Medication Audit Criteria and Guidelines

Tricyclic Antidepressants: Amitriptyline (Elavil®), Amoxapine (Asendin®), Clomipramine (Anafranil®), Desipramine (Norpramin®), Doxepin (Sinequan®), Imipramine (Tofranil®), Maprotiline (Ludiomil®), Nortriptyline (Pamelor®), Protriptyline (Vivactil®), Trimipramine (Surmontil®)

PEFC Approved: July 2022

Indications

This document lists only FDA-approved indications from the product labeling. The PEFC acknowledges that there are off-label indications for use that have supporting evidence for efficacy. If a medication is prescribed for an off-label indication, documentation in the patient chart is recommended.

- Amitriptyline: major depressive disorder, neuropathy due to diabetes mellitus
- Amoxapine: major depressive disorder, severe depression with psychotic features
- Clomipramine: obsessive–compulsive disorder
- Desipramine: major depressive disorder
- Doxepin: depression and/or anxiety associated with alcoholism, major depressive disorder, depression–psychotic disorder, insomnia
- Imipramine: major depressive disorder
- Maprotiline: bipolar disorder–depressed phase, major depressive disorder, dysthymia, mixed anxiety and depressive disorder
- Nortriptyline: major depressive disorder
- Protriptyline: major depressive disorder
- Trimipramine: major depressive disorder

Black Box Warning

- Increased risk of suicidal thinking and behavior in children, adolescents and young adults (≤ 24 years) taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors.

Contraindications

- Concomitant use of MAOIs, including linezolid and IV methylene blue, use of MAOIs within 14 days of trimipramine discontinuation, or use of trimipramine

within 14 days of discontinuing an MAOI; increased risk of serotonin syndrome
- Hypersensitivity to agent or other dibenzazepines; risk of cross-sensitivity reaction
- Myocardial infarction, during the acute recovery period (except doxepin)
- Coadministration with cisapride; may cause QT interval prolongation and increase the risk of arrhythmia (amitriptyline and protriptyline)
- Glaucoma, untreated narrow angle (doxepin)
- Urinary retention, tendency towards or severe (doxepin)
- Known or suspected seizure disorders (maprotiline)

Warnings and Precautions

- Activation of mania/hypomania
- Angle-closure glaucoma
- Avoid with alcohol (doxepin)
- Blood dyscrasias
- Blood sugar increases or decreases may occur with TCA use
- Cardiovascular disease due to an increased risk of myocardial infarction, stroke, congestive heart failure, cardiac conduction defects, arrhythmias, and tachycardia
- Complex sleep-related behaviors may occur (doxepin)
- Concomitant use with agents that impair metabolism of serotonin (e.g., MAO inhibitors including phenelzine, tranylcypromine, linezolid, methylene blue)
- Concomitant use with other serotonergic agents (e.g., SSRIs, SNRIs, triptans, TCAs, fentanyl, lithium, tramadol, buspirone, St John's wort, tryptophan)
- Diagnosis of a seizure disorder or history of seizures
- Discontinuation syndrome
- Disease states where increased anticholinergic activity may complicate disease course (narrow-angle glaucoma, benign prostatic hypertrophy, urinary retention)
- Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported (clomipramine)
- Elderly patients may show a greater predisposition to adverse effects
- Elective surgery - discontinue drug several days before surgery if possible
- Electroconvulsive therapy (ECT) - limit concurrent use to essential treatment, as greater electroshock hazards may occur
- Extrapyramidal symptoms (amoxapine, doxepin, trimipramine)
- Hepatic function impairment
- Hyperthermia (clomipramine)

- Hyperthyroidism or hypothyroidism (e.g., patients receiving thyroid supplementation) due to the risk of cardiovascular toxicity
- Hyponatremia, increased risk in elderly, volume-depleted patients, and with concomitant use of diuretics (clomipramine)
- Male sexual dysfunction (clomipramine)
- Neuroleptic malignant syndrome (amoxapine, clomipramine)
- Photosensitivity (imipramine)
- Psychosis may occur in patients with schizophrenia
- Serotonin syndrome
- Severe sleep apnea – not recommended to use (doxepin)
- Significant renal impairment (clomipramine, imipramine)
- Significant weight gain (clomipramine)
- Stroke
- Tardive dyskinesia (amoxapine)

Adverse Reactions

Side Effects Which Require Medical Attention

- Anticholinergic side effects (blurred vision, constipation, urinary retention, xerostomia, cognitive impairment, delirium)
- Blood dyscrasias
- Cardiovascular (heart block, heart failure, myocardial infarction, orthostatic hypotension prolonged QT interval, sudden cardiac death, tachycardia)
- CNS depression (fatigue, somnolence)
- Discontinuation syndrome
- Extrapyramidal symptoms (amoxapine, doxepin, trimipramine)
- Hepatotoxicity and jaundice
- Hyperglycemia or hypoglycemia
- Hyperthermia (amoxapine, clomipramine, desipramine)
- Nephrotoxicity (doxepin, imipramine, trimipramine)
- Neuroleptic malignant syndrome (amitriptyline, amoxapine, desipramine, nortriptyline, trimipramine)
- Orthostatic hypotension
- Reduced seizure threshold
- Serotonin syndrome
- Sexual function impairment
- Stroke
- Symptoms of prolactin elevation (galactorrhea, amenorrhea, gynecomastia) (amoxapine)
- Syndrome of inappropriate antidiuretic hormone secretion
- Tardive dyskinesia (amoxapine, doxepin, trimipramine)
- Tremor

- Weight changes

Drug Interactions of Major Significance

- Concomitant use with strong inhibitors or inducers of Cytochrome 450. The following are the major metabolic pathways for the tricyclic antidepressants:
  - Amitriptyline: Substrate of 2C19 and 2D6
  - Clomipramine: Substrate of 1A2, and 2D6, inhibitor of 2D6
  - Desipramine: Substrate of 2D6
  - Doxepin: Substrate of 2C19 and 2D6, inhibitor of 2D6
  - Imipramine: Substrate of 2D6
  - Nortriptyline: Substrate of 2D6

See: Indiana Univ Drug Interaction Table

See: Lexicomp, Micromedex for more information

Special Populations

- Pediatrics/Adolescents
  - Clomipramine: See "Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health (6th Version)" for specific details.
  - Imipramine: Reviewed but not included/ recommended by the Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health (6th Version)
  - Amitriptyline, amoxapine, desipramine, doxepin, maprotiline, nortriptyline, protriptyline, and trimipramine: Safety and effectiveness not established in pediatric patients
- Geriatric
  - Avoid use in elderly patients
  - Usually require lower dose and more gradual dose titrations to minimize adverse effects
- Renal
  - Patients with reduced renal function may require reduced doses (except amoxapine, maprotiline, and protriptyline)
- Hepatic
  - Patients with liver disease may require reduced doses (except amoxapine and protriptyline)
- Hemodialysis
  - No dosage adjustments provided in the manufacturer's labeling
- Pregnancy and Breastfeeding
  - Review product-specific labeling. Consider risks/benefits in reviewing medication-specific labeling

Patient Monitoring Parameters

Baseline Tests:

- Pregnancy test (females)
- Blood pressure and heart rate
- ECG
- Hepatic function panel (clomipramine)
- Sodium level in high risk patients (e.g., older than 65 years, previous history of antidepressant-induced hyponatremia, low body weight, concomitant use of thiazides or other hyponatremia-inducing agents, experiencing symptoms of hyponatremia)
- Weight
- TD assessment (amoxapine only)
- EPS evaluation (exam for rigidity, tremor, akathisia) (amoxapine only)
- Height & weight (children & adolescents)

Ongoing:

- Pregnancy test (females) as clinically indicated
- Blood pressure and heart rate during dosage titration and as clinically indicated
- ECG as clinically indicated
- Hepatic function panel (clomipramine) as clinically indicated
- Sodium level in high-risk patients, 4 weeks and as clinically indicated
- Therapeutic blood levels (not amoxapine) as clinically indicated
- Weight at 3, 6, and 12 months, then yearly
- TD and EPS assessment every 3 months and as clinically indicated (amoxapine only)
- Monitor for emergence of suicidal ideation or behavior
- Prolactin level yearly if symptoms of prolactin elevation (e.g., gynecomastia, amenorrhea)
- Height & weight (children & adolescents) as clinically indicated

Dosing

- See HHSC Psychiatric Drug Formulary for dosage guidelines
- Exceptions to maximum dosage must be justified as per medication rule