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Prior Authorization Criteria Update: Low-Dose Quetiapine

Conclusions:

- Quetiapine is not well tolerated in people with generalized anxiety disorder (GAD), but there is moderate quality evidence that extended-release (ER) quetiapine improves anxiety symptoms, improves function and induces remission of GAD, as evidenced by statistically significant improvement in Hamilton Anxiety Scale (HAM-A) scores from multiple randomized placebo-controlled trials.

Policy Recommendations:

- Update clinical prior authorization (PA) criteria to allow coverage of quetiapine ER for GAD, as proposed.

Background and Recommendations from the Mental Health Clinical Advisory Group:

The Mental Health Clinical Advisory Group (MHCAG), tasked by the Oregon legislature to develop evidence-based treatment guidelines for mental health disorders, published a treatment algorithm for GAD in 2023 (see **Appendix 1**). The MHCAG recommend extended-release (ER) quetiapine, in consultation with a mental health provider, as an adjunctive treatment option after other recommended adjuncts have been tried. Current Oregon Health Plan (OHP) fee-for-service clinical PA criteria do not permit coverage of quetiapine ER for GAD. The tolerability and safety of quetiapine is already established: sedation, dyslipidemia, hyperglycemia, weight gain, and rare but fatal arrhythmias from QT prolongation, require routine monitoring and limit broad use of the drug except when needed. This brief review summarizes the efficacy of quetiapine ER in people with GAD to determine if the current clinical PA criteria should be changed to allow off-label coverage of quetiapine ER for GAD when prescribed by, or in consultation with, a mental health provider.

Evidence Summary:

Four high-quality systematic reviews were identified that evaluated the efficacy and tolerability of quetiapine ER for treatment of GAD. Trials compared quetiapine to placebo and SSRIs. The primary efficacy endpoint used to assess improvement in anxiety symptoms, treatment response, and remission was the HAM-A. Study durations were 10 to 14 weeks.

A systematic review and meta-analysis of double-blind, randomized controlled trials (RCTs) reviewed the comparative remission rates and tolerability of medications for GAD. GAD remission rates (HAM-A scores ≤7) and tolerability with quetiapine ER were studied in 4 eligible trials at daily doses of 50 mg, 150 mg and 300 mg.[1] Quetiapine was found to be superior to placebo at inducing remission in patients with GAD (OR 1.88; 95% CI, 1.39-2.55) but was also much less tolerable than placebo, leading to more treatment discontinuations due to adverse events (OR 4.05; 95% CI, 2.89-5.65).[1]

A systematic review and meta-analysis of 3 RCTs (n=2,678) reviewed the efficacy (HAM-A) and tolerability (discontinuation rates due to adverse events) of quetiapine ER in patients with GAD.[2] Mean differences in HAM-A scores were 2.19 points lower (95% CI, -2.94 to -1.45) with quetiapine than with placebo.[2] Quetiapine also resulted in both higher response rates (≥50% HAMA-A reduction) than placebo (RR 1.24; 95% CI, 1.16 to 1.32) and higher remission rates (HAMA-A ≤7) than placebo (RR 1.27; 95% CI, 1.13 to 1.42).[2] The 50 mg, 150 mg, 300 mg daily doses of quetiapine studied all showed statistically significant

reductions in HAM-A scores versus placebo, but only the 50 mg and 150 mg daily doses resulted in statistically significant higher response and remission rates.[2] The 2 eligible trials that compared quetiapine ER to an SSRI did not find statistically significant differences in any efficacy endpoints between the groups studied.[2] Quetiapine was less tolerable than placebo, as evidenced by overall higher discontinuation rates due to adverse events (RR 3.18; 95% CI, 2.52 to 4.00).[2] Only the quetiapine 50 mg daily dose was comparable in tolerability to SSRIs; higher doses were subject to higher discontinuation rates due to adverse events.[2]

A systematic review and meta-analysis analyzed evidence for off-label uses of second-generation antipsychotics in adults, including quetiapine for GAD.[3] The review included some trials that overlapped with the systematic reviews previously described. Data from the trials that could be pooled showed that quetiapine ER resulted in a 26% increase in the chance of treatment response at 8 weeks (≥50% HAMA-A reduction; number needed-to-treat = 8) for quetiapine ER in patients with GAD at daily doses of 50 mg to 300 mg.[3] No differences in efficacy were identified when quetiapine was compared to escitalopram or paroxetine for treatment of GAD.[3]

The most recently published systematic review included clinical trials of all medications that have been studied for treatment GAD, including SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), pregabalin, bupropion, imipramine, mirtazapine, buspirone, hydroxyzine, quetiapine, benzodiazepines and others.[4] By meta-analysis, the study found that quetiapine had the largest effect on HAM-A versus placebo than any of the other medications studied (mean difference vs. placebo: -3.60; 95% CI, -4.83 to -2.39), but it was also poorly tolerated versus placebo as evidenced by higher study discontinuation (OR 1.44; 95% CI, 1.16 to 1.80).[4]

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Appendix 1. MHCAG GAD Algorithms

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.*

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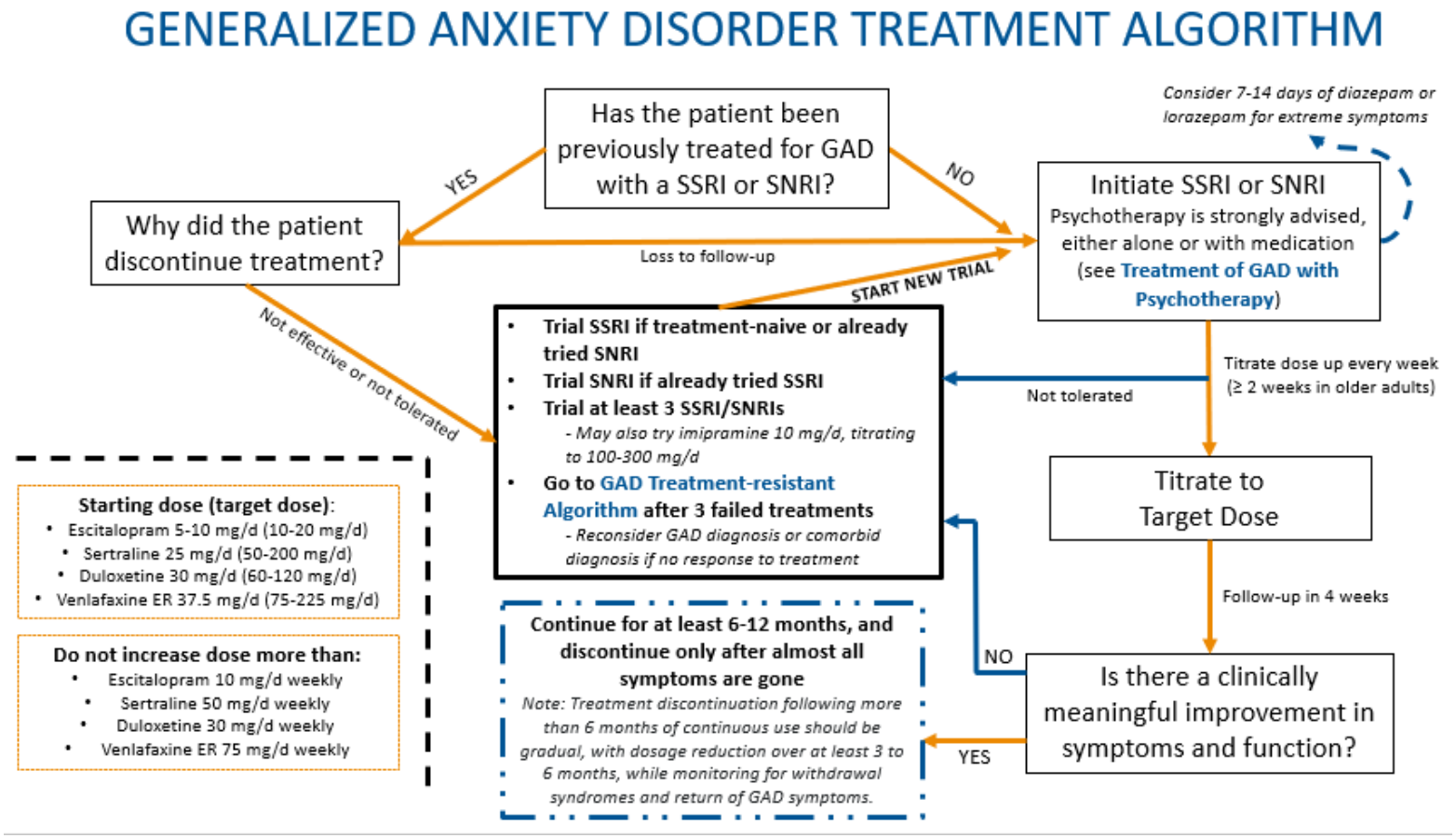
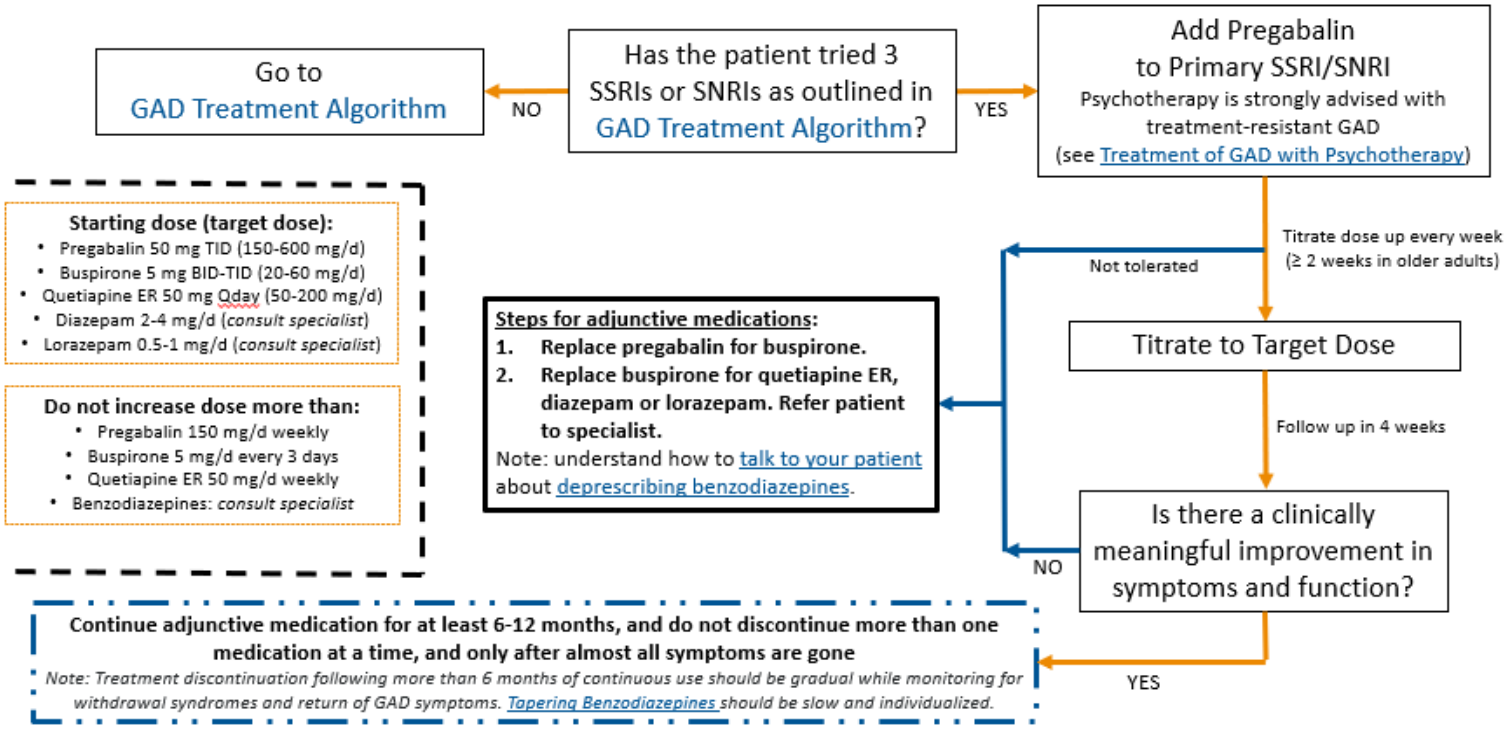
Appendix



GENERALIZED ANXIETY DISORDER TREATMENT-RESISTANT ALGORITHM



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