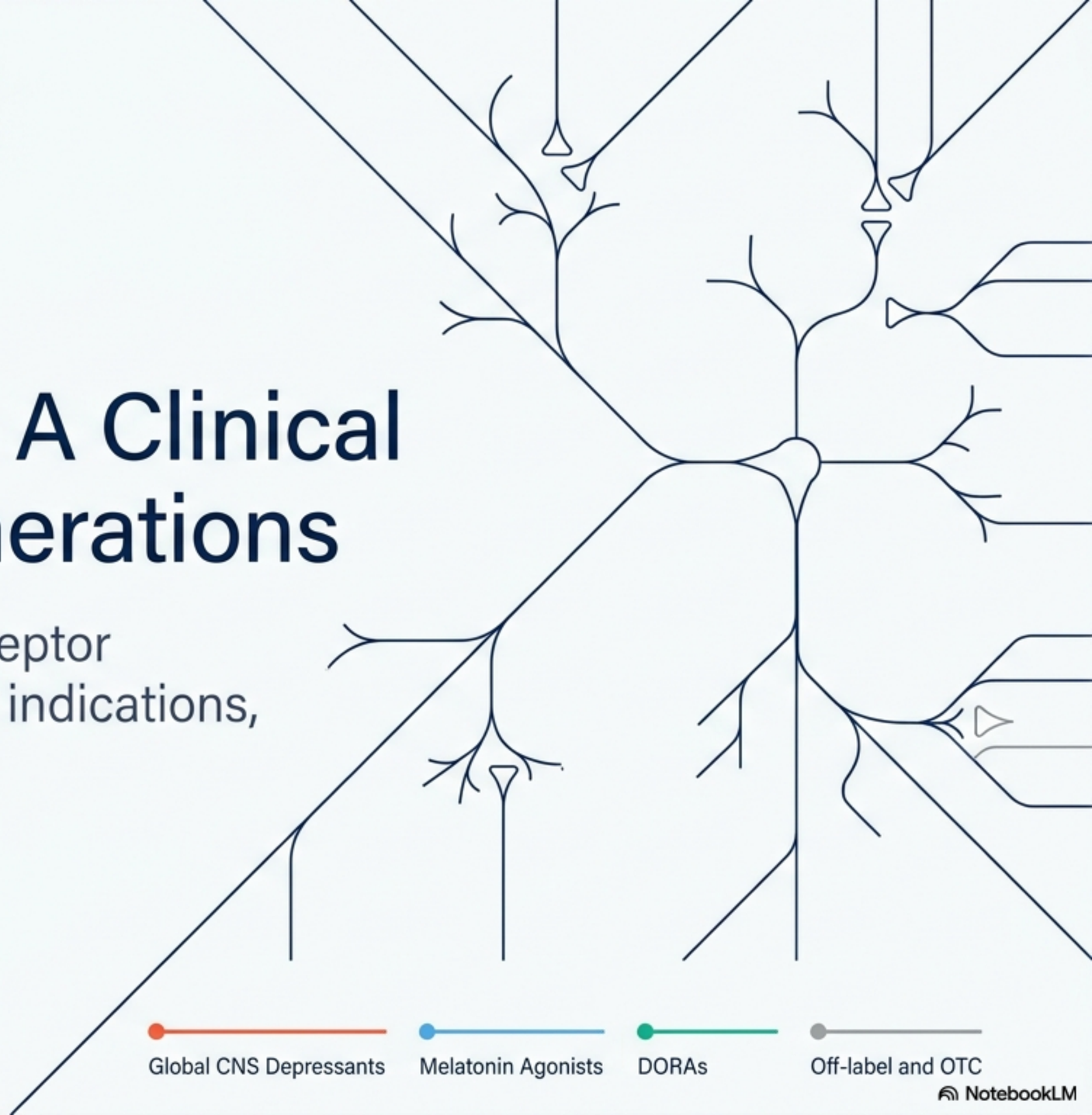
Sleep Medications: A Clinical Review Across Generations

From barbiturates to dual orexin receptor antagonists—mechanisms, evolving indications, side effects, and clinical selection.



160 Years of Sleep Pharmacology

1 1864–1960s: Barbiturates

Profound GABA-A positive allosteric modulation.

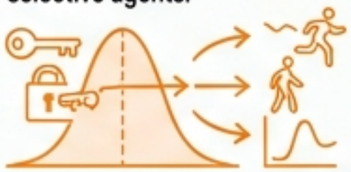
Dangerously narrow therapeutic window between sedation and fatal respiratory depression.

2 1960s–1980s: Benzodiazepines

Wider therapeutic index than barbiturates, but rapid development of physical dependence, tolerance,

3 1993–2000s: Z-Drugs

Marketed as cleaner alpha-1 selective agents.



4 2005: Ramelteon

The first major mechanistic departure. MT1/MT2 agonist.

No abuse potential, no dependence.

5 2014–2022: DORAs

Suvorexant, Lemborexant, and Daridorexant.

Orexin receptor antagonism.

Preserves sleep architecture without physical dependence.

Therapeutic Window

"Stepping Stone" Timeline

1864

2022

2 1960s–1980s: Benzodiazepines

Wider therapeutic index than barbiturates, but rapid development of physical dependence, tolerance, and withdrawal risk.

3 1993–2000s: Z-Drugs

Marketed as cleaner alpha-1 selective agents.

Ultimately demonstrated equivalent dependence profiles to BZDs, plus complex sleep behaviors.

4 2005: Ramelteon

The first major mechanistic departure. MT1/MT2 agonist.

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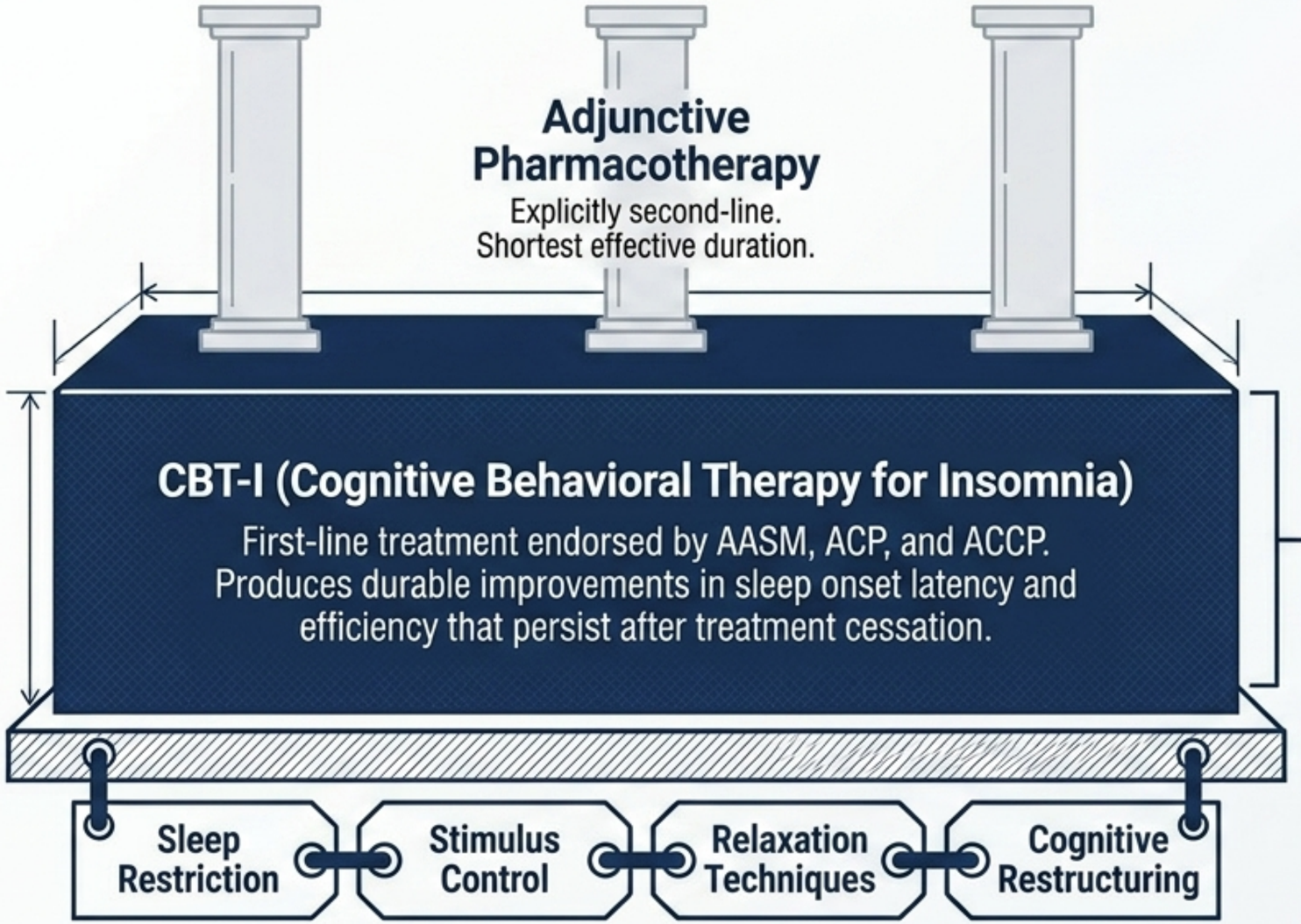
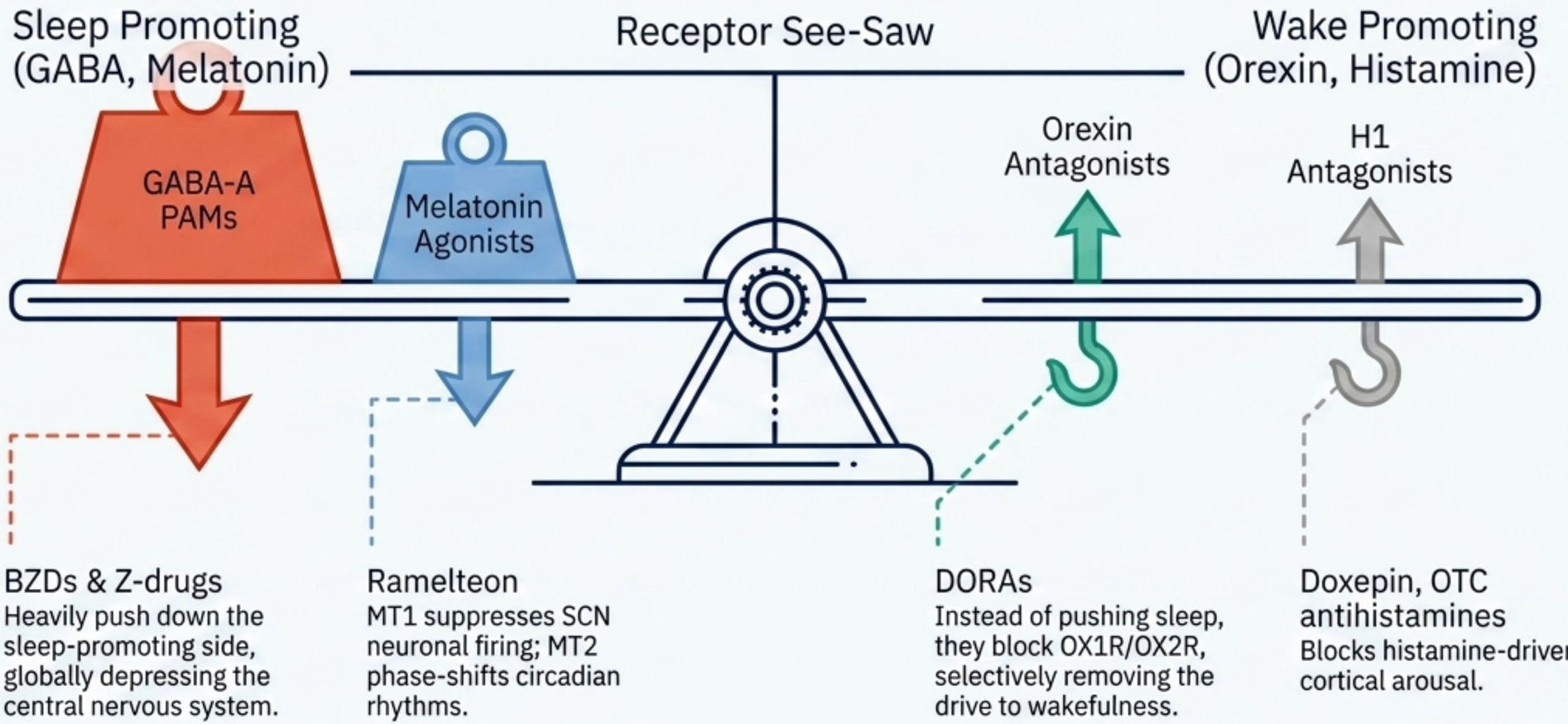
The Unshakable Foundation: CBT-I



Scalable Access

Digital CBT-I platforms (e.g., Somryst) are FDA-cleared and offer viable alternatives when face-to-face therapy is unavailable.

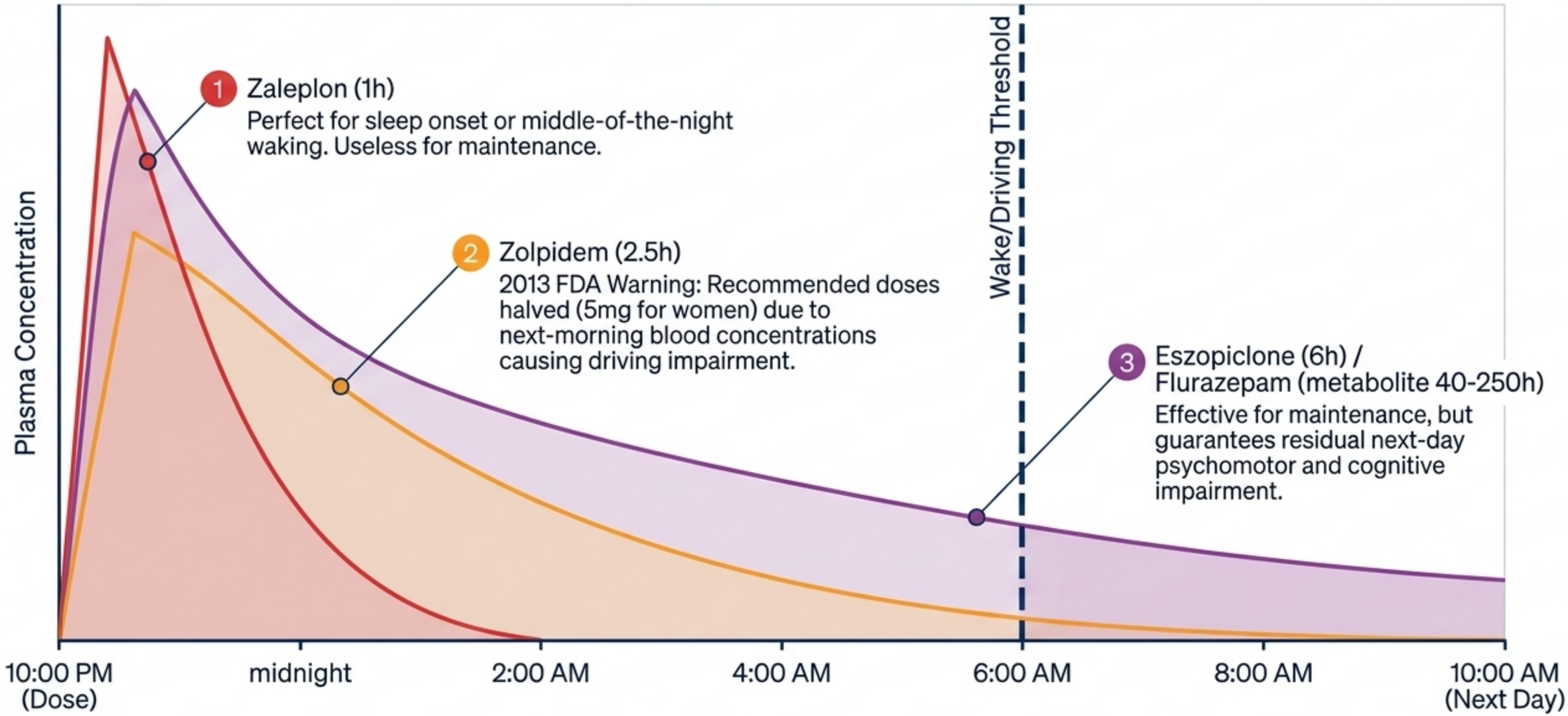
The Sleep-Wake Switchboard



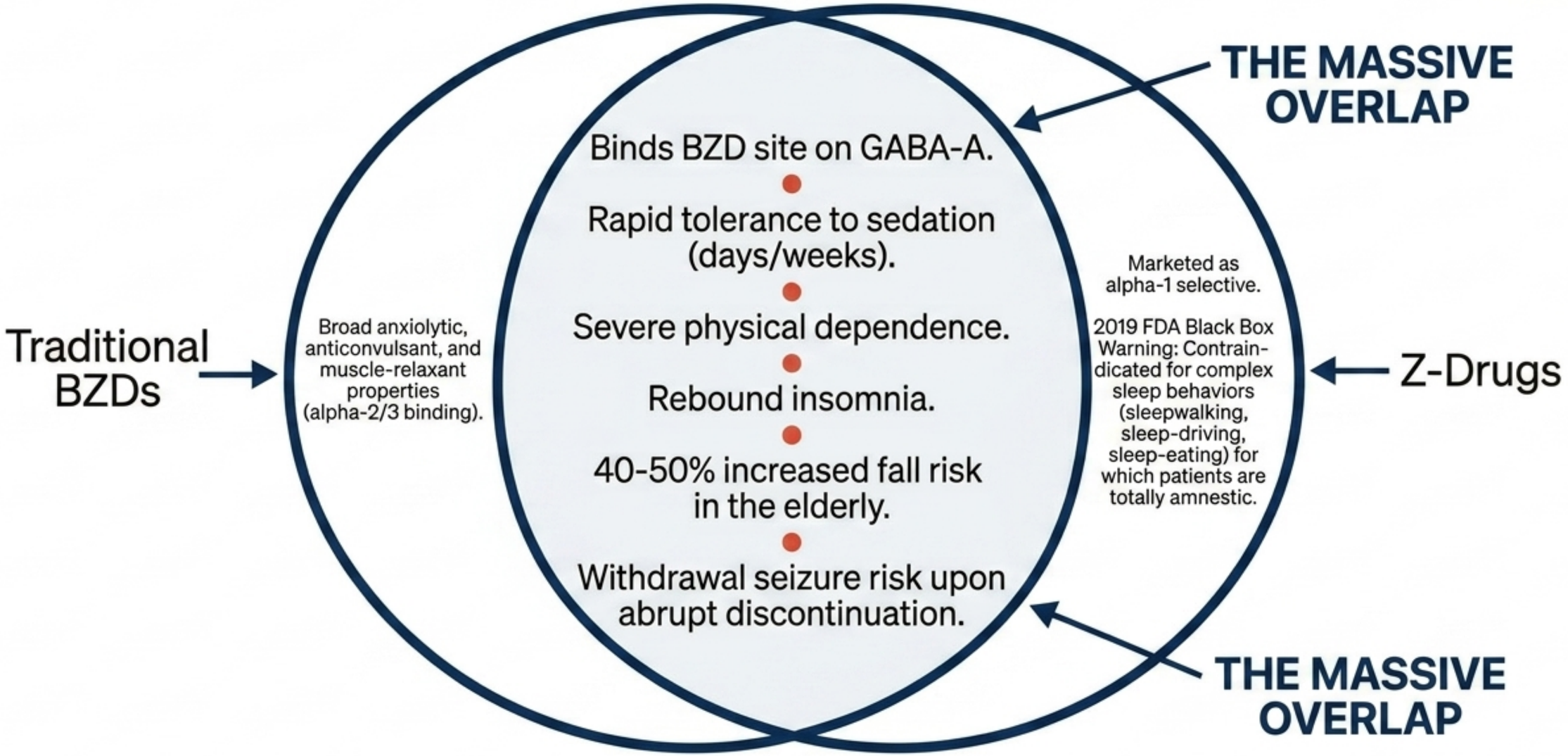
The Pharmacokinetic Master Matrix

Specific Agent	Drug Class	Mechanism	Half-Life	Schedule	Critical Clinical Catch
Temazepam	Benzodiazepine	GABA-A PAM	8–20h	Sched IV	Dependence, rebound, falls.
Triazolam	Benzodiazepine	GABA-A PAM	1.5–5h	Sched IV	Anterograde amnesia.
Flurazepam	Benzodiazepine	GABA-A PAM	40–250h	Sched IV	Prolonged next-day impairment.
Zolpidem	Z-Drug	GABA-A PAM	2.5h	Sched IV	Complex sleep behaviors (Black Box).
Eszopiclone	Z-Drug	GABA-A PAM	6h	Sched IV	Complex behaviors, metallic taste.
Ramelteon	MT Agonist	MT1/MT2 Agonist	1–2.6h	Not Sched	CYP1A2 interactions (Fluvoxamine CI).
Daridorexant	DORA	OX1R/OX2R Antag.	8h	Sched IV	Cost. (Only DORA with daytime function data).
Suvorexant	DORA	OX1R/OX2R Antag.	12h	Sched IV	Next-day somnolence at high doses.
Doxepin 3-6mg	TCA (Low)	H1 Antagonist	15h	Not Sched	Sleep maintenance only.

The Half-Life Horizon: Matching Kinetics to Clinical Need



The Z-Drug vs. Benzodiazepine Illusion



Forcing Sleep vs. Inhibiting Wakefulness

A Stepping on the Brakes

GABAergics (BZDs & Z-Drugs)

Forcing Sleep. Acting as global CNS depressants, these agents force sedation. This bludgeon approach disrupts natural sleep architecture, depresses respiratory drive, and guarantees physical dependence.

B Taking the Foot off the Gas

Orexin Antagonists (DORAs)

Inhibiting Wakefulness. By selectively blocking the orexin wake-promoting signal, DORAs simply reduce the drive to stay awake. This permits natural sleep architecture (including REM) to emerge safely, maintains respiratory drive, and eliminates physical dependence.

Clinical Milestone: Daridorexant (HERALD trial) marks the first time a sleep drug showed statistically significant improvement in patient-reported daytime functioning (IDSIQ), proving the value of architectural preservation.

The Off-Label & OTC Landscape

Trazodone (SARI)

The most widely prescribed off-label sleep agent in the US.
Modulates 5-HT2A and H1.
Lacks robust RCT data for pure insomnia.

The Catch:
Orthostatic hypotension risk.
Rare but severe priapism risk (1 in 6,000–8,000 male patients)—a urological emergency requiring counseling.

Low-Dose Quetiapine

(12.5–100mg).
Heavily relies on H1 blockade.
Highly controversial off-label use.

The Catch:
Exposes patients to antipsychotic class risks (metabolic syndrome, dyslipidemia, QTc prolongation, tardive dyskinesia) without a psychiatric indication.

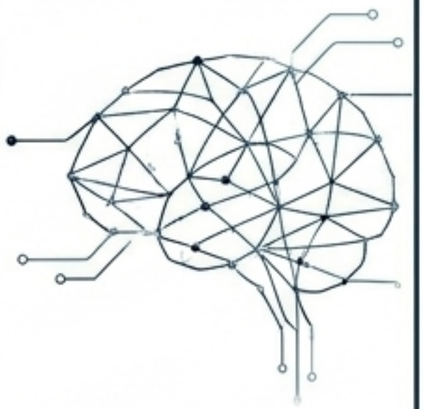
OTC Antihistamines

(Diphenhydramine/Doxylamine).
Acts via H1 receptor blockade in the cortex.

The Catch:
Severe anticholinergic burden (confusion, urinary retention, blurred vision) especially in older adults.
Rapid tolerance develops within just 3–4 days, prompting dose escalation.

The Burden of Harm: Side Effect Profiles Across Generations

	Dependence	Next-Day Impairment	Falls Risk	Cognitive Effects	Respiratory Depression	Metabolic Effects
Benzodiazepines (Accent Red)						
Z-Drugs (Accent)						
Ramelteon	Pale					
DORAs	Pale					
Trazodone	Low				Low	
Mirtazapine	Low		Low	Low		
Antihistamines	Low				Low	
Low-Dose Quetiapine	Low			Low		



Shading indicates clinical severity. Note the pristine safety profile of Ramelteon and DORAs compared to legacy GABAergics.

The Geriatric Cliff: Navigating the 2023 AGS Beers Criteria

⚠ THE ABSOLUTE RULE

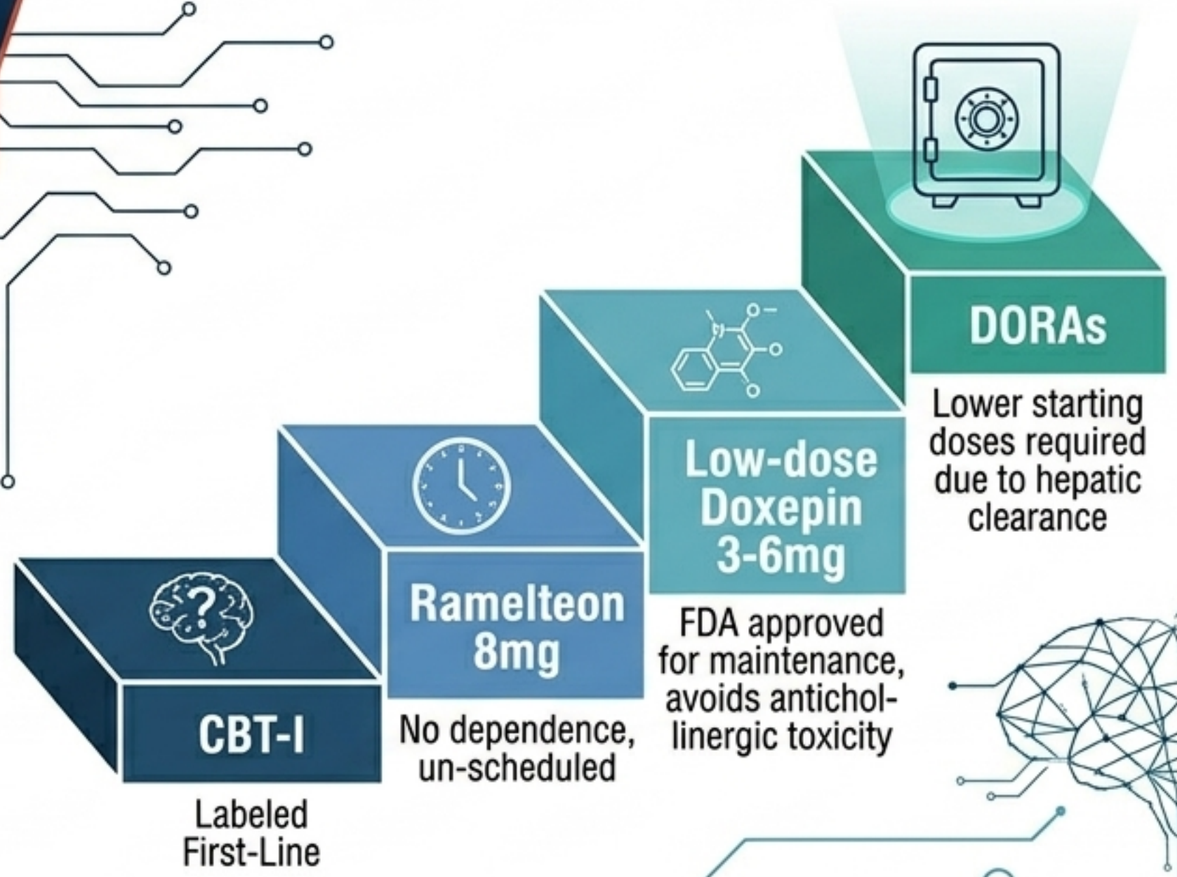
The 2023 Beers Criteria places all benzodiazepines and Z-drugs in the **AVOID** category for adults ≥65 years, regardless of duration or indication.

40–50% Increased fall risk with BZD/Z-drug use in older adults.

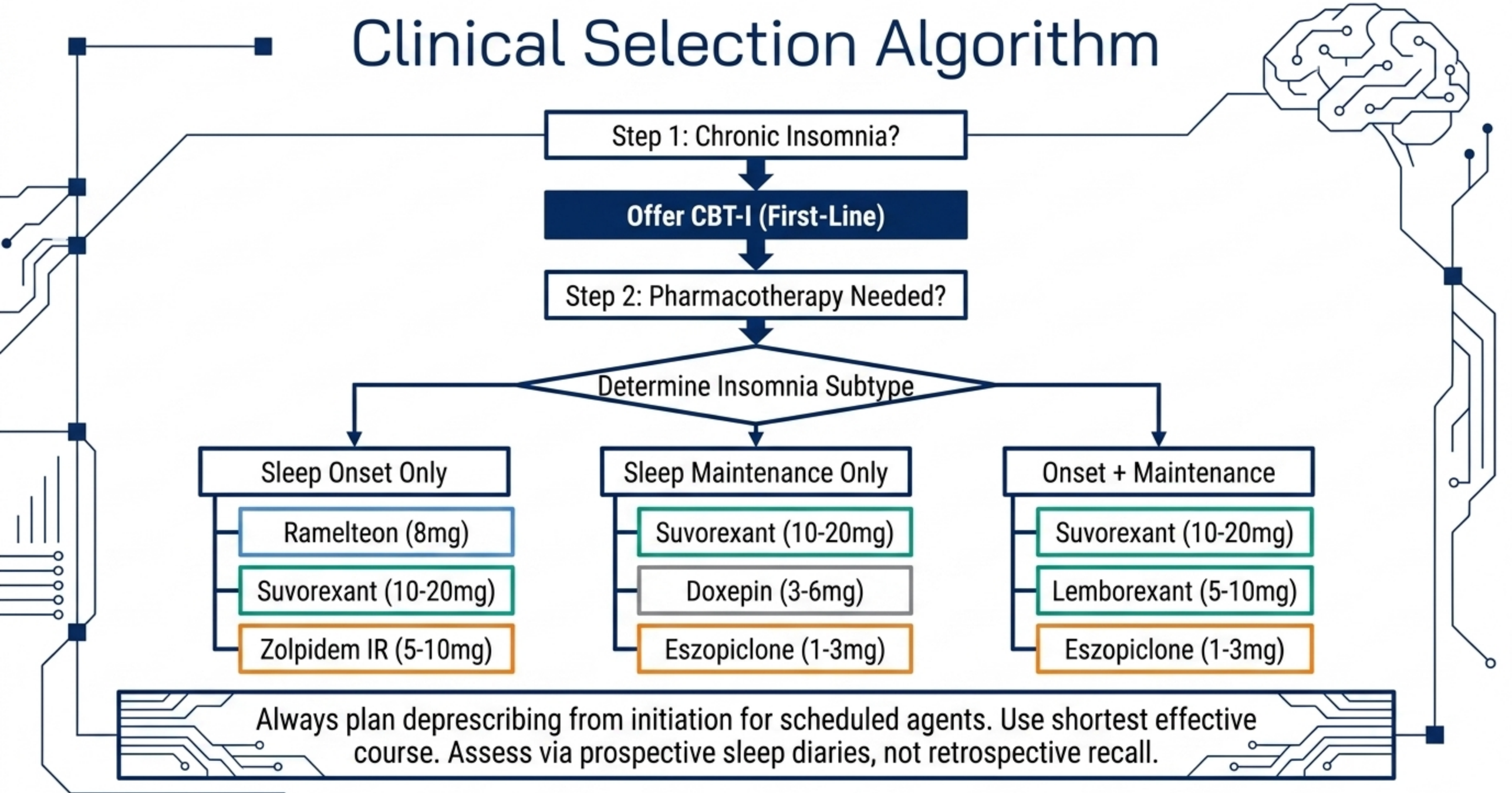
~50% Increased hip fracture risk associated with BZD use.

1.2–1.5x Increased odds ratio for dementia with chronic BZD use.

The Safe Path
(Guideline-Backed Alternatives)



Clinical Selection Algorithm



Navigating Special Populations and Comorbidities

Substance Use Disorder (SUD)

Avoid all scheduled GABAergics due to cross-tolerance and addiction transfer risk.

Preferred:

- **Ramelteon** (unscheduled, zero abuse potential)
- **DORAs** (Schedule IV purely precautionary, no clinical abuse demonstrated)
- **Low-dose Doxepin**

Pregnancy

No clear pharmacological preference. BZDs carry neonatal withdrawal risk.

Preferred:

- **CBT-I** must be primary.
- **Doxylamine** (off-label via Diclegis) occasionally utilized, but individualized risk-benefit discussion is mandatory.

Comorbidities

- **Depression:** Mirtazapine (if weight gain is acceptable) or Trazodone.
- **Circadian Disorder** (Shift work/Jet lag): Ramelteon.
- **COPD/Sleep Apnea:** DORAs (preserves respiratory drive).

WARNING: Fluvoxamine increases Ramelteon AUC by 190x (CYP1A2 interaction)—absolute contraindication

The Deprescribing Staircase: Safely Tapering Scheduled Agents

The Principle: Unwinding BZDs/Z-drugs requires patience. Prescribing with no defined endpoint is the primary driver of dependence.

10–25% Drops

Reduce dose by 10-25% every 2 weeks. Flexible, patient-guided tapers outperform rigid schedules.

Pharmacokinetic Bridging

Switch short-acting agents (triazolam, zolpidem) to longer half-life equivalents (diazepam) to prevent peak/trough withdrawal spikes.

Manage Expectations

Rebound insomnia is guaranteed for the first 1-2 weeks. Concurrent CBT-I is the highest predictor of taper success.

⚠ The Cliff Warning

Abrupt discontinuation in a dependent patient precipitates life-threatening withdrawal seizures. It is a clinical emergency requiring immediate reinstatement and subsequent controlled taper.