Medication Treatment for Adults with Generalized Anxiety Disorder

- Generalized Anxiety Disorder (GAD) frequently has a waxing and waning course, so medication treatment should continue for 6-12 months after remission to reduce risk of relapse.[1]
- It is useful to monitor for clinically meaning improvement of symptoms and function using the Hamilton Anxiety Scale (HAM-A), the Generalized Anxiety Disorder-7 (GAD-7), or another validated grading scale routinely used in the provider's practice.
- At any point before or during treatment, immediate referral is needed for patients with severe anxiety and marked functional impairment in conjunction with:
  - Risk of self-harm or suicide, or
  - Significant comorbidity, such as substance misuse, personality disorder or complex physical health problems, or
  - Self-neglect.[2]

This guidance may be helpful to the primary care provider to complement their clinical judgement.

Primary Therapy

First-line Treatment

- The selective serotonin reuptake inhibitors (SSRI) **escitalopram** or **sertraline**, or alternatively the serotonin norepinephrine reuptake inhibitors (SNRI) **duloxetine** or **extended-release venlafaxine**, are recommended as first-line primary treatment for GAD regardless of baseline symptom severity based on high-quality evidence for efficacy (symptoms, remission), fewer drug interactions relative to other SSRIs and SNRIs, and overall tolerability.[1,3-6]
- SSRIs are generally better tolerated at higher doses than SNRIs. Consider the overall side-effect profile, drug interactions, and patient preference before prescribing treatment.

Other Primary Treatment Options

Generally, non-SSRI/SNRI antidepressants lack evidence of effectiveness or may not be well tolerated.[13] However, a few may be worth trying, especially if there are other indications for doing so:

- The tricyclic antidepressant **imipramine** is effective for treatment of GAD.[1,4] However, side effects and potential for toxicity limits its use.
- Limited evidence suggests **extended-release bupropion** may be as effective as escitalopram.[7]

See Appendix for example treatment algorithm.

Adjunctive Therapy

Adjunctive treatment may be effective in adults with GAD who have had an inadequate response (e.g., < 50% improvement in HAM-A) to multiple trials of antidepressants after adequate adherence, dosage and therapy duration (4-6 weeks) are confirmed.[1] However, adjunctive therapy may add additional complexity:

- If improvement occurs with adjunctive therapy, it may be unclear whether it is due to the second medication or the combination of medications.
- Combination therapy also increases risk of adverse effects and drug interactions.

First-line Adjunct Treatment

- The anticonvulsant **pregabalin** is effective for treatment of GAD based on high-quality evidence.[1,3,4,8] Pregabalin is recommended as a first-line adjunct with an SSRI or SNRI, but it can also be used as a primary treatment option for patients who cannot tolerate antidepressants.[2] However, not everyone will tolerate pregabalin well. It is also a controlled substance with potential for abuse.

Second-line Adjunct Treatment

- **Buspirone** may be effective for the treatment of GAD.[1,5] However, there is low quality evidence for effectiveness versus first-line antidepressants, and buspirone has a slow onset of therapeutic effect (4-6 weeks) and short half-life which requires frequent daily dosing.[1]

See Appendix for example treatment algorithm.

Other Adjunct Treatments

- **Extended-release quetiapine**, a second-generation antipsychotic, has moderate evidence for the management of GAD and may be as effective as antidepressants.[10-13] However, sedation, metabolic side effects and poor tolerability limits use.[4,12,13] Quetiapine ER should be reserved after other adjuncts have been tried, and a specialist should be consulted.
- **Hydroxyzine** may be as effective for the treatment of GAD, but sedation, anticholinergic effects, and limited clinical experience are barriers to long-term use.[1,17]
- Benzodiazepines like **diazepam** or **lorazepam** can provide immediate, short-term relief of somatic symptoms of GAD, but at increased risk for adverse events.[3,14,15] This strategy can be especially useful in patients with severe symptoms of GAD during the first weeks of antidepressant treatment.[1]
    - Use with caution for longer than 2 weeks because regular use increases risk of abuse, misuse, addiction, physical dependence and withdrawal reactions.[16]
    - Withdrawal from benzodiazepines after regular use is a complex process and highly variable between individuals. Providers should consult MHCAG guidance for tapering off benzodiazepines.

Medication Dosing for GAD in Older adults and Pregnancy

- Use these medications with great caution in older adults, who are more susceptible to adverse effects of psychoactive medications. Start at low doses and titrate slowly with dose adjustments no more than every 2 weeks. Drug-drug interactions are also more common in older adults who may be on multiple medications which can interact with each other and increase risk for intolerances and adverse effects.
- Many of these medications cross the placenta but there is little documented evidence of teratogenic effects. Until more information is available, administer these medications during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.
- A pregnancy registry (National Pregnancy Registry for Antidepressants) is available for antidepressants; healthcare providers can register patients by contacting 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants.
- A North American Antiepileptic Drug (NAAED) Pregnancy Registry has been established to monitor the effects of *in utero* exposure to pregabalin, and patients are encouraged to enroll themselves by calling 1-888-233-2334. Patients may also obtain information on the NAAED website: www.aedpregnancyregistry.org/
- Use benzodiazepines during pregnancy only during serious or life-threatening emergencies where safer drugs cannot be used or are ineffective.

Discontinuation of Treatment

- *Continue treatment of GAD for at least 6-12 months. Do not discontinue more than one medication for GAD at a time, and only after almost all symptoms are gone. Tapering off SSRIs, SNRIs, quetiapine can take 3 to 6 months or longer.* Tapering off benzodiazepines *can take much longer and must be individualized.*

You can get this document in other languages, large print, braille or a format you prefer.
Contact Oregon Prescription Drug Program, Amanda Parish at 503-383-8142 or email amanda.b.parish@dhsoha.state.or.us.
We accept all relay calls or you can dial 711.

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Oregon Health Authority
HEALTH POLICY AND ANALYTICS
Office of Delivery Systems Innovation

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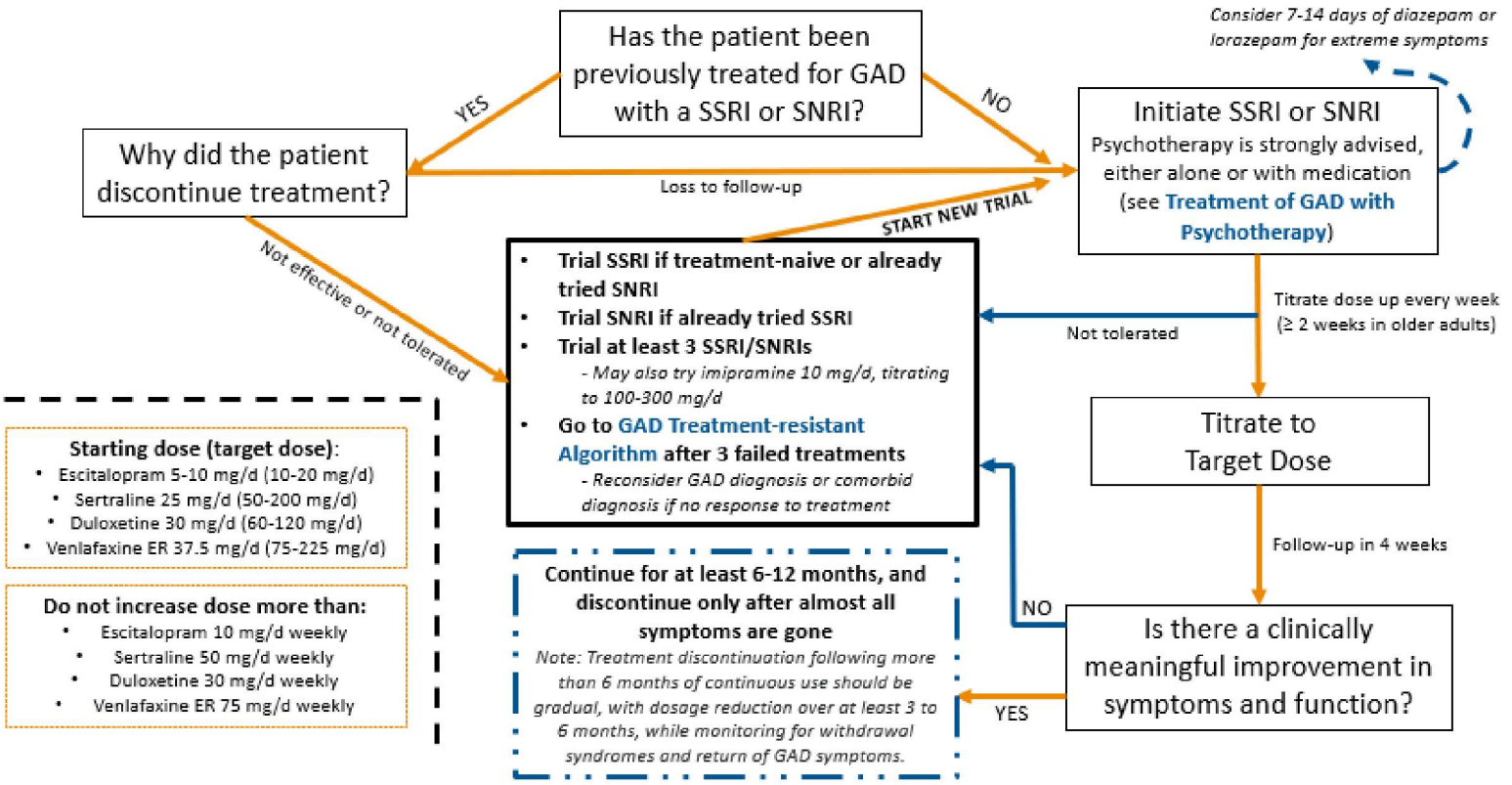
Appendix

GENERALIZED ANXIETY DISORDER TREATMENT ALGORITHM



GENERALIZED ANXIETY DISORDER TREATMENT-RESISTANT ALGORITHM