Pharmacotherapy of Anxiety Disorders in Adults

Treatment options for anxiety disorders include pharmacotherapy and non-pharmacological therapy (e.g., cognitive behavioral therapy).[1] They can be used in combination.[1] In older adults, non-pharmacological therapy is preferred first-line for anxiety symptoms.[1] Treatment choice will depend on availability of psychological treatment, symptom severity, patient preference, medical or psychiatric comorbidities (e.g., depression, bipolar disorder, chronic pain), contraindications, response history, and adverse effects.[1,5] Address contributing medications or conditions (e.g., benzodiazepine withdrawal, substance abuse, stimulant use).[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** have a good risk/benefit balance, making them good first-line options.[28] See **footnote a** for more information on SSRIs and SNRIs. **Benzodiazepines** have a limited role (see **footnote b**). **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, using dosing recommendations for labeled indications as a guide**. Some dosing guidance is provided in the chart below. Consider using a validated tool such as the GAD-7, PAS, SPS/SIAS, or OCI-R to assess response.[1,30] For responders, continue treatment for at least six to 12 months.[27,31] For inadequate response, options may include adding/changing psychological therapy, adding a medication, or switching to a different medication, depending on degree of response and tolerability of the first treatment, and the specific remaining symptoms.[5,27] When a medication is discontinued, taper it over weeks or months.[27]

Anxiety Disorder	First-Line Agents[a]	Second-Line Agents
Generalized Anxiety Disorder *Continued…*	SSRI or SNRI[1,5,27,28,a]	Alternative antidepressants: • Bupropion XL. 150 mg once daily, increased to 300 mg once daily after at least four days.[9,14] ○ Little data; avoid in older adults.[1,29] • Vortioxetine. Consider 2.5 to 10 mg once daily.[10] ○ In theory, could help with concentration.[29] ○ Little data; avoid in older adults.[1,27] • Imipramine. Consider 10 to 25 mg once daily, titrated to 75 to 300 mg/day, divided.[27] ○ Avoid in patients at risk of suicide.[27] ○ Avoid in older adults due to anticholinergic effects, sedation, and orthostatic hypotension (Beers Criteria drug).[2] • Mirtazapine. No data in GAD, but is used clinically.[3] Also see **footnote c**. ○ Avoid in older adults due to lack of data.[1] Non-antidepressants • Buspirone (mild-to-moderate GAD).[1,27] FDA- and Health Canada approved indication. ○ Slower onset (seven to ten days; max effect three to four weeks) than benzodiazepines.[16] Not for "as needed" use.[16] ○ Well-tolerated.[7] No abuse potential, physical dependence, or withdrawal.[7,16]

Anxiety Disorder	First-Line Agents[a]	Second-Line Agents
Generalized Anxiety Disorder, continued		○ Generally as effective as benzodiazepines.[7,16] However, it has a reputation for limited effectiveness in clinical practice, and may be less effective in patients previously treated with a benzodiazepine.[27,30] ○ Typical effective daily dose is 30 mg.[7] Starting dose is 7.5 mg BID (5 mg BID or TID daily in older adults).[1,9] Can increase by 5 mg every two to three days.[9] Max dose 60 mg/day max (30 mg/day in older adults) in two (preferred) or three divided doses.[1,9,16] • Pregabalin (monotherapy or adjunct to SSRI or SNRI)[1,5,27] ○ Moderate effect size, at best.[8] ○ Side effects may limit use (e.g., drowsiness, dizziness, weight gain, peripheral edema, sexual dysfunction [uncommon], misuse potential)[5,9] ○ Avoid in elderly.[1] ○ Consider 50 to 150 mg, divided (25 mg once daily in older adults), increased to 150 to 600 mg/day, divided (max 150 mg BID in older adults).[1,27] Reduce dose in kidney impairment.[9] ○ Onset as early as one week.[8] ○ No data with gabapentin, but is used clinically.[7] • Hydroxyzine.[27] ○ Consider for patients with insomnia (e.g., 50 mg at bedtime).[7,27] ○ Usual dose 25 mg up to four times/day.[27] Can be used "as needed."[9] Due to QT prolongation, limit total daily dose to 100 mg (50 mg in elderly).[26] ○ Avoid in older adults due to anticholinergic effects.[2] Beers Criteria drug.[2] • Quetiapine XR. Consider 50 mg once daily, increased to 100 to 200 mg once daily. Max dose 300 mg once daily.[1] ○ Weight gain and metabolic side effects (e.g., insulin resistance).[7] ○ Avoid in frail older adults due to poor tolerability.[1] • Benzodiazepine[1,5,27] (see **footnote b**)
Panic Disorder	SSRI or venlafaxine XR[27,a]	• Mirtazapine. Consider 15 mg once daily with evening meal, increased to 30 mg once daily after two weeks [Evidence level B-1].[6] Also see **footnote c**. • Tricyclics (clomipramine, imipramine, or nortriptyline). Consider 10 to 25 mg/day, increased to 75 to 200 mg/day (clomipramine), or 75 to 300 mg/day, divided (imipramine).[27] • Gabapentin (severe symptoms only).[27] Consider 100 to 300 mg/day, increased to 300 to 3600 mg/day, divided.[27] Reduce dose in kidney impairment.[9] • Benzodiazepine (see **footnote b**)[5,27,29]

Anxiety Disorder	**First-Line Agents[a]**	**Second-Line Agents**
Obsessive-Compulsive Disorder	SSRI[5,a]	Alternative antidepressants: • Clomipramine. FDA- and Health Canada-labeled indication. • Venlafaxine XR.[11] Consider 37.5 to 75 mg once daily titrated every four to seven days to 225 to 300 mg once daily. Alternatively, start with 75 mg once daily for two weeks, then 150 mg once daily for two weeks, then 225 mg once daily for two weeks, then 300 mg once daily.[9] • Mirtazapine (monotherapy or SSRI adjunct).[12,13] See **footnote c**. Non-antidepressants: • Risperidone (SSRI adjunct).[17,18] Consider 0.5 to 3 mg total daily dose.[18] Best-studied augmenting agent.[17] • Aripiprazole (SSRI adjunct).[17,18] Consider 5 to 10 mg once daily.[17] • Memantine (SSRI or clomipramine adjunct). Consider 5 mg once daily, increased by 5 mg every week to 10 mg BID, as tolerated.[9,18] • Lamotrigine (SSRI adjunct).[20] Follow labeled dosing instructions to reduce the risk of serious dermatologic reactions.[9] Consider a target dose of 100 to 200 mg/day.[18] Well-tolerated.[18] • Topiramate (SSRI adjunct)[20] o May be more effective for compulsions than obsessions [Evidence level B-1].[19] o Poorly tolerated.[24] Not all studies have been positive.[19,24] o Titrate over eight weeks from 25 mg daily to 200 mg BID.[9,19] Mean effective total daily dose 175 mg.[18,19]
Social Anxiety Disorder	SSRI or venlafaxine XR[5,27,c]	• Pregabalin[5,27] o Efficacy may require titration to 450 to 600 mg total daily dose.[3] Reduce dose in kidney impairment.[9] o Side effects may limit use (e.g., drowsiness, dizziness, weight gain, sexual dysfunction [uncommon], peripheral edema, abuse potential).[5,9,27] • Gabapentin.[5,27] 100 mg to 300 mg/day, titrated to 900 to 3,600 mg total daily dose.[21,27] Reduce dose in kidney impairment.[9] o Side effects may limit use. See pregabalin, above. • Buspirone (adjunct).[22] Minimal evidence, but good adverse effect profile.[22] • Benzodiazepine (alprazolam, clonazepam).[27] Can use as needed for performance anxiety subtype.[27] (see **footnote b**).

Anxiety Disorder	First-Line Agents[a]	Second-Line Agents
Acute Anxiety in Hospital Patients	Education, relaxation exercises, or brief supportive psychotherapy.[23] Rule out withdrawal from skipped home meds.	• Cautious use of a short-acting benzodiazepine or hypnotic.[23] See our toolbox, *Appropriate Use of Oral Benzodiazepines* or help choosing, dosing, and tapering benzodiazepines • **Melatonin** may have efficacy similar to benzodiazepines for pre-procedural anxiety, without causing respiratory depression, cognitive or psychomotor impairment, or anterograde amnesia [Evidence level B-2].[25] Consider a dose of 3 to 10 mg.[25]

Abbreviations: BID = twice daily; GAD = generalized anxiety disorder; OCI-R = Obsessive Compulsive Inventory-Revised; PAS = Panic and Agoraphobia Scale; SNRI = serotonin norepinephrine reuptake inhibitor; SPS/SIAS = Social Phobia Scale/Social Interaction Anxiety Scale; SSRI = selective serotonin reuptake inhibitor; TID = three times daily.

a. **SSRIs and SNRIs** with labeled indication: **panic disorder**: fluoxetine (US), paroxetine, paroxetine CR, sertraline, venlafaxine XR; **social anxiety disorder**: paroxetine, paroxetine CR, sertraline (US), venlafaxine XR; **obsessive-compulsive disorder**: clomipramine, escitalopram (Canada), fluoxetine, fluvoxamine, paroxetine, sertraline; **generalized anxiety disorder**: duloxetine, escitalopram, paroxetine, venlafaxine XR.
   - SSRIs have a broad spectrum of efficacy, and may be preferred over SNRIs due to tolerability or blood pressure elevation.[5] However, an SNRI might be preferred for patients with comorbid chronic pain.[29]
   - Some antidepressants are more activating than others (e.g., fluoxetine, SNRIs).[16] Give SNRIs or SSRIs no later than midday, at least initially, to minimize agitation and insomnia.[4]
   - The antidepressant starting dose for anxiety disorders should generally be lower than the starting dose for depression.[29] In practice, the effective dose is often the same or higher than in depression although clinical trials have not clearly shown a dose-response relationship.[5,29] In patients with a history of worsening anxiety with serotonergic drugs, consider starting with half the usual starting dose.[1]
   - Avoid paroxetine in older adults due to anticholinergic effects and drug interactions (i.e., strong CYP2D6 inhibition).[1] Weight gain and sedation may be bothersome.[15] Paroxetine may be more difficult to discontinue than other SSRIs.[5]
   - Generally, expect at least some response by two to four weeks (eight weeks for OCD), and up to 12 weeks for maximum effect.[1,5,18,27,29,30] For help switching to another SSRI or SNRI, see our chart, *Choosing and Switching Antidepressants*.

b. **Benzodiazepines**. Avoid in patients with substance abuse history.[28] Use scheduled doses short-term for acute, severe symptoms; until the SSRI/SNRI starts to work; or long-term for patients who require pharmacotherapy but have failed or don't tolerate other options (e.g., have tried at least three other therapies).[1,4,5,27,29,30] Benzodiazepines can potentiate the CNS depressant effects of other CNS depressants (e.g., pregabalin).[9] Could hamper cognitive behavioral therapy.[27] Consider clonazepam over alprazolam to minimize abuse and withdrawal.[16] See our toolbox, *Appropriate Use of Oral Benzodiazepines* or help choosing, dosing, and tapering benzodiazepines.

c. **Mirtazapine**. Unlikely to worsen anxiety.[16] Sedating, especially at doses ≤30 mg. Less sedating at higher doses (45 mg) due to more noradrenergic activity.[15] Due to paucity of data to guide dosing, consider dosing as for depression (15 mg at bedtime, increased every one to two weeks to a maximum of 45 mg/day).[9] When using as an SSRI adjunct, monitor for serotonergic side effects, central nervous system effects (e.g., sedation), and QT prolongation.[9]

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*****	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*****	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician 2004;69:548-56. https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

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