



















SLEEP: SEDATIVE COMPARISON CHART

Generic	-TRADE	Equivalent Dose /Class	Peak Levels/ Onset of action	Average t _{1/2} * /Active Metabolite	COMMENTS	INITIAL & (MAX DOSE)	USUAL SEDATIVE DOSE	\$  /MONTH
Zaleplon (5,10mg cap)	-STARNOC ✗ ♂	5mg pyrazolopyrimidine Gaba A ₁ α ₁	0.9-1.5hr Rapid(15-30min)	1 hr None	Duration of action of ~4 hrs ; little tolerance SE: headache, somnolence, dizziness Least hangover effect; DI: cimetidine & rifampin	 5mg (20mg)	5mg po hs 10mg po hs	25 34
Zopiclone (5, 7.5 ^s mg tab)	-IMOVANE / RHOVANE ✗ ♂	5mg cyclopyrrolone Gaba A ₁	1-1.5hr Rapid (30min)	5 hr Yes	√ Sedative/hypnotic-Good Choice .↓ tolerance SE: dry mouth, bitter taste , residual sedation DI's: erythromycin, ketoconazole, rifampin	 3.75mg (15mg)	5mg po hs 7.5mg po hs (Rhovane less money)	15 16
Clonazepam (0.25 ^x ▼; 0.5 ^s ;1,2 ^s mg tab)	-RIVOTRIL	0.25mg Nitro	1-4hr Intermed. (20-60min)	34 (19-60) hr None	CAUTION: ↑ falls & vehicle accidents in elderly, dependence , may ↓ cognition (esp. long-term use) √ Sedatives/hypnotic-Good BZ choices: temazepam ; possibly oxazepam, lorazepam Clonazepam good sedative if daytime anxiety ; √Anticonvulsant, Panic; (Also used: Social phobia, BPAD Manic phase or for akathisia) Flurazepam (not recommended, Accumulation/hangover →confusion) Triazolam (not recommended, Behavioral changes/anterograde amnesia, DI's & withdrawal effects) Less DI'S: temazepam, oxazepam & lorazepam	 0.25mg (10mg)	0.5mg po hs 1mg po hs	10 15
Flurazepam (15,30mg cap)	-DALMANE	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
Lorazepam (0.5,1 ^s ;2 ^s mg tab); (0.5,1,2mg sl ^v tab;4mg/ml amp⊗) x	-ATIVAN	1mg 3- Hydroxy	PO 1-4hr, SL/IM 1hr, IV 5 min Intermed.(30-60min)	15 (8-24) hr None		 0.5mg (10mg)	0.5mg po hs 1mg po hs	8 9
Oxazepam (10 ^s ;15 ^s ;30 ^s mg tab)	-SERAX	15 3-Hydroxy	1-4 hr Intermediate→slow	8 (3-25) hr None		 10mg (120mg)	15mg po hs 30mg po hs	10 11
Temazepam (15,30mg cap)	-RESTORIL	10mg 3- Hydroxy	2-3 hr Intermediate→slow	11 (3-25) hr None		 15mg (60mg)	15mg po hs 30mg po hs	12 13
Triazolam (0.125 ^s ;0.25 ^s mg tab)	-HALCION	0.25mg Triazolo	1-2hr Rapid (15-30min)	2 (1.5-5) hr None		 0.125mg (0.5mg)	0.125mg po hs 0.25mg po hs	9 10
Chloral hydrate - NOCTEC (500mg/5ml syrup) Ⓢ ⊗		500mg	30-60min Rapid (30min)	4 - 8 hr Yes		√Sedative; (not recommended: Fatal 4-5gm; DI's; SE: gastric irritation, arrhythmias, rash)	 500mg (2gm)	500mg po hs 1gm po hs
Diphenhydramine OTC^x▼ -Benadryl, Nytol, Simply Sleep, Sleep aid, Sleepeze D, Sominex, Unisom (12.5mg chew ^s ; 25,50mg cap/tab, 1.25mg/ml liquid, 2.5mg/ml elix, 50mg/ml inj)		50mg Antihistamine	1-4 hrs Slow(60-180min)	4 - 8hr None	√ Allergic reactions, sleep aid -but residual sedation SE: anticholinergic (dry mouth, urinary retention etc.), cognitive impairment	 25mg (200-300mg)	25mg po hs 50mg po hs	11 11
Doxylamine OTC -UNISOM-2 (25 mg tab) ✗ ⊗		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
Methotrimeprazine (NOZINAN) (2,5,25,50 mg tab, 5mg/ml& 40mg/ml soln); (25mg/ml amp ^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	10 13
Trazodone -DESYREL (50 ^s ;100 ^s mg tab); (75mg, Dividose 150mg) ✗▼ *		50mg Antidepressant	0.5-2 hr Intermediate	4 - 7.5hr Yes	√ Antidepressant, Agitated dementia , √Sedative- antidepressant induced insomnia SE: orthostatic hypotension, priapism	 25mg (600mg)	50mg po hs 100mg po hs	14 18
Amitriptyline ELAVIL (10,25,50); (75mg ✗▼) Or less SE's		Antidepressant Nortriptyline 10-25mg po hs ≤\$15	<4 hr Slow	15hr Yes- nortriptyline -26hr	√ Antidepressant, Sedative-but performance impairment SE: hypotension, anticholinergic,cognitive impairment	 10mg (300mg) ~2hr pre hs	10-25mg po hs 50mg po hs	9-11 15
L-Tryptophan -TRYPTAN (250,500,750mg,1gm tab, 500mg cap) ✗⊗ *		Watch for serotonin syndrome esp. if used with SSRI or MAOI's. Eosinophilia-myalgia syndrome before due to impurities.			√Adjunct in BPAD/may potentiate lithium √ Sedative- no tolerance reported SE: GI upset, dry mouth, dizzy, headache	 500mg (5gm)	500mg po hs 1g po hs	23 46
Melatonin (By Special Access) (1,3mg cap, 2mg CR cap) ✗⊗ *?		mfg synthetic metabolite of 5HT	0.5-2hr Slow(60-120min)	1 hr None	Limited studies-? dose/sedative/jet lag SE: h/a, ↑ heart rate, pruritis, nightmares	 1mg (10mg) give 2hr before hs	1mg po hs 2mg CR po hs	3 5
Valerian Root OTC-VALERIAN, NYTOL & UNISOM NATURAL SOURCE (400 mg tab) ✗⊗ *?		? valepotriates ? valerenic acid ? pyridine alkaloids	Not known (mild effect)	Not known	Limited studies-? dose/sleep aid; Purity concerns SE: nausea,headache,morning hangover	 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: Depressive symptom, 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 (TPPI/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 ✗ =non-formulary Sask. Ⓢ =↓ dose for renal dysfx ⊗ =not covered NIHB ▼ =covered NIHB

SEDATIVES: A CONCISE OVERVIEW

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

GENERAL APPROACH TO INSOMNIA:

Non-pharmacologic

- ♦Resolve any **underlying medical, psychiatric or environmental** causes first
- ♦Consider / rule out **drug causes** (See Table 1); note common social drug causes such as (caffeine, alcohol & nicotine)
- ♦Changing sleep habits, relaxation techniques and cognitive therapy are preferred & often more effective than drugs
- ♦Consider restricting/avoiding daytime naps
- ♦Provide counseling, encouragement, and reinforcement

Pharmacologic

- ♦Sedatives should 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)
- ♦Prescription sedatives are all equally effective and all, to varying degrees, may cause daytime drowsiness & confusion
- ♦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 sleep time by 20mins 2 nights before stopping the medication. Consider stopping at a low stress time such as on a weekend.
- ♦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** Early NEM 03 —assess/replace iron stores; dopaminergics (levodopa, pergolide, pramipexole, ropinirole); clonazepam. If painful, may consider gabapentin or opiates.

Table 1: Drug Causes of Insomnia

alcohol	interferon	propranolol
amantadine	ipratropium	pseudoephedrine
atenolol	lamotrigine	quinidine
bupropion	leuprolide	salbutamol
caffeine e.g. coffee, tea, soft drinks	levodopa	salmeterol
clonidine	medroxyprogesterone	selegiline
corticosteroids	methylodopa	SSRI's* (eg. fluoxetine, paroxetine, sertraline)
daunorubicin	methylphenidate	terbutaline
decongestants	nicotine	theophylline
dextroamphetamine	oral contraceptives	thyroid hormones
diuretics	pemoline	venlafaxine
donepezil	phenylephrine	
fluoxetine	phenytoin	
flutamide	pindolol	
	progesterone	

* consider dosing in AM

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
- ♦Minimize noise, light & extreme temperature in the bedroom
- ♦Exercise regularly during the day, but avoid vigorous exercise within 3 hrs of retiring
- ♦Develop relaxing bedtime rituals (e.g. 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)	Zaleplon Zopiclone	Starnoc Imovane ♦little effect on sleep structure ♦ less problem with tolerance than BZ; still have problem with dependence ♦zaleplon lasts ≤4hr & has least hangover effect ; however limited studies
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, poor cognition/coordination, increased risk of accidents & falls; "hangover effect" = residual sedation
Antidepressants - Non-TCA	Trazodone	Desyrel ♦trazodone preserves normal sleep structure ; REM/ Delta effect neutral ♦useful at low-doses (≤50-100mg) for longer-term sedation in agitated dementia & antidepressant induced insomnia
Antidepressants - TCAs	Amitriptyline(3 ^o) trimipramine (3 ^o) nortriptyline (2 ^o)	Elavil Surmontil Aventyl ♦some effect on sleep structure which may be corrective in some patients ♦low-doses of 3 ^o TCAs (e.g. amitriptyline/trimipramine 10-50mg) useful for sleep disorders especially in patients with chronic pain , depression, etc. ♦2 ^o TCAs such as nortriptyline are an alternative for patients intolerant of amitriptyline, especially if concomitant pain & in elderly
Antipsychotics Highly sedating SE profile	methotrimeprazine	Nozinan ♦potent/useful in severe cases of insomnia ; non-addictive ♦atypical antipsychotics also options; e.g. low-dose quetiapine (Seroquel)
Miscellaneous	see chart	♦most other sedatives have limited evidence / usefulness; see chart

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

We would especially like to thank Dr. S. Shrikhande, Dr. V. Bennett, Dr. L. Thorpe & Dr. F. Remillard for their assistance.

Copyright 2004 Saskatoon Health Region; All Rights Reserved www.RxFiles.ca

DISCLAIMER: The content of this newsletter represents the research, experience and opinions of the authors and not those of the Board or Administration of Saskatoon Health Region. Neither the authors nor Saskatoon Health Region nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information.

Any use of the newsletter will imply acknowledgment of this disclaimer and release any responsibility of Saskatoon Health Region, its employees, servants or agents. Readers are encouraged to confirm the information contained herein with other sources.

References:

Clinical Handbook of Psychotropic Drugs 13th edition 2003 (Bezchlibnyk-Butler,Jeffries)

Drug Information Handbook 10th edition 2002-2003

Drugs in Pregnancy & Lactation 6th edition 2002

Earley CJ. Clinical practice. Restless legs syndrome. N Engl J Med. 2003 May 22;348(21):2103-9. Review.

Eddy M, Walbroehl GS. Insomnia. Am Fam Physician 1999;59:1911-1916.

Geriatric Dosage Handbook 7th Edition 2002

Handbook of Clinical Drug Data 10th edition 2002

Hypnotic Drugs, Medical Letter Aug7/2000

Kupfer DJ, Reynolds CF. Management of insomnia NEJM 1997;336:341-346.

Micromedex 2004

Pharmacotherapy Handbook 2nd edition (Wells,Dipiro et al.)

Schapira AH. Restless legs syndrome: an update on treatment options. Drugs. 2004;64(2):149-58.

Thase, ME. Depression, Sleep, and Antidepressants. J Clin Psychiatry 1998;59(suppl 4):55-65.

The Search for Sleep, Pharmacy Practice Oct/2000 p45-51.

Therapeutic Choices 4th edition 2003

Wagner J, Wagner ML, Hening. Beyond Benzodiazepines: Alternative Pharmacologic Agents for the Treatment of Insomnia. Ann Pharmacother 1998;32:680-91.