



















































SLEEP: SEDATIVE COMPARISON CHART

Generic	TRADE g=generic avail.	Equivalent Dose /Class	Peak Levels/ Onset of action	Average t _{1/2} * /Active Metabolite	COMMENTS	INITIAL & (MAX DOSE)	USUAL SEDATIVE DOSE	\$  /MONTH
Zolpidem SUBLINOX <small>Ambien-USA</small> (10mg ODT) X   <small>(USA: ER AMBIEN CR, SL EDLIAR, INTERMEZZO & spray ZOLPIMIST Formulations)</small>	5mg imidazopyridine	Gaba A _{1α1}	~ 1.4 hr	2.7 hr / None <small>(may impair morning fx)</small>	Indicated: for Age ≤65yrs; concern if mixed with alcohol. SE: drowsy, dizzy, diarrhea. DI: Cyp-3A4	 10mg hs <small>(5mg avail in USA)</small>	10mg SL hs, on empty stomach	53
Zaleplon SONATA <small>USA previous STARNOIC CDN: pyrazolopyrimidine</small> Gaba A _{1α1} ; peak 0.9-1.5hr; onset ≤30min; t _{1/2} =1 hr, duration ≤4hr; SE: headache, somnolence, dizziness, dependence . DI: cimetidine & rifampin; dose 5-10mg po hs; <small>(max 20mg).</small>	5mg cyclopyrrolone	Gaba A ₁	1-1.5hr Rapid (30min)	5 hr / Yes	√ Sedative-Good Choice : ↓tolerance & withdrawal? SE: dry mouth, bitter taste , residual sedation DI: s erythromycin, ketoconazole, rifampin. Dependence	 3.75mg (15mg)	5mg po hs 7.5mg po hs <small>(Rhovane & g less money)</small>	10 22
Zopiclone -IMOVANE / RHOVANE <small>g?</small> (5, 7.5 ² mg tab) X  	0.25mg Nitro	B E N Z O D I A Z E P I N E	1-4hr Intermed.(20-60min)	34 (19-60) hr None	CAUTION: ↑ falls/fractures, accidents esp. elderly dependence ; ↓ cognition long-term use, dizzy, incoordination √ Sedatives/hypnotic-Good BZ choices: temazepam ; possibly oxazepam, lorazepam Clonazepam good sedative if daytime anxiety ; √ Anticonvulsant, Panic ; (Also used: social phobia, BPAD manic phase, restless leg syndrome & akathisia) Flurazepam not recommended. Accumulation/hangover →confusion; impairment Triazolam (not generally recommended, Behavioral changes/anterograde amnesia, DI's & withdrawal ; marked rebound insomnia) Less DI's: temazepam, oxazepam & lorazepam	 0.25mg (10mg)	0.5mg po hs 1mg po hs	10 13
Clonazepam -RIVOTRIL <small>g</small> (0.25 ⁵ ; 0.5 ⁵ , 1, 2 ⁵ mg tab)	15mg 2-Keto		0.5-1hr Intermed.(30-60min)	100 (40-250) hr Yes-Desalkyl		 15mg (60mg)	15mg po hs 30mg po hs	10 11
Flurazepam -DALMANE <small>g</small> (15,30mg cap) 	1mg		PO 1-4hr, SL/IM 1hr, IV 5 min	15 (8-24) hr None		 0.5mg (10mg)	0.5mg po hs 1mg po hs	8 9
Lorazepam -ATIVAN <small>g</small> (0.5, 1 ² , 2 ⁵ mg tab); (0.5, 1, 2mg sl* tab; 4mg/ml amp )*	15 3-Hydroxy		1-4hr Intermediate→ slow	8 (3-25) hr None		 10mg (120mg)	15mg po hs 30mg po hs	9 10
Oxazepam -SERAX <small>g</small> (10 ⁵ , 15 ⁵ , 30 ⁵ mg tab)	10mg 3- Hydroxy		2-3hr Intermediate→ slow	11 (3-25) hr None		 15mg (60mg)	15mg po hs 30mg po hs	10 11
Temazepam -RESTORIL <small>g</small> (15,30mg cap)	0.25mg Triazolo		1-2hr affect sleep latency Rapid (15-30min)	2 (1.5-5) hr None		 0.125mg (0.5mg)	0.125mg po hs 0.25mg po hs	12 15
Triazolam -HALCION <small>g</small> (0.125 ⁵ , 0.25 ⁵ mg tab)	500mg		30-60min Rapid (30min)	4 - 8 hr Yes		√Sedative { not recommended : Fatal ≥4gm; DI's; SE: gastric irritation, arrhythmias, rash}	 500mg (2gm)	500mg po hs 1gm po hs
Chloral hydrate - NOCTEC <small>g</small> (500mg/5ml syrup)  	50mg	Antihistamine	1-4 hrs Slow(60-180min)	4 - 8hr None	√ Allergic reactions, sleep aid SE: anticholinergic (dry mouth, urinary retention), cognitive impairment; residual daytime sedation & tolerance	 25mg (200-300mg)	25mg po hs 50mg po hs	<10 <10
Diphenhydramine OTC <small>X</small>  -Benadryl, Nytol, Simply Sleep, Sleep aid, Sleepeze D, Sominex, Unisom <small>g</small> (12.5mg chew ⁵ ; 25, 50mg cap/tab, 1.25mg/ml liquid, 2.5mg/ml elix, 50mg/ml inj)	25mg Antihistamine	2-4hr Slow(60-120min)	10 hr Yes-? Active	√ Sedative/hypnotic -but residual daytime sedation SE: anticholinergic , cognitive impairment	 25mg (75-150mg)	25mg po hs 50mg po hs	10 20	
Doxylamine OTC -UNISOM-2 <small>g</small> (25 mg tab) X  	Phenothiazine Neuroleptic	1-3hr Slow	15-30 hr None	√Antipsychotic, sedative (non addictive), analgesia SE: hypotension, extrapyramidal reactions , anticholinergic, cognitive impairment	 5mg (1000mg)	5-10mg po hs 25-50mg po hs	15 16-20	
Methotrimeprazine NOZINAN <small>g</small> 2.5, 25, 50 mg tab, (5mg/ml soln <small>X</small>  ); (25mg/ml amp <small>X</small>   : Palliative care)	50mg Antidepressant	0.5-2 hr Intermediate	4 - 7.5hr Yes	√ Antidepressant, Agitated dementia , √Sedative- antidepressant induced insomnia SE: orthostatic ↓BP; headache, rare priapism in ♂	12.5 - 25mg  (600mg)	50mg po hs 100mg po hs	10 12	
Trazodone -DESYREL <small>g</small> (50 ⁵ , 100 ⁵ mg tab); (75mg, Dividose 150mg) X  	Or - Mirtazapine Remeron 3.75 - 7.5 - 15mg po hs ≤\$20	Or - Quetiapine Seroquel 12.5-50mg po hs ≤\$25 but off label use	Or - Nortriptyline 10-25mg po hs ≤\$15 In USA: Doxepin Silenor 3,6mg tab 30min pre hs	√ Antidepressant, Sedative-but performance impairment SE: hypotension, anticholinergic, cognitive impairment	10mg  (300mg)	10-25mg po hs 50mg po hs	9-11 15	
Amitriptyline ELAVIL <small>g</small> (10, 25, 50); (75mg <small>X</small>  )	Watch for serotonin syndrome esp. if used with SSRI or MAOI's. Eosinophilia-myalgia syndrome before due to impurities.	15hr Yes- nortriptyline -26hr	<4 hr Slow	√Adjunct in BPAD <small>Bipolar</small> /may potentiate lithium √Sedative- no tolerance reported SE: GI upset, dry mouth, dizzy, headache	 500mg (5gm)	500mg po hs 1g po hs	16 35	
L-Tryptophan-TRYPTAN <small>g</small> (250, 500, 750mg, 1gm tab, 500mg cap) X  	manufactured synthetic metabolite of 5HT	0.5-2hr Slow(60-120min)	1 hr None	Limited studies <small>short & conflicting data</small> ; ?dose; ?jet lag 0.5-5mg SE: headache; ↑heart rate, pruritis, nightmares, ?seizures.	 1mg (5 ⁻¹⁰ mg)	give 2-5hrs before hs	1-3mg po hs 2mg CR po hs	3 5
Melatonin OTC <small>X</small>   (1, 3mg cap, 2mg CR cap; 3mg SL) <small>X</small>  	In USA: Ramelteon ROZEREM X   8mg po hs. DI: cipro, fluvoxamine <small>1A2</small> , rifampin; melatonin receptor agonist. SE: dizziness, nausea, fatigue, headache; ↑prolactin, ↓testosterone.	Can Ped Society 2012: an option for certain kids & adolescents						
Valerian Root OTC <small>-VALERIAN,</small> <small>NYTOL & UNISOM NATURAL SOURCE</small> (400 mg tab) X  	? valepotriates ? valerenic acid ? pyridine alkaloids	Not known (mild effect)	Not known	Limited studies -? dose/sleep aid; Purity concerns SE: nausea, headache, morning <small>hangover</small> , hepatotoxic <small>report</small>	 400mg (800mg)	400mg po hs 800mg po hs	6 10	

Guidelines: Use lowest dose, use agents with **short/intermediate half lives** to avoid daytime sedation, use **intermittent dosing** (2-4 x/wk), use for no more than 3-4 weeks, **D/C gradually**, & be aware of rebound insomnia.
Consider/Rule Out: Depression insomnia may be first Sx, Mania/hypomania, primary sleep disorder (eg **sleep apnea**) altered sleep cycle & other drug use (Decrease total daily dose/change timing of other meds/agents as in Table 1).
Misc products: **Herbal Sleep Aid:** valerian, hops flower, passion flower; **Naturarest:** valerian, St. Johns wort, catnip herb; **Nighty Night Herbal tea:** passion flower, chamomile, catnip, hops. * little effect on sleep structure
 √official indication (TPB/FDA) or use **BZ**=benzodiazepines **DI**=drug interaction **SE**=side effect * **t 1/2 average(range)** half-life: ↑ in geriatric pts & altered by drug interactions **X** =non-formulary Sask.  =↓ dose for renal dysfx c =scored  =not covered NIHB  =covered NIHB
 Found in as adulterants in some herbal products: Estazolam found in Eden Herbal Formulations Sleep Ease & Serenity Pills II, Salt Spring Herbals Sleep Well & in Sleeppees. Other: avoid Kava hepatotoxicity risk without benefit. St John's Wort useful only if depressed.

GOALS OF THERAPY FOR INSOMNIA:

- ♦To improve sleep (ie. decrease time it takes to fall asleep, decrease the frequency of nighttime awakenings & increase the duration of sleep) without dependence on drug therapy
- ♦To improve daytime functioning
- ♦To avoid daytime drowsiness & psychomotor impairment (caution when driving if affected)

GENERAL APPROACH TO INSOMNIA:

Non-pharmacologic

- ♦Resolve any **underlying medical, psychiatric or environmental** causes {e.g. HF, anxiety, depression, sleep apnea, nocturia, pain, thyroid fx, RLS, anemia & chronic pain (for nighttime pain consider long-acting HS analgesic e.g. acetaminophen ER)} {A 24hr Sleep History: useful in evaluating patterns}
- ♦Consider **drug causes** (See Table 1); note common social drug causes (caffeine, alcohol & nicotine)
- ♦**Changing sleep habits, relaxation techniques and cognitive therapy are preferred** for chronic insomnia & often more effective than drugs
- ♦Consider restricting/avoiding daytime naps
- ♦Provide counseling, encouragement & reinforcement

Patient Info^{JAMA}: <http://jama.jamanetwork.com/article.aspx?articleid=196583>

Pharmacologic

- ♦Sedatives should only be used in combination with non-drug measures to promote sleep (see Table 2 - Sleep Hygiene)
- ♦Ideally, sedatives should be taken only for short periods depending on the medication (2-4 weeks)
- ♦Rx sedatives are all equally effective; all to varying degrees, cause daytime drowsiness & confusion {In elderly: benzo-like; **NNT=13**; **NNH=6**; ↑sleep time ½hr; ↓wakings/night 0.6}^{Class}}
- ♦Low doses of short-acting sedatives have a lower risk for side effects when taken on a short-term basis
- ♦Sedatives can be "**habit forming**". Expect **2-3 nights of poor sleep** when stopped. One suggestion is to decrease total sleep time by 20mins 2 nights before stopping the medication. Consider stopping at a low stress time such as on a weekend. Cognitive behavioral techniques can be helpful in 1° insomnia.
- ♦Use the lowest dose possible & only when required; intermittent use (e.g. up to 4 nights/week) sometimes recommended to minimize tolerance & dependence
- ♦Generally, begin with mild agents, and gradually move to more potent medications as necessary
- ♦**Restless Leg Syndrome (RLS)** – see Q&A/Chart – page 78. {dopaminergics (levodopa, pramipexole, ropinirole); clonazepam?. If painful, may consider gabapentin or opiates.}

Table 1: Drug Causes of Insomnia

alcohol [→] fragmented sleep	H ₂ blockers eg. cimetidine	pseudoephedrine
amantadine	interferon	quinidine
amphetamines	ipratropium	salbutamol
aripiprazole*	lamotrigine	salmeterol
atenolol	leuprolide	selegiline
bupropion	levodopa	senna ^{stimulant laxatives}
caffeine ^{effect lasts 8-14hr in elderly e.g. coffee, tea, colas}	medroxyprogesterone	sibutramine
clonidine	methylodopa	SSRI's* (eg. fluoxetine, paroxetine, sertraline)
corticosteroids	methylphenidate	terbutaline
daunorubicin	modafinil	theophylline
decongestants	modafinil	thyroid hormones
dextroamphetamine	nicotine	tranylcypromine
diuretics* ^{if late in the day}	oral contraceptives	venlafaxine
donepezil*	phenylephrine	ziprasidone
fluoxetine	phenytoin	
flutamide	pindolol	
	progesterone	
	propranolol	

* consider dosing in AM

Sleep diary: <http://yoursleep.aasmnet.org/pdf/sleepdiary.pdf>

Table 2: Good Sleep Hygiene Measures

- ♦Maintain a **regular schedule** for bedtime and awakening
- ♦Go to bed only when sleepy
- ♦Avoid daytime naps or going to bed too early in evening.
- ♦Reserve the bedroom for sleep & sexual activity (no TV)
- ♦Avoid **caffeine** & nicotine especially within 4-6hrs of bedtime
- ♦Do not drink alcohol (especially within 4hrs of bedtime), since it causes fragmented sleep
- ♦Avoid heavy meals before going to bed, but a light carbohydrate snack before bedtime is acceptable
- ♦Do not eat chocolate or large amounts of sugar before bedtime
- ♦Avoid drinking excessive amounts of fluid in the evening
- ♦Take "water pills" in the morning or early afternoon
- ♦**Exercise** regularly during the day, but avoid vigorous exercise within 3 hrs of retiring (eg. a walk after supper is a great idea)
- ♦Minimize noise, light & extreme temperature in the bedroom
- ♦Develop relaxing bedtime rituals (eg. reading, listening to music)
- ♦**Get the clock out of visible range** to avoid watching!
- ♦Get out of bed & go to another room if unable to sleep within 20 minutes. Return when sleepy.

Table 3: Sedatives – General Classification & Comments

Classification	Examples	Comments (see also detailed comparison chart)	
Non-BZ but BZ-Like MOA (mechanism of action)	Zopiclone (z) Zolpidem	Imovane Sublinox	♦SysRev's & RCTs: AE rates Z=BZ rates; ↓rebound insomnia & withdrawal ♦NICE Appraisal: lack of clinically useful differences with short-acting BZs ♦ Less tolerance than BZ. Problems: dependence, next day performance
Benzodiazepines (BZ)	Temazepam Oxazepam Lorazepam	Restoril Serax Ativan	♦Significant adverse effects on sleep structure (e.g. ↓REM & Delta sleep) ♦Option for transient, short-term insomnia; clonazepam if long-term/anxiety ♦Problems: tolerance, dependence, withdrawal , ↓ cognition/coordination, disinhibition, ↑risk of accidents & falls; "hangover effect" =residual sedation Impaired next day performance! ↑ risks in overdose if with other CNS depressants!
Antidepressants - Non-TCA	Trazodone Mirtazapine	Desyrel Remeron	♦Trazodone preserves sleep structure ; REM neutral; may ↑Δwave/deep sleep Useful low-dose (≤50-100mg) for long-term sedation in agitated dementia (e.g. sundowning) & antidepressant induced insomnia; non-habit forming. ♦Mirtazapine: may be less sedating at doses above 15mg hs
Antidepressants - TCAs - Off label use	Amitriptyline(3°) Trimipramine (3°) Nortriptyline (2°)	Elavil Surmontil Aventyl	♦Some effect on sleep structure; may ↑Δwave/deep sleep; may be helpful ♦Low-doses of 3° TCAs (e.g. amitriptyline/trimipramine 10-50mg) useful for sleep disorders especially in patients with chronic pain , depression, etc. ♦2° TCAs such as nortriptyline are an alternative for patients who are elderly, intolerant of 3° TCAs or need higher doses for concomitant pain.
Avoid amitriptyline in elderly! Per BEER's list & STOP criteria; see pg 77b.			
Antipsychotics (AP) -Highly sedating SE profile -Off label use	Methotrimeprazine Quetiapine	Nozoran Seroquel	♦Potent/useful in severe insomnia ; non-dependent; rare ↑liver tests ♦Atypical antipsychotics eg. low-dose quetiapine ^{12.5-100mg hs} lack evidence for insomnia & used off label. Reserve for those requiring AP for other reason.
Miscellaneous	see chart p 111		♦Most other sedatives have limited evidence / usefulness; see chart

AE= adverse event; NNT=number needed to treat to benefit; NNH=number needed to treat to harm; RCT=randomized controlled trial; SysRev=systematic review

Prepared by Loren Regier & Brent Jensen in consultation with RxFiles advisors & reviewers.

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SEDATIVE COMPARISON CHART

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