DSM V DIAGNOSTIC CRTIERIA FOR INSOMNIA:

Predominant complaint of dissatisfaction with sleep quantity or quality:

- Difficulty initiating or maintaining sleep, or having non-restorative sleep for at least a month
- Early morning awakenings (can't go back to sleep)
- Causes clinically significant distress or impairment in social, occupational, academic or other important areas of functioning
- Occurs at least 3x/week for at least 3 months
- Not explained by anything else

CLASSIFICATION OF INSOMNIA:

- Primary: psychophysiological
- Secondary: psychiatric, medical, substance use
  - Co-existing clinical conditions are most common

CATEGORIES OF INSOMNIA:

- Episodic: 1 – 3 months
- Persistent: > 3 months
- Recurrent: ≥2 episodes/year

MEDICATIONS THAT CAN CAUSE OR WORSEN INSOMNIA:

- Antidepressants: bupropion, fluoxetine, SNRIs, MAOIs, TCAs
- Antihypertensives: beta blockers, methyldopa
- Sympathomimetic amines: amphetamines, methylphenidate, caffeine, cocaine, decongestants, appetite suppressants, bronchodilators
- Miscellaneous: nicotine, corticosteroids, anticonvulsants, levodopa, quinidine, hormones

NONPHARMACOLOGICAL OPTIONS:

- Proper sleep hygiene
- Relaxation exercises and tapes
- Stimulus control
- Sleep restriction
- Sleep diary
- Cognitive therapy
- Cognitive behavioral therapy (CBT)
- Increase aerobic exercise earlier in the day (45 mins and should induce sweating)

6 BASIC PRINCIPLES:

- Use lowest effective dose
- Intermittent dosing (PRN) – e.g. < 4 times/week
- Short-term treatment (2-4 wks) depending on presentation
- Need for medication tapering if longer term
- Select and monitor medications by assessing daytime functioning and adverse effects
- Patient plays an active role in treatment

BENZODIAZEPENE WITHDRAWAL:

- Physical dependence: down-regulation of BZD receptor sensitivity → need to continue to use drug to relieve or avoid physical withdrawal symptoms
  - Nausea, depression, ataxia, hyperreflexia, blurred vision, fatigue, confusion, delirium, anxiety, insomnia, irritability, muscle aches/weakness, psychomotor agitation, seizures, psychosis
  - Onset, duration, severity dependent on:
    - Dose/potency
    - Duration of treatment
    - Speed of withdrawal
    - Elimination half-life
- Abuse: recreational & continued use despite negative consequences, with dose escalation & loss of control over use
- Discontinuation syndromes:
  - **RELAPSE:** recurrence of original sx of underlying syndrome
  - **REBOUND:** similar to recurrence of original sx, but more intense
  - **WITHDRAWAL:** implies actual physical dependence

GOALS OF THERAPY:

- Promote sound and restorative sleep
- Minimize external (stress, noise, environment) & internal (anxiety, mood, pain) factors
- Reduce daytime impairment (fatigue, concentration) & complications of lack of sleep
- Improve the effectiveness of behavioral interventions in managing patients with primary, chronic insomnia

SLEEP HISTORY:

- Time data: napping, bed time, lights, how long to fall asleep, how many times awoken, longest awake period, time out of bed, hours of sleep
- Sleep period: physical symptoms preventing sleep (pain), mental or emotional sx (worry, anxiety), what awakens during the night (snoring, gasping for air, nightmares), sx when waking up (headache, confusion sleepiness)
- Questions for bed partner: snoring, gasping, breathing; leg twitching, jerking, kicking; alcohol. nicotine. caffeine. other drugs: change in mood or emotional state

TREATMENT OF INSOMNIA:

- Step 1: consider possible underlying causes of insomnia
- Step 2: nonpharmacological therapy
- Step 3: pharmacological options

SLEEP HYGIENE:

1. Keep a regular sleep/wake schedule 7 days a week
2. Limit daily "in-bed" time to average sleep time prior to the sleep disturbance
3. Avoid sleeping in or daytime naps
4. Stop offending medications/substances (caffeine, nicotine, alcohol, stimulants)
5. Avoid evening stimulation
6. Try a warm, 20 minute bath near bedtime
7. Eat regularly during the day and avoid large meals near bedtime
8. Use bedroom for sleep & intimacy – not for TV or something that keeps you too alert

PHARMACOLOGICAL OPTIONS:

• Antihistamines	• Melatonin
• Benzodiazepines	• Ramelteon* (melatonin receptor agonist)
• Zopiclone	• Chloral hydrate
• Eszopiclone*	• Antipsychotics
• Zaleplon*/Indiplon*	• L-tryptophan
• Zolpidem	• Alcohol? Barbiturates?
• Antidepressants (trazodone)	• Herbs (valerian, chamomile)

* = not available in Canada

BENZODIAZEPINES:

MOA	• Bind to gamma sub-unit of GABA-A receptor → increase in GABA-A activity	
Efficacy	Effective in promoting sleep onset and maintaining sleep • Reduce REM sleep • Decrease sleep latency • Decrease nocturnal awakenings	
Problems	Short-term	• Adverse effects • Carry-over effects • Cognition • Anterograde amnesia
	Long-term	• Tolerance • Withdrawal • Rebound • Dependence
	Elderly	• Increased risk of higher cortical impairment → confusion and falls • Reduced Phase I metabolism • Reduced GFR and hepatic blood flow • Use LOT – lorazepam, oxazepam, temazepam
Adverse Effects	• Daytime drowsiness/tiredness • Cognitive impairment • Rebound insomnia (even after 2 wks) • Anterograde amnesia • Incoordination and falls • Paradoxical effects • Respiratory depression • Dependence/tolerance • Sleep walking?	

ZOPICLONE:

MOA	• Acts at the benzodiazepine receptor • NOT a benzodiazepine	
Benefits over BZDs	Less or no: • Rebound insomnia • Tolerance and dependence • Amnesic effects • Morning hang-over (short half-life)	
Health Canada Dose Warning	• Starting dose reduced to 3.75 mg • Should not exceed 5 mg in elderly pts, pts with hepatic or renal impairment, or if on potent CYP3A4 inhibitors • Dose adjustment with concomitant use of other CNS-depressant drugs • Wait 12 hours after dosing before driving or engaging in other activities requiring full mental alertness, especially for elderly pts or pts taking 7.5 mg dose	
PK	• Absorption in elderly: 75 – 94% • Protein binding: 45% • Metabolism: extensively hepatic • $T_{1/2}$: 5 hours (elderly: 7 hrs ; hepatic impairment: 11.9 hrs) • Time to peak,: < 2 hours (hepatic impairment: 3.5 hrs) • Excretion: urine (75%); feces (16%)	
Drug interactions	• CNS depressants • CYP2C9 and CYP3A4 drugs (inducers & inhibitors)	
AEs	• Bitter/metallic taste • Dry mouth • Headache • Somnolence	• Suicidal ideation • Aggression • Worsening of depression

ANTIPSYCHOTICS:

Efficacy	• Not FDA approved for insomnia • Quetiapine & ziprasidone shown to increase total sleep time & sleep efficiency
Dose	• Lower than those for treating psychosis
AEs	• Associated with weight gain • Increased risk for diabetes, high BP, restless leg syndrome, muscle spasm, Parkinson-like symptoms

ZOLPIDEM:

MOA	• Binds to omega-1 (BZ-1) receptor subtype of GABA-A receptor complex • NOT a benzodiazepine	
PK/PD	• Rapid onset of action; sleep onset/duration • $T_{1/2}$: 2.5 – 3 h	
Dose	• 5-10 mg sublingual or 6.25 mg CR before bedtime	
AEs	• Nausea • Dizziness • Drowsiness • Rebound insomnia	• Suicidal ideation • Worsening of depression • Aggressive behavior
Contra-indications	• Severe hepatic impairment • Respiratory insufficiency	

DOXEPIN:

MOA	• Tricyclic antidepressant
Dose	• 1-3 mg
Efficacy	• 3 mg > placebo for all measures • 1 mg > placebo for some outcomes

TRAZODONE:

MOA	• Antidepressant	
Efficacy	• Limited data in primary insomnia • Lack of objective efficacy measures • Short duration of trials (longest is 6 wks) • Less effective than zolpidem	
SEs	• Sedation • Dizziness • Priapism	• Orthostasis • Psychomotor impairment

SUMMARY OF DRUGS:

Drug	Night-time dose	Half-life (hours)	Metabolites	Comments
Lorazepam	0.5 – 1 mg	10 – 20	Inactive	• No hangover effects • May cause more rebound insomnia on withdrawal than temazepam or oxazepam • May cause amnesia with higher doses
Oxazepam	15 – 30 mg	5 – 10	Inactive	• Slowly absorbed = delayed onset of action → take 60-90 mins before bed • No hangover effects
Temazepam	7.5 – 30 mg	10 – 12	Inactive	• Short duration of action limits morning sedation (low-mod risk of morning hangover) • Does not accumulate
Triazolam	0.125 – 0.25 mg	2 – 3	Inactive	• Anterograde amnesia (especially with higher dose, concomitant alcohol) • Dose-related SEs: rebound insomnia, daytime anxiety • Absence of hangover effects = major advantage • AVOID if possible
Zopiclone	3.75 – 7.5 mg (5 mg max for elderly, kidney/liver disease, concomitant meds)	5 – 10	N-desmethyl (active) & N-oxide (some activity)	• Does not accumulate • Free of cognitive effects; minimal additive effects with low doses of alcohol • Major adverse effect is bitter/metallic taste • May cause less rebound on withdrawal • Risk of physical tolerance and dependence • Should allow at least eight hours in bed
Zolpidem	5 – 10 mg			• Less chance of morning hang-over effect • Rapid onset of action • Risk of physical tolerance and dependence • Should allow at least eight hours in bed
Doxepin	3 – 6 mg			• Indicated only for sleep maintenance • No fall risk of cognitive side effects seen • Minimal risk of physical tolerance or dependence • Higher doses have traditional TCA SE profile
Trazadone	25 – 100 mg			• Short half-life = lower risk of morning hang-over effect • Minimal risk of tolerance/dependence • Risk of orthostatic hypotension