PHARMACIST'S LETTER

PL Detail-Document **#301006**

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PHARMACIST'S LETTER / PRESCRIBER'S LETTER

October 2014

PRESCRIBER'S LETTER

Pharmacotherapy of Anxiety Disorders

Treatment options for anxiety disorders include pharmacotherapy and psychological therapy (e.g., cognitive behavioral therapy). They can be used alone or in combination.[1] Treatment choice will depend on factors such as availability of psychological treatment, patient preference and response history, disease severity, comorbidities, and potential side effects and drug interactions.[1,5] Patients should be educated about their disorder and its treatment, including when to expect improvement, side effects, exacerbating factors, and symptoms of relapse. Patients can also be directed to reputable self-help books or websites.[1] Ideally, the goal of therapy is remission, but this might not be achievable, and goals can be individualized.[1] A response is often considered a 25% to 50% improvement on a validated scale such as the Hamilton Anxiety Rating Scale (http://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-ANXIETY.pdf).[1] First- and second-line agents for various anxiety disorders are listed in the chart below, based on efficacy evidence and side effect profiles. SSRIs and SNRIs treat a broad spectrum of symptoms and have efficacy for common comorbidities such as depression, making them good first-line options.[1] Some antidepressants are more activating than others (e.g., fluoxetine, sertraline, SNRIs).[16,24] "Start low, go slow" no matter which agent is chosen, to minimize side effects.[5] **In general, appropriate dosing for off-label agents for anxiety disorders is not well-characterized**. **Therefore, it would be prudent to start low and increase the dose slowly, not exceeding the dosing recommendations for labeled indications**. Some dosing guidance is provided in the chart below. For antidepressants, response may occur at a lower dose than labeled for depression.[12] Discontinue (with tapering, if appropriate) agents that don't provide net benefit.[13]

Abbreviations: PTSD = post-traumatic stress disorder; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Anxiety Disorder	First-Line Agents[a]	Second-Line Agents

Generalized Anxiety Disorder	SSRI or SNRI[1,c]	• Buspirone (*Buspar*; monotherapy or adjunct)[1,7]
		  • Slower onset and considered less effective than benzodiazepines, but no abuse potential.[7]
		• Bupropion XL[1] 150 mg once daily, increased to 300 mg once daily[14]
		• Hydroxyzine[1]
		• Imipramine[1] 10 to 25 mg once daily, titrated to 50 to 100 mg total daily dose[18,22]
		  • Avoid in patients at risk of suicide.[5]
		• Pregabalin (*Lyrica*; monotherapy or adjunct)[1,5]
		  • Good evidence of efficacy compared to other second-line agents [Evidence level A; high-quality RCTs], but side effects may limit use (e.g., drowsiness, dizziness, weight gain, sexual dysfunction [uncommon], abuse potential)[5]
		  • Efficacy may plateau at 300 to 450 mg total daily dose.[8] Renal dose adjustment needed.[9]
		  • Onset as early as one week.[23]
		• Quetiapine SR[1] 150 mg once daily[11]

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Anxiety Disorder	First-Line Agents[a]	Second-Line Agents
Generalized Anxiety Disorder, continued		• Vortioxetine (*Brintellix*, U.S.)[1] (5 to 10 mg once daily effective in some studies).[10] • Benzodiazepine[1,b]
Panic Disorder	SSRI or venlafaxine XR[1,c]	• Mirtazapine (*Remeron*) 7.5 mg once daily, increased to 15 to 30 mg after seven days. Max dose 45 mg once daily.[1,6,15] • Tricyclics (clomipramine [total daily target dose 50 to 150 mg]; imipramine [initial, 10 mg daily; total daily target dose 150 mg; max total daily dose 300 mg])[1,8] • Benzodiazepine[1,b]

Obsessive-Compulsive Disorder	SSRI[1,c]	• Aripiprazole (adjunct)[1] 10 mg once daily[17]
		• Clomipramine[1]
		• Mirtazapine[1]
		• Quetiapine (adjunct)[1] up to a total daily dose of 600 mg[8]
		• Risperidone (adjunct)[1] 2 to 4 mg total daily dose[8]
		• Topiramate (adjunct)
		  • May be more effective for compulsions than obsessions.[19]
		  • Titrate over eight weeks from 25 mg daily to 400 mg max total daily dose.[19]
		• Venlafaxine XR[1]

Social Anxiety Disorder	SSRI or venlafaxine XR[1,c]	• Gabapentin[1] 300 mg twice daily, titrated to 900 to 3600 mg total daily dose.[21] Renal dose adjustment needed.[9]
		• Buspirone (adjunct)[4,5]
		• Pregabalin[1,5]
		  • Efficacy may require 600 mg total daily dose.[1] Renal dose adjustment needed.[9]
		  • Side effects may limit use (e.g., drowsiness, dizziness, weight gain, sexual dysfunction [uncommon], abuse potential).[5]
		• Benzodiazepine[1,b]

Anxiety Disorder	First-Line Agents[a]	Second-Line Agents
Post-Traumatic Stress Disorder	SSRI[1] or venlafaxine XR[1,c]	• Mirtazapine[1] • Eszopiclone (*Lunesta* [U.S.]; adjunct for sleep)[1,20] • Olanzapine (adjunct; consider for hyperarousal and re-experiencing)[1,20] • Risperidone (adjunct; consider for hyperarousal and re-experiencing)[1,20]

a. SSRIs and SNRIs with labeled indication: panic disorder: fluoxetine (U.S.), paroxetine, paroxetine CR, sertraline, venlafaxine XR; social anxiety disorder: paroxetine, paroxetine CR, sertraline (U.S.), venlafaxine XR; obsessive-compulsive disorder: clomipramine, escitalopram (Canada), fluoxetine, fluvoxamine, paroxetine, sertraline; generalized anxiety disorder: duloxetine, escitalopram, paroxetine, venlafaxine XR; post-traumatic stress disorder: paroxetine, sertraline (U.S.)[1-3]

b. Avoid benzodiazepines in patients with substance abuse history.[1,6] Use scheduled doses short-term for acute, severe symptoms; until the SSRI/SNRI starts to work (e.g., four weeks); or long-term for patients who require pharmacotherapy but have failed or don't tolerate other options.[1,4,5] Benzodiazepines can potentiate the CNS depressant effects of other CNS depressants (e.g., pregabalin).[9] Consider clonazepam over alprazolam to minimize abuse and withdrawal.[6] See our *PL Chart*, *Benzodiazepine Toolbox*, for help choosing, dosing, and tapering benzodiazepines.

c. If there is no response after four to six weeks of an SSRI/SNRI, try another SSRI/SNRI, or a second-line agent.[4] For help choosing an agent, see our *PL Chart*, *Choosing and Switching Antidepressants*. SSRIs may be preferred over SNRIs due to tolerability or blood pressure elevation.[5] Paroxetine may be more difficult to discontinue than other SSRIs.[5] In addition, paroxetine has mild anticholinergic effects, and constipation, weight gain, and sedation may be bothersome.[16]

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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Cite this document as follows: PL Detail-Document, Pharmacotherapy of Anxiety Disorders. Pharmacist's Letter/Prescriber's Letter. October 2014.

PHARMACIST'S LETTER *Evidence and Recommendations You Can Trust…* PRESCRIBER'S LETTER

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PL Detail-Document **#300806**
–This PL Detail-Document gives subscribers
additional insight related to the Recommendations published in–
PHARMACIST'S LETTER / PRESCRIBER'S LETTER
August 2014

Benzodiazepine Toolbox

Benzodiazepines are among the treatment options for several conditions. They are not usually the drugs of first choice for chronic use, but they are commonly prescribed. Benzodiazepines carry risks of abuse, dependence, and withdrawal.[1] Hospital admissions for benzodiazepine abuse tripled between 1998 and 2008.[79] Adverse effects include sedation, sleep apnea, cognitive impairment, and falls, especially in the elderly or when combined with opioids.[1] Benzodiazepine use has also been associated with suicidal behaviors, although causation has not been proven.[1] In COPD, benzodiazepines are associated with exacerbations and pneumonia.[77] Benzodiazepine receptor agonists ("Z Drugs," e.g., zolpidem) have not been proven to be safer.[81] Use of hypnotics is associated with increased risk of death regardless of comorbidities.[78] Consequently, questions often arise regarding the safe use of benzodiazepines and Z drugs. To this end, **this toolbox contains information to help you choose the most appropriate agent and dose** based on indication, potential for drug interactions, half-life, liver and kidney function, and age. **Tips for tapering are included**. Chart information may differ from product labeling.

Metabolism of Oral Benzodiazepines and Benzodiazepine Receptor Agonists

This chart provides benzodiazepine metabolic pathways and elimination half-lives. *In general*, a shorter half-life leads to higher dependence liability and more significant withdrawal.[6] Using the lowest effective dose of a longer-half-life agent for the shortest time possible (preferably "as needed") may ease discontinuation.[58] See our *PL Chart*, *Cytochrome P450 Drug Interactions* for help identifying potential drug interactions based on metabolic pathway.

Drug	Half-Life (hours)	Metabolic Pathway	Active Metabolites	Comments
Alprazolam (*Xanax*, etc., generics)	12 to 15[1]	CYP3A4[12]	Yes (clinically insignificant)[1]	
Bromazepam (Canada) (*Lectopam*, generics)	8 to 30[52,b]	CYP1A2 (uncertain), CYP2D6 (uncertain)[50]	Yes (thought to have little clinical effect)[51]	
Chlordiazepoxide (*Librium* [U.S.], generics)	Over 100[1,b]	CYP1A2[12]	Yes[1]	Metabolized to desmethyldiazepam,[a] then to oxazepam.[1]
Clobazam (*Onfi* [U.S.]; *Frisium*, generics [Canada])	10 to 46[52,b]	CYP2C19[12]	Yes[52]	
Clonazepam (*Klonopin* [U.S.], *Clonapam* [Canada], generics)	20 to 50[1]	CYP3A4[12]	Yes (clinically insignificant)[1]	

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Drug	Half-Life (hours)	Metabolic Pathway	Active Metabolites	Comments
Clorazepate (*Tranxene* [U.S.], generics)	Over 100[1,b]	Decarboxylation in GI tract, CYP3A4, CYP2C19[14]	Yes	Prodrug metabolized to desmethyldiazepam (active moiety),[a] then to oxazepam (minor).[14]
Diazepam (*Valium*, generics)	Over 100[1,b]	CYP3A4, CYP2C9, CYP2C19, CYP1A2[12]	Yes[1]	High lipid solubility, fast onset/offset = high abuse potential despite long half-life.[1] Metabolized to temazepam (minor), and desmethyldiazepam (major),[a] then to oxazepam (minor).[1,14]
Estazolam (U.S.)	10 to 24[9]	CYP3A4[9]	Yes (clinically insignificant)[1]	
Eszopiclone (U.S.) (*Lunesta*, generics)	6[15]	CYP3A4, CYP2E1[15]	Yes (much lower potency than eszopiclone)[15]	
Flurazepam (*Dalmane* [Canada], generics)	Over 100[1,b]	CYP3A4[26]	Yes[1]	Avoid in elderly; long half-life[52]
Lorazepam (*Ativan*, generics)	10 to 20[1]	Glucuronidation[1]	No[1]	Preferred in liver disease.[1]
Nitrazepam (Canada) (*Mogadon*, generics)	16 to 55[52]	Hepatic nitroreduction[48]	No[52]	
Oxazepam (*Oxpam* [Canada], generics)	5 to 14[1]	Glucuronidation[1]	No[1]	Preferred in liver disease.[1]
Quazepam (U.S.) (*Doral*, generics)	47 to 100[1,b]	CYP3A4, CYP2C9[25]	Yes[1]	Metabolized to desmethyldiazepam,[a] then to oxazepam.[1]
Temazepam (*Restoril*, generics)	3.5 to 18.4[31]	Glucuronidation[1]	No[1]	Preferred in liver disease.[1]

More. . .

Drug	Half-Life (hours)	Metabolic Pathway	Active Metabolites	Comments
Triazolam (*Halcion* [U.S.], generics)	1.5 to 5.5[6]	CYP3A4[12]	No (presumably)[32]	
Zaleplon (U.S.) (*Sonata*)	1[33]	CYP3A4 (partial)[33]	No[33]	
Zolpidem (*Ambien*, etc., generics [U.S.]; *Sublinox* [Canada])	2.5 (immediate-release formulation)[60]	CYP3A4[12]	No[34,35]	
Zopiclone (Canada) (*Rhovane*, etc., generics)	3.8 to 6.5[36]	CYP3A4, CYP2C8[36]	Yes (minimal)[36]	

a. Long-acting metabolite responsible at least in part for therapeutic and toxic effects of diazepam, clorazepate, chlordiazepoxide, and quazepam.[1,14]
b. Includes active metabolites.

Preferred Oral Benzodiazepine or Benzodiazepine Receptor Agonist per Indication

Benzodiazepines are among the treatment options for several conditions, although they are NOT usually the drugs of first choice. For additional information to help you choose the best agent, see the other tables within this document.

Indication	Preferred Benzodiazepine or Benzodiazepine Receptor Agonist[c]	Comments
Alcohol withdrawal	• Chlordiazepoxide (not a Health Canada-approved indication) or diazepam for long-acting coverage[27,52] • Lorazepam (not an approved indication) or oxazepam if excessive sedation a concern (e.g., elderly, advanced liver disease, serious medical comorbidity)[27]	• Benzodiazepines are the drugs of choice for this indication.[27] • Diazepam has fastest onset of action.[27] • Parenteral forms of diazepam and lorazepam available.
Anxiety	• No agent clearly superior.[1] • Consider agent with medium or long half-life.[2] Clonazepam (not an approved indication), lorazepam, and diazepam are often used.[1] Shorter acting agents pose higher risk of withdrawal, rebound, and dependence.[53]	• Ideally, for short-term use only (e.g., for a few weeks, until antidepressant starts to work, then taper).[1-5,37,82] • Other roles include treatment of patients who have failed other medications (e.g., SSRI, SNRI), patients who cannot tolerate other medication classes, and situational use.[5,37,53,82] • Alprazolam is one of the most abused benzodiazepines; a quick onset leads to euphoria.[1] Accounts for one in ten ER visits in U.S. due to drug misuse.[72] More toxic in overdose than other benzos.[72] Missed doses or discontinuation can cause significant withdrawal

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Indication	Preferred Benzodiazepine or Benzodiazepine Receptor Agonist[c]	Comments
Anxiety, cont.		quickly.[13,58] May be difficult to taper/discontinue.[46] Risk of breakthrough anxiety with immediate-release product.[58] Sustained-release product (U.S.) may have less abuse potential (anxiety not an approved indication).[18,58] • Diazepam has fastest onset (<1 hour), oxazepam slowest (>3 hours).[52] • Diazepam duration of effect shorter than lorazepam despite long half-life.[1] • Consider propranolol for performance anxiety.[73]
Insomnia, sleep onset	Benzodiazepine receptor agonists (a.k.a. Z drugs): • Eszopiclone (*Lunesta* [U.S.])[7,15] • Zaleplon (*Sonata* [U.S.])[7,60] • Zolpidem (*Ambien*, *Ambien CR*, generics; *Edluar*, *ZolpiMist*; *Sublinox* [Canada])[7,60] • Zopiclone (*Rhovane*, etc., generics [Canada])[7,16,36]	• "Z drugs" have less hangover, rebound, tolerance, and dependence, and less effect on sleep cycle than benzos.[16,60] • Eszopiclone has highest risk of hangover of the Z-drugs.[60] • Another first-line option is ramelteon (*Rozerem* [U.S.]).[60] • Triazolam is not a first-line agent due to rebound insomnia and anxiety, and anterograde amnesia.[55,60]
Insomnia, sleep maintenance	Benzodiazepine receptor agonists (a.k.a. Z drugs): • Eszopiclone (*Lunesta* [U.S.])(particularly early morning awakening)[7,60] • Zolpidem (*Ambien*, *Ambien CR*, generics; *Edluar*, *ZolpiMist*; *Sublinox* [Canada])[7,60] • Zopiclone (*Rhovane*, etc., generics [Canada])[7,16,36] • Temazepam (*Restoril*, generics)(particularly early morning awakening)[60] if a benzodiazepine is preferred.	• "Z drugs" have less hangover, rebound, tolerance, and dependence, and less effect on sleep cycle than benzos.[16,60] • Temazepam more likely to cause hangover than Z-drugs.[60] • Low-dose sedating antidepressants (e.g., doxepin, trazodone) are second-line options.[10,11,55,60] • Triazolam not a first-line agent due to rebound insomnia and anxiety, and anterograde amnesia.[55,60]
Insomnia, middle of the night	• Zolpidem (*Intermezzo* [U.S.])	• Provided patient has at least four hours of bedtime remaining.[63]

Indication	Preferred Benzodiazepine or Benzodiazepine Receptor Agonist[c]	Comments
Panic attacks	• Clonazepam (easy to dose; less severe withdrawal than with alprazolam);[13] not a Health Canada-approved indication.[43] • Alprazolam (has most data).[13] • May consider oxazepam; slow onset reduces euphoria (not an approved indication).[13,29,52]	• Benzodiazepines generally not first-line. Can use as adjunct to antidepressant to achieve symptom control acutely or to relieve residual anxiety.[13] • Alprazolam is one of the most abused benzodiazepines; quick onset leads to euphoria.[1] Accounts for one in ten ER visits in U.S. due to drug misuse.[72] More toxic in overdose than other benzos.[72] Missed doses or discontinuation can cause significant withdrawal quickly.[13,58] May be difficult to taper/discontinue.[13] Risk of breakthrough anxiety with immediate-release product. Sustained-release product (U.S.) may have less abuse potential.[58]
Low back pain	Most evidence for diazepam. Consider 2 to 10 mg three or four times daily for five to 14 days only.[22,75,76]	See out *PL Chart, Treatment of Chronic Low Back Pain* for benzodiazepine alternatives.

c. Approved indications in U.S. and Canada unless otherwise specified.

Geriatric Dosing for Anxiety Disorders or Insomnia

Benzodiazepines are among the medications that pose the greatest fall risk in the elderly, especially with high doses.[8] They double the risk of falls, hip fractures, and car accidents.[74] Longer acting agents may pose a higher fall risk than shorter acting agents.[56] The elderly are also prone to benzo-associated confusion, cognitive impairment, paradoxical excitation, and night wandering.[16] Benzos are among the drugs that should generally be avoided in dementia.[61] Consider benzo alternatives first, including nondrug therapy. Benzodiazepine receptor agonists ("Z Drugs," e.g., zolpidem) have not been proven to be safer than benzos.[81] Dose these drugs conservatively when they are needed. In general, geriatric doses are one-third to one-half the recommended adult dose.[52] For any hypnotic, some experts recommend starting at half the usual adult dose and titrating as necessary.[16]

Drug	Oral Dosing[d] (Geriatric dosing unless indicated as "adult" dose)	Comments
Alprazolam (*Xanax*, etc., generics)	Immediate release: Initial: 0.25 mg two or three times daily (anxiety or panic [U.S.]);[17] Canada: 0.125 mg two or three times daily (anxiety)[38] Max adult dose: 4 mg (3 mg Canada) divided three or four times daily (anxiety); 10 mg divided three or four times daily (panic)[17,38] Extended release (U.S.): Initial: 0.5 mg once daily (panic)[18] Max adult dose: 10 mg once daily or divided twice daily (panic)[13,18]	Avoid daily doses over 2 mg in elderly.[61]

Drug	Oral Dosing[d] (Geriatric dosing unless indicated as "adult" dose)	Comments
Bromazepam (Canada) (*Lectopam*, generics)	Initial: 3 mg/day, divided[49] Max adult dose: 60 mg/day, divided[49]	
Chlordiazepoxide (*Librium* [U.S.], generics)	5 mg two to four times daily (anxiety)[20]	Avoid in elderly; long half-life.[52,61]
Clonazepam (*Klonopin* [U.S.], *Clonapam* [Canada], generics)	Geriatric dose not specified; start low and monitor.[21]	Consider renal, hepatic, and cardiac function, drug interactions, and comorbidities when selecting dose.[21]
Clorazepate (*Tranxene* [U.S.], generics)	Initial: 7.5 to 15 mg once daily at bedtime or divided (anxiety [U.S.]);[19] Canada: 3.75 mg once daily, preferably at bedtime (anxiety)[39] Max adult dose: 60 mg once daily at bedtime[h] or divided (anxiety)[19]	Avoid in elderly; long half-life.[52]
Diazepam (*Valium*, generics)	Initial: 2 to 2.5 mg (2 mg Canada) once or twice daily (anxiety)[22,40] Max adult dose: 40 mg divided four times daily (anxiety)[22]	Avoid in elderly; long half-life.[52] Consider monitoring renal function.[22]
Estazolam (U.S.)	Initial: 0.5 to 1 mg at bedtime[23] Max adult dose: 2 mg at bedtime[23]	Not a preferred agent in the elderly.
Eszopiclone (U.S.) (*Lunesta*, generics)	Initial: 1 mg at bedtime[15] Max: 2 mg at bedtime[15]	One of the better options in the elderly for insomnia if appropriately dosed.[7]
Flurazepam (*Dalmane* [Canada], generics)	15 mg at bedtime[24]	Avoid in elderly; long half-life.[52]
Lorazepam (*Ativan*, generics)	Initial: 1 to 2 mg/day, divided;[28] Canada: 0.5 mg once daily (anxiety).[41] (**Note**: Some clinicians start with doses as low as 0.25 mg/dose.) Max adult dose: 10 mg/day, divided (anxiety);[28] Canada: 6 mg/day, divided (anxiety);[41] 4 mg at bedtime (insomnia due to anxiety [U.S.])[28]	Has intermediate half-life, and kinetics not significantly affected by age.[28] One of the better benzodiazepines options in the elderly for anxiety if appropriately dosed. Avoid daily doses over 3 mg in elderly.[62]

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Drug	Oral Dosing[d] (Geriatric dosing unless indicated as "adult" dose)	Comments
Nitrazepam (Canada) (*Mogadon*, generics)	Initial: 2.5 mg at bedtime[48] Max: 5 mg at bedtime[48]	
Oxazepam (*Oxpam* [Canada], generics)	Initial: 10 mg three times daily (anxiety); Canada: 5 mg once daily (anxiety).[42] Max: 15 mg three or four times daily (anxiety)[29] Canada: 5 mg twice daily (anxiety).[42]	Has intermediate half-life, and age (65 to 79 years) does not seem to affect kinetics.[29] One of the better benzodiazepine options in the elderly for anxiety if appropriately dosed. Avoid daily doses over 60 mg in elderly.[62]
Quazepam (U.S.) (*Doral*, generics)	Initial: 7.5 mg at bedtime[30] Max adult dose: 15 mg at bedtime[30]	Avoid in elderly due to long half-life.[62]
Temazepam (*Restoril*, generics)	Initial: 7.5 mg at bedtime[31] (Canada: 15 mg at bedtime)[54] Max adult dose: 30 mg at bedtime[31]	One of the better benzodiazepine options in the elderly for insomnia if appropriately dosed. Avoid doses over 15 mg in elderly.[62]
Triazolam (*Halcion* [U.S.], generics)	Initial: 0.125 mg at bedtime[32] Max: 0.25 mg at bedtime[32]	Avoid in elderly due to risk of anterograde amnesia and cognitive/behavior problems.[16,52]
Zaleplon (U.S.) (*Sonata*)	Initial: 5 mg at bedtime[33] Max: 10 mg at bedtime[33]	One of the better options in the elderly for insomnia if appropriately dosed.[7]
Zolpidem (*Ambien*, etc., generics; *Sublinox* [Canada])	Immediate-release tablet, sublingual tablet (*Edluar*; U.S.), oral spray (*ZolpiMist*, U.S.): 5 mg at bedtime[34,64,65] Extended-release tablet [U.S.]: 6.25 mg at bedtime[35] *Intermezzo* [U.S.]: 1.75 mg taken in the event of a middle-of-the-night awakening, provided at least four hours of bedtime remain.[63]	One of the better options in the elderly for insomnia if appropriately dosed.[7]

More. . .

Drug	Oral Dosing[d] (Geriatric dosing unless indicated as "adult" dose)	Comments
Zopiclone (Canada) (*Rhovane*, etc., generics)	Initial: 3.75 mg at bedtime[36] Max: 7.5 mg at bedtime[36]	One of the better options in the elderly for insomnia if appropriately dosed.[7]

d. Dosing from Canadian labeling included if more conservative than U.S. labeling.
h. Clorazepate: can consolidate to once or twice daily dosing, depending on tolerability, with the majority of the daily dose given at bedtime.[39]

Comparative Dosing of Oral Benzodiazepines and Benzodiazepine Receptor Agonists

Dose equivalencies are **approximate**. Consider indication, dosing frequency, drug interactions, comorbidities, and age when switching. Do not exceed maximum adult dose.

Drug	Approximate Equivalent Daily Dose[1,52]	Indications (adult): initial/max total daily adult dose[e]	Usual Adult Dosing Frequency[f]
Alprazolam (*Xanax*, etc., generics)	1 mg	Immediate release: • Anxiety: 0.75 to 1.5 mg/4 mg (Canada: 0.5 mg to 0.75 mg/3 mg)[17,38] • Panic: 1.5 mg/10 mg (Canada: 0.5 mg to 1.5 mg/10 mg)[17,38] Extended release (U.S.): • Panic: 0.5 to 1 mg/10 mg[18]	• Panic: three or four times daily[13,17,38] (Canada: can start with 0.5 to 1 mg at bedtime)[38] • Anxiety: three times daily (Canada: two or three times daily)[17,38] • Extended release: once or twice daily[13,18]
Bromazepam (Canada) (*Lectopam*, generics)	6 mg	• Anxiety: 6 to 18 mg/60 mg[49]	• Divided[49]
Chlordiazepoxide (*Librium* [U.S.], generics)	20 mg	• Anxiety: 15 to 40 mg (mild to moderate)/60 to 100 mg (severe)[20] • Alcohol withdrawal (U.S.): 50 to 100 mg/300 mg[20]	• Three or four times daily[20]
Clobazam (*Onfi* [U.S.]; *Frisium*, generics [Canada])	20 mg	• Seizures (adjunct): 5 to 10 mg/20 to 80 mg (dosed based on weight)[66] (Canada: 5 to 15 mg/80 mg)[67]	• Divide doses over 5 mg.[66] (Canada: daily doses up to 30 mg can be taken as a single dose at bedtime.)[67]

Drug	**Approximate Equivalent Daily Dose**[1,52]	**Indications (adult): initial/max total daily adult dose**[e]	**Usual Adult Dosing Frequency**[f]
Clorazepate (*Tranxene* [U.S.], generics)	15 mg	• Anxiety: 15 mg/60 mg[19] • Alcohol withdrawal: 60 to 90 mg, then taper[19] (Canada: 30 to 90 mg, then taper)[39] • Seizures, adjunct (U.S.): 22.5 mg/90 mg[19]	• Divided[19] • May give once daily at bedtime[h] for anxiety[19] • Seizures, adjunct (U.S.): three times daily[19]
Clonazepam (*Klonopin* [U.S.], *Clonapam* [Canada], generics)	0.5 mg	• Seizures: 1.5 mg/20 mg[21] (Canada: can use doses >20 mg with caution)[43] • Panic (U.S.): 0.5 mg/4 mg[21]	• Seizures: three times daily[21] • Panic (U.S.): twice daily or at bedtime[21]
Diazepam (*Valium*, generics)	10 mg	• Anxiety: 4 mg to 40 mg, usual dose range[22] • Alcohol withdrawal: 30 to 40 mg, then taper[22] • Muscle spasms (adjunct): 6 mg to 40 mg, usual dose range[22] • Seizures (adjunct; U.S.): 4 to 40 mg, usual dose range[22]	• Anxiety or seizures: two to four times daily[22] • Alcohol withdrawal or muscle spasms: three or four times daily[22]
Estazolam (U.S.)	2 mg	• Insomnia: 1 mg/2 mg[23]	• At bedtime[23]
Eszopiclone (U.S.) (*Lunesta*, generics)	NA	• Insomnia: 1 mg/3 mg[15]	• At bedtime[15]
Flurazepam (*Dalmane* [Canada], generics)	30 mg	• Insomnia: 15 mg (15 to 30 mg in men)/30 mg[24] (Canada: usual dose 30 mg; 15 mg may suffice)[44]	• At bedtime[24]
Lorazepam (*Ativan*, generics)	2 mg	• Anxiety: 2 to 3 mg/10 mg[28] (Canada: 2 mg/6 mg)[41]	• Anxiety: two or three times daily (may give 2 to 4 mg once daily at bedtime for insomnia due to anxiety [U.S.])[28]

Drug	**Approximate Equivalent Daily Dose**[1,52]	**Indications (adult): initial/max <u>total daily</u> adult dose**[e]	**Usual Adult Dosing Frequency**[f]
Nitrazepam (Canada) (*Mogadon*, generics)	10 mg	• <u>Insomnia</u>: 5 to 10 mg (usual dose)[48]	• At bedtime[48]
Oxazepam (*Oxpam* [Canada], generics)	30 mg	• <u>Anxiety</u>: 30 to 120 mg (usual dose)[29] • <u>Alcohol withdrawal</u>: 45 to 120 mg (usual dose);[29] (Canada: 30 to 120 mg)[42]	• Three or four times daily[29] (Canada: three times daily)[42]
Quazepam (U.S.) (*Doral*, generics)	15 mg	• <u>Insomnia</u>: 7.5 mg/15 mg[30]	• At bedtime[30]
Temazepam (*Restoril*, generics)	30 mg	• <u>Insomnia</u>: 7.5 to 15 mg/30 mg[31] (Canada: 15 to 30 mg)[54]	• At bedtime[31]
Triazolam (*Halcion* [U.S.], generics)	0.5 mg	• <u>Insomnia</u>: 0.25 mg (0.125 mg may be sufficient)/ 0.5 mg[32] (Canada [indicated for sleep onset insomnia only]: 0.125 mg/0.5 mg)[45]	• At bedtime[32]
Zaleplon (U.S.) (*Sonata*)	NA	• <u>Insomnia, sleep onset</u>: 10 mg (5 mg may be sufficient for low-weight adults)/20 mg[33]	• At bedtime[33]
Zolpidem (*Ambien, Ambien CR*, etc., generics [U.S.]; *Sublinox* [Canada])	NA	• <u>Insomnia, sleep onset, immediate-release tablet, sublingual tablet (*Edluar* [U.S.]), or oral spray (*ZolpiMist* [U.S.])</u>: 5 mg women, 5 to 10 mg men/ 10 mg (immediate-release tablet)[34,64,65] • <u>Insomnia, sleep onset and/or maintenance, extended-release tablet (U.S.)</u>: 6.25 mg women, 6.25 to 12.5 mg men/12.5 mg[35] • <u>Insomnia, middle-of-the night awakening</u>: 1.75 mg women, 3.5 mg men (*Intermezzo* [U.S.])	• All at bedtime, except *Intermezzo* (for middle-of the-night awakening, provided at least four hours of bedtime remains)[34,35,63-65]

Drug	**Approximate Equivalent Daily Dose**[1,52]	**Indications (adult): initial/max <u>total daily</u> adult dose**[e]	**Usual Adult Dosing Frequency**[f]
Zopiclone (Canada) (*Rhovane*, etc., generics)	NA	• <u>Insomnia</u>: 7.5 mg[36]	• At bedtime[36]

e. Canadian indications and initial/max doses same as U.S. unless otherwise noted. See dosing information for geriatric and hepatic/renal impairment patients in other parts of this document.
f. Labeled Canadian dosing frequency same as U.S. unless otherwise noted.
h. Clorazepate: can consolidate to once or twice daily dosing, depending on tolerability, with the majority of the daily dose given at bedtime.[39]

Dose Adjustment for Hepatic or Renal Impairment

Drug	**Use in Hepatic Impairment**[g]	**Use in Renal Impairment**[g]
Alprazolam (*Xanax*, etc., generics)	<u>Immediate-release</u>: For patients with advanced liver disease, initial dose is 0.25 mg two or three times daily. Check blood counts, blood chemistry, and urinalysis periodically in all patients.[17] (Canada: for patients with advanced liver disease, the usual dose is 0.125 to 0.25 mg two to three times daily. May increase as needed/tolerated.)[38] <u>Extended release (U.S.)</u>: For patients with advanced liver disease, initial dose is 0.5 mg once daily. Check blood counts, blood chemistry, and urinalysis periodically in all patients.[18]	Use caution. Check blood counts, blood chemistry, and urinalysis periodically in all patients.[17,18] (Canada: for patients with advanced renal disease, the usual dose is 0.125 to 0.25 mg two to three times daily. May increase as needed/tolerated.)[38]
Bromazepam (Canada) (*Lectopam*, generics)	Dose cautiously. Follow closely. Check blood counts and liver function tests periodically in all patients.[49]	Dose cautiously. Follow closely. Check blood counts and liver function tests periodically in all patients.[49]

Drug	Use in Hepatic Impairment[g]	Use in Renal Impairment[g]
Chlordiazepoxide (*Librium* [U.S.], generics)	Use caution.[20] Check blood counts and liver function tests periodically in all patients.[71]	Use caution.[20] Check blood counts and liver function tests periodically in all patients.[71]
Clobazam (*Onfi* [U.S.], *Frisium*, generics [Canada])	U.S.: In mild to moderate impairment, initial dose is 5 mg once daily. Then titrate per weight-based dosing in labeling, but use half the usual recommended dose. No dosing information available for severe impairment.[66] Canada: Contraindicated in severe impairment. Use reduced dose in patients with less severe impairment. Check blood counts, liver, renal, and thyroid function tests periodically in all patients.[67]	U.S.: No dose adjustment for mild or moderate renal impairment. No data for severe renal impairment.[66] Canada: Use reduced dose. Check blood counts, liver, renal, and thyroid function tests periodically in all patients.[67]
Clonazepam (*Klonopin* [U.S.], *Clonapam* [Canada], generics)	Contraindicated in significant liver disease. Use caution in patients with less severe impairment. Check blood counts and liver function tests periodically in all patients.[21]	Use caution. Check blood counts and liver function tests periodically in all patients.[21]
Clorazepate (*Tranxene* [U.S.], generics)	Use caution. Check blood counts and liver function tests periodically in all patients.[19]	Use caution. Check blood counts and liver function tests periodically in all patients.[19]
Diazepam (*Valium*, generics)	Contraindicated in severe hepatic insufficiency.[22] In patients with less severe impairment, start with a low dose and increase slowly.[40] Check blood counts and liver function tests periodically in all patients.[22]	Start with a low dose and increase slowly.[40] Check blood counts and liver function tests periodically in all patients.[22]
Estazolam (U.S.)	Caution patients to self-monitor for excessive sedation or cognitive impairment. Check blood counts, blood chemistry, and urinalysis periodically in all patients.[23]	Caution patient to self-monitor for excessive sedation or cognitive impairment. Check blood counts, blood chemistry, and urinalysis periodically in all patients.[23]

Drug	Use in Hepatic Impairment[g]	Use in Renal Impairment[g]
Eszopiclone (U.S.) (*Lunesta*)	For patients with severe liver disease, initial dose is 1 mg at bedtime; max dose 2 mg at bedtime.[15]	Dose adjustment does not appear necessary.[15]
Flurazepam (*Dalmane* [Canada], generics)	Contraindicated in severe hepatic insufficiency. Use caution in patients with less severe impairment. Check blood counts, liver, and kidney function periodically in all patients (Canada).[44]	Use caution. Check blood counts, liver, and kidney function periodically in all patients (Canada).[44]
Lorazepam (*Ativan*, generics)	Use caution. Check blood counts and liver function tests periodically in all patients.[28]	Use caution.[28] Check blood counts and liver function tests periodically in all patients.[28]
Nitrazepam (Canada) (*Mogadon*, generics)	Contraindicated in severe hepatic insufficiency. Use caution in patients with less severe impairment.[48]	Use caution.[48]
Oxazepam (*Oxpam* [Canada], generics)	Use caution.[42] Check blood counts and liver function tests periodically in all patients.[29]	Use caution.[42] Check blood counts and liver function tests periodically in all patients.[29]
Quazepam (U.S.) (*Doral*, generics)	May be more sensitive.[30]	May be more sensitive.[30]
Temazepam (*Restoril*, generics)	Use caution.[31]	Use caution.[31]
Triazolam (*Halcion* [U.S.], generics)	Use caution.[32] (Canada: see geriatric dosing.)[45]	Use caution.[32] (Canada: see geriatric dosing.)[45]
Zaleplon (U.S.) (*Sonata*)	For patients with mild to moderate hepatic impairment, the dose is 5 mg at bedtime. Not recommended for patients with severe hepatic impairment.[33]	No dose adjustment for mild or moderate renal impairment. No data for severe renal impairment.[33]

Drug	Use in Hepatic Impairment[g]	Use in Renal Impairment[g]
Zolpidem (*Ambien*, etc., generics [U.S.]; *Sublinox* [Canada])	See geriatric dosing.[34,35,63-65] Canada: contraindicated in severe hepatic impairment.[68]	Monitor closely.[68]
Zopiclone (Canada) (*Rhovane*, etc., generics)	Contraindicated in severe hepatic insufficiency. For patients with less severe liver impairment, initial dose is 3.75 mg at bedtime; max dose 7.5 mg at bedtime.[36]	Start with 3.75 mg at bedtime.[36]

g. Information from Canadian labeling included if more conservative than U.S. labeling.

Tips for Tapering Oral Benzodiazepines

- Educating cognitively healthy elderly patients about the harms of benzodiazepine use increases by five-fold the likelihood that they will successfully discontinue or at least reduce their benzodiazepine use.[70]
- Tapering benzodiazepines reduces risk of relapse or rebound of condition being treated, and reduces withdrawal symptoms (sweating, tachycardia, muscle cramps, tremor, insomnia, anxiety, agitation, nausea, vomiting, hallucinations, seizures).[1,46]
- Risk factors for withdrawal: use over one year, high dose, short duration of action (e.g., triazolam [*Halcion*], alprazolam [*Xanax*; especially if daily dose >4 mg for >12 weeks], lorazepam [*Ativan*]).[1,46,17,18]
- Withdrawal symptoms have been seen after as little as six to eight weeks of treatment with alprazolam.[13]
- Consider adjunctive cognitive-behavioral therapy, especially in panic disorder.[13,47]
- With use over one year, taper only after condition being treated is well-controlled.[57]
- In general, second half of taper should take longer than first half of taper.[57]
- Depending on taper regimen and patient reliability, pharmacist may need to dispense weekly, twice weekly, or even daily.[59]
- Tapering schedules vary; it is unknown which method is best.[69] There is probably not one "best" method. Individualize based on patient response.[59] Choose a regimen based on drug, dose, duration, and indication. **Some suggested approaches are given below**.
- In panic disorder, taper the benzodiazepine by no more than 10% of the dose weekly, such that the taper is completed over two to four months.[13]
- Alprazolam: decrease by no more than 0.5 mg every three days.[17,18,38] Some patients may need a slower taper (e.g., those taking >4 mg/day for >3 months).[17,18] Per Canadian labeling, if ≥6 mg/day it may be appropriate to decrease by 0.5 mg every two to three weeks. When at 2 mg/day, decrease by 0.25 mg every two to three weeks.[38]

- Direct taper option 1: Decrease by 25% the first week, by 25% the second week, then by about 10% every week. Monitor patient for withdrawal or worsening of condition treated. If needed, continue present dose for a few extra weeks, or return to higher dose if needed.[46]
- Direct taper option 2: Taper to diazepam 10 mg or equivalent, maintain dose for one to two months, then taper over four to eight weeks.[57]
- Direct taper option 3: Taper by 10% every one to two weeks until 20% of the original dose is reached. Then taper by 5% every two to four weeks.[59]
- Direct taper option 4: Taper by no more than diazepam 5 mg or equivalent every week. When diazepam 20 mg or equivalent is reached, slow the rate of taper to 1 to 2 mg diazepam or equivalent per week.[59]
- Clonazepam switch and taper (for patients intolerant of direct taper): For patients taking a benzo dose within the usual therapeutic range, start clonazepam 0.5 mg twice daily. (Some patients may need a higher or lower dose. See "Comparative Dosing," above, for guidance). During the first week of clonazepam, the patient can also take their usual benzo dose "as needed." After the first week, stop "prn" use. (If the patient is uncomfortable, the clonazepam dose may need to be increased temporarily.) Then, decrease the dose of clonazepam by half a tablet every week of two.[80] Or, taper off of clonazepam using one of the other tapering options.[59]
- If low dose use: decrease by 20% each week. Monitor patient for withdrawal or worsening of condition treated. If needed, continue present dose for a few extra weeks, or return to higher dose if needed.[46]
- If short-term use of long-half-life agent: (e.g., up to four weeks' use of clorazepate or clonazepam): taper over one week.[57]

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Cite this PL Detail-Document as follows: PL Detail-Document, Benzodiazepine Toolbox. Pharmacist's Letter/Prescriber's Letter. August 2014.

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