Texas Vendor Drug Program

Drug Use Criteria: Antidepressant Drugs – Other

Publication History

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Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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TEXAS Health and Human Services | Medical and Social Services

1 Dosage

1.1 Adults

The FDA requires that all antidepressant drugs display a black box warning describing the potential for increased suicidal thinking and behavior when prescribed to young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders. In short-term clinical trials, the suicide risk was increased in young adults managed with antidepressants compared to those receiving placebo in the first few months of treatment. Suicide risk was not shown to increase in adults over 24 years of age, and patients 65 years of age and older manifested a decreased suicide risk. Young adult patients prescribed antidepressant drugs should be closely monitored for changes in behavior.

Nonselective serotonin reuptake inhibitor monotherapy antidepressant drugs are FDA-approved for use in MDD, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and panic disorder (PD). Additionally, bupropion is FDA-approved for seasonal affective disorder (AD) and smoking cessation (SC), milnacipran is FDA-approved for fibromyalgia (F) management, and duloxetine is FDA-approved for neuropathic pain (NP), F, and chronic musculoskeletal pain in adults (CMP). Recently, doxepin has received FDA approval for insomnia in adults (I). Vilazodone, a selective serotonin reuptake inhibitor (SSRI) as well as a partial agonist at the 5-HT1A receptor, is FDA-approved for MDD. Levomilnacipran (Fetzima®), a serotonin and norepinephrine reuptake inhibitor (SNRI) and an enantiomer of milnacipran, has also been FDA-approved for use in treating MDD. The antidepressant agent, vortioxetine, an SSRI that also acts as an agonist at 5-HT1A receptors and an antagonist at 5-HT3 receptors, has gained FDA approval to manage MDD. Combination therapy is FDA-approved for severe depression, treatment-resistant depression (TRD), and moderate anxiety/agitation/depression.

Maximum recommended daily doses for antidepressant drugs in adults, including the elderly population, are summarized in Tables 1-6. Maximum recommended dosages for antidepressant combination therapy are summarized in Table 7. However, in all patients, the lowest effective antidepressant dose should be utilized to minimize unwanted adverse effects. Patient profiles with antidepressant dosages exceeding these recommendations will be reviewed.

Table 1: Table 1. Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) - Tricyclic Antidepressants

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	amitriptyline (generics)	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg tablets	• Less than or equal to 65 years: 150 mg/day • Greater than 65 years: 150 mg/day
MDD	amoxapine (generics)	25 mg, 50 mg, 100 mg, 150 mg tablets	• Less than or equal to 65 years: 300 mg/day* • Greater than 65 years: 300 mg/day*
OCD	clomipramine (Anafranil®, generics)	25 mg, 50 mg 75 mg capsules	• Less than or equal to 65 years: 250 mg/day • Greater than 65 years: 250 mg/day
MDD	desipramine (Norpramin®, generics)	generics: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg tablets Norpramin®: 10 mg, 25 mg tablets	• Less than or equal to 65 years: 300 mg/day • Greater than 65 years: 150 mg/day
MDD	doxepin (generics)	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg capsules; 10 mg/mL oral concentrate	• Less than or equal to 65 years: ‣ mild to moderate illness: ‣ 150 mg/day ‣ severe illness: ‣ 300 mg/day • Greater than 65 years: ‣ mild to moderate illness: ‣ 150 mg/day ‣ severe illness: ‣ 300 mg/day
Anxiety#	doxepin (generics)	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg capsules; 10 mg/mL oral concentrate	• Less than or equal to 65 years: ‣ mild to moderate illness: ‣ 150 mg/day ‣ severe illness: ‣ 300 mg/day • Greater than 65 years: ‣ mild to moderate ‣ illness: ‣ 150 mg/day ‣ severe illness: ‣ 300 mg/day
I	doxepin (Silenor®)	3 mg, 6 mg tablets	• Less than or equal to 65 years: 6 mg/day • Less than or equal to 65 years: 6 mg/day

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	imipramine (Tofranil®, generics)	generics:10 mg, 25 mg, 50 mg tablets; 75 mg 100 mg, 125 mg, 150 mg capsules Tofranil®: 10 mg, 25 mg, 50 mg tablets	• Less than or equal to 65 years: 200 mg/day • Less than or equal to 65 years: 100 mg/day^
MDD	nortriptyline (Pamelor®, generics)	10 mg, 25 mg, 50 mg, 75 mg capsules; 10 mg/5 mL oral solution (generic only)	• Less than or equal to 65 years: 150 mg/day • Less than or equal to 65 years: 50 mg/day
MDD	protriptyline (generics)	5 mg, 10 mg tablets	• Less than or equal to 65 years: 60 mg/day • Less than or equal to 65 years: 30 mg/day+
MDD	trimipramine (Surmontil®, generics)	25 mg, 50 mg 100 mg capsules	• Less than or equal to 65 years: 200 mg/day • Less than or equal to 65 years: 100 mg/day

- I = insomnia
- MDD = major depressive disorder
- OCD = obsessive-compulsive disorder
- * = The maximum amoxapine dose in elderly patients and in most adults is 300 mg/day. Those patients less than or equal to 65 years of age who have not responded adequately to a two-week trial utilizing 300 mg/day may receive a trial of 400 mg amoxapine per day.
- + = Elderly patients should usually be given lower than average protriptyline doses. Elderly patients receiving protriptyline doses greater than 20 mg daily should receive close cardiac monitoring.
- # = Doxepin is also recommended for depression and anxiety associated with psychoneurosis, alcoholism, and organic disease.
- ^ = May increase to 150 mg/day if needed; doses usually do not exceed 100 mg/day in geriatric patients

Table 2: Table 2. Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) - Tetracyclic Antidepressants

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	maprotiline (generics)	25 mg, 50 mg, 75 mg tablets	• Less than or equal to 65 years: 150 mg/day** • Greater than 65 years: 150 mg/day**

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	mirtazapine (Remeron®, generics)	7.5 mg, 15 mg, 30 mg, 45 mg tablets; 15 mg, 30 mg, 45 mg orally disintegrating tablets	• Less than or equal to 65 years: 45 mg/day • Greater than 65 years: 45 mg/day

- MDD = major depressive disorder
- ** = Maximum maprotiline doses listed are for outpatient use; maprotiline is also used for anxiety associated with depression, dysthymic disorder and the depressive component of bipolar disorder

Table 3: Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) - Monoamine Oxidase Inhibitors

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	isocarboxazid (Marplan®)	10 mg tablets	• Less than or equal to 65 years: 60 mg/day • Greater than 65 years: 60 mg/day•
MDD	phenelzine (Nardil®, generics)	15 mg tablets	• Less than or equal to 65 years: 90 mg/day • Greater than 65 years: 90 mg/day•
MDD	tranylcypromine (Parnate®, generics)	10 mg tablets	• Less than or equal to 65 years: 60 mg/day • Greater than 65 years: 60 mg/day•

- MDD = major depressive disorder
- ▪ = Use MAOIs cautiously in elderly patients due to a greater risk of morbidity if hypertensive crisis develops

Table 4: Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) – Serotonin and Norepinephrine Reuptake Inhibitors

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	desvenlafaxine (Pristiq®, generics, Khedezla®)	25 mg, 50 mg 100 mg 24-hour ER tablets	• Less than or equal to 65 years: 50 mg/day^ • Greater than 65 years: 50 mg/day^
CMP, F, NP	duloxetine (Cymbalta®, generics)	20 mg, 30 mg, 40 mg 60 mg delayed-release capsules	• Less than or equal to 65 years: 60 mg/day • Greater than 65 years: 60 mg/day
GAD, MDD	duloxetine (Cymbalta®, generics)	20 mg, 30 mg, 40 mg 60 mg delayed-release capsules	• Less than or equal to 65 years: 120 mg/day# • Greater than 65 years: 120 mg/day#

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	levomilnacipran (Fetzima®)	20 mg, 40 mg 80 mg, 120 mg 24-hour ER capsules	• Less than or equal to 65 years: 120 mg/day • Greater than 65 years: 120 mg/day
F	milnacipran (Savella®)	12.5 mg, 25 mg, 50 mg 100 mg tablets	• Less than or equal to 65 years: 200 mg/day • Greater than 65 years: 200 mg/day
MDD	venlafaxine (generics)	25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg IR tablets	• Less than or equal to 65 years: 375 mg/day~ • Greater than 65 years: 375 mg/day~
GAD, MDD, PD	venlafaxine (Effexor XR®, generics)	37.5 mg, 75 mg, 150 mg 24-hour ER capsules	• Less than or equal to 65 years: 225 mg/day • Greater than 65 years: 225 mg/day
SAD	venlafaxine (Effexor XR®, generics)	37.5 mg, 75 mg, 150 mg 24-hour ER capsules	• Less than or equal to 65 years: 75 mg/day • Greater than 65 years: 75 mg/day
MDD	venlafaxine (generics)	37.5 mg, 75 mg, 150 mg, 225 mg 24-hour ER tablets	• Less than or equal to 65 years: 225 mg/day • Greater than 65 years: 225 mg/day
SAD	venlafaxine (generics)	37.5 mg, 75 mg, 150 mg, 225 mg 24-hour ER tablets	• Less than or equal to 65 years: 75 mg/day • Greater than 65 years: 75 mg/day

- CMP = chronic musculoskeletal pain
- F = fibromyalgia
- GAD = generalized anxiety disorder
- MDD = major depressive disorder
- NP = neuropathic pain
- PD = panic disorder
- SAD = social anxiety disorder

- ^ = In studies, desvenlafaxine doses up to 400 mg per day were no more effective than 50 mg daily doses and were associated with increased adverse events.
- # = Duloxetine doses of 120 mg, while effective, are no more effective than 60 mg daily doses.
- ~ = The maximum recommended venlafaxine dose is 225 mg/day for moderately depressed outpatients. Dosages greater than 225 mg/day in moderately depressed outpatients do not demonstrate additional efficacy.

However, more severely depressed inpatients may respond to venlafaxine dosages up to 375 mg/day.

Table 5: Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) – Selective Serotonin Reuptake Inhibitors (SSRIs)/5-HT1A Receptor Agonists and SSRIs/5-HT1A Receptor Agonists/5-HT3 Receptor Antagonists

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	vilazodone (Viibryd®)	10 mg, 20 mg, 40 mg tablets	• Less than or equal to 65 years: 40 mg/day • Greater than 65 years: 40 mg/day
MDD	vortioxetine (Trintellix®)	5 mg, 10 mg, 20 mg tablets	• Less than or equal to 65 years: 20 mg/day • Greater than 65 years: 20 mg/day

- MDD = major depressive disorder

Table 6: Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) – Miscellaneous Agents

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	bupropion (generics)	75 mg, 100 mg IR tablets	• Less than or equal to 65 years: 450 mg/day • Greater than 65 years: 450 mg/day
MDD	bupropion (Forfivo XL®, Wellbutrin XL®, generics)	Wellbutrin XL®, generics: 150 mg, 300 mg 24-hour ER tablets Forfivo XL®, generics: 450 mg 24-hour-ER tablets	• Less than or equal to 65 years: 450 mg/day • Greater than 65 years: 450 mg/day
MDD	bupropion (Wellbutrin SR®, generics)	200 mg 12-hour ER tablets	• Less than or equal to 65 years: 400 mg/day • Greater than 65 years: 400 mg/day
MDD	bupropion (Aplenzin®)	174 mg, 348 mg, 522 mg 24-hour ER tablets	• Less than or equal to 65 years: 522 mg/day • Greater than 65 years: 522 mg/day
AD	bupropion (Aplenzin®)	174 mg, 348 mg, 522 mg 24-hour ER tablets	• Less than or equal to 65 years: 348 mg/day • Greater than 65 years: 348 mg/day
AD	bupropion (Wellbutrin XL®, generics)	Wellbutrin XL®, generics: 150 mg, 300 mg 24-hour ER tablets	• Less than or equal to 65 years: 300 mg/day • Greater than 65 years: 300 mg/day

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
SC	bupropion (Zyban®, generics)	150 mg 12-hour ER tablets	• Less than or equal to 65 years: 300 mg/day • Greater than 65 years: 300 mg/day
MDD	nefazodone (generics)	50 mg, 100 mg, 150 mg, 200 mg, 250 mg tablets	• Less than or equal to 65 years: 600 mg/day • Greater than 65 years: 600 mg/day
MDD	trazodone (generics)	50 mg, 100 mg, 150 mg, 300 mg IR tablets	• Less than or equal to 65 years: outpatients: • 400 mg/day • Greater than 65 years: outpatients: • 400 mg/day
MDD	trazodone (Oleptro®)	150 mg, 300 mg 24-hour ER tablets	• Less than or equal to 65 years: 375 mg/day • Greater than 65 years: 375 mg/day

- AD = seasonal affective disorder
- MDD = major depressive disorder
- SC = smoking cessation

Table 7: Adult Maximum Recommended Antidepressant Dosages (Combination Therapy)

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
severe depression	chlordiazepoxide/ amitriptyline (generics)	5 mg/ 12.5 mg, 10 mg/25 mg tablets	60 mg/150 mg/day*
anxiety/ agitation/de pression	perphenazine/ amitriptyline (generics)	2 mg/10 mg, 4 mg/10 mg, 2 mg/25 mg, 4 mg/25 mg, 4 mg/50 mg tablets	16 mg/200 mg/day

- * = Lower chlordiazepoxide/amitriptyline dosages and close monitoring are recommended in elderly patients due to greater risks for impaired cognitive/motor function

1.2 Pediatrics

The FDA requires that all antidepressant drugs display a black box warning describing the potential for increased suicidal thinking and behavior when prescribed to children and adolescents with MDD and other psychiatric disorders. In short-term clinical trials, the suicide risk occurred twice as frequently with

antidepressant-treated children/adolescents compared to those receiving placebo (4% vs. 2%, respectively) in the first few months of treatment. Pediatric patients prescribed antidepressant drugs should be closely monitored for changes in behavior.

Maximum recommended doses for non-SSRI antidepressants approved for use as monotherapy in pediatric patients are summarized in Tables 8-10. Dosages exceeding these recommendations will be reviewed.

Table 8: Pediatric Maximum Recommended Antidepressant Drug Dosages (Monotherapy) – Tricyclic Antidepressants

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	amitriptyline (generics)	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg tablets	Greater than or equal to 12 years of age: 10 mg three times daily and 20 mg at bedtime
OCD	clomipramine (Anafranil®, generics)	25 mg, 50 mg 75 mg capsules	Greater than or equal to 10 years of age: 3 mg/kg/day or 200 mg/day, whichever is smaller
MDD	desipramine (Norpramin®, generics)	generics: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg tablets Norpramin®: 10 mg, 25 mg tablets	adolescents: 150 mg/day
MDD	imipramine (Tofranil®, generics)	generics:10 mg, 25 mg, 50 mg tablets; 75 mg 100 mg, 125 mg, 150 mg capsules Tofranil®: 10 mg, 25 mg, 50 mg tablets	adolescents: 100 mg/day
nocturnal enuresis	imipramine (Tofranil®, generics)	generics:10 mg, 25 mg, 50 mg tablets; 75 mg 100 mg, 125 mg, 150 mg capsules Tofranil®: 10 mg, 25 mg, 50 mg tablets	6-11 years of age: 2.5 mg/kg/day up to 50 mg/day Greater than or equal to 12 years of age: 75 mg/day

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	nortriptyline (Pamelor®, generics)	10 mg, 25 mg, 50 mg, 75 mg capsules; 10 mg/5 mL oral solution (generic only)	adolescents: 50 mg/day
MDD	protriptyline	5 mg, 10 mg tablets	adolescents: 30 mg/day*
MDD	trimipramine (Surmontil®)	25 mg, 50 mg 100 mg capsules	adolescents: 100 mg/day

- * = Adolescents should usually be given lower than average protriptyline doses.

Table 9: Pediatric Maximum Recommended Antidepressant Drug Dosages (Monotherapy)– Monoamine Oxidase Inhibitors

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	isocarboxazid (Marplan®)	**10 mg tablets**	Greater than or equal to 16 years of age: 60 mg/day

Table 10: Pediatric Maximum Recommended Antidepressant Drug Dosages (Monotherapy) – Serotonin and Norepinephrine Reuptake Inhibitors

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
GAD	duloxetine (Cymbalta®, generics)	20 mg, 30 mg, 40 mg 60 mg delayed-release capsules	7-17 years of age: 120 mg/day

1.3 Renal Impairment

Many antidepressants do not require significant dosage modifications in renal impairment. However, dosage guidelines for select non-SSRI antidepressants in renal impairment are available. Tables 11-14 summarizes dosage modifications and/or restrictions for specific non-SSRI antidepressant medications.

Table 11: Select non-SSRI Antidepressant Dosage Modifications in Renal Impairment – Tetracyclic Antidepressants

Drug Name	Dosage in Renal Impairment
Mirtazapine	Initiate with lowest dosage and titrate slowly as renal clearance reduced by approximately 30% in moderate (CrCl 11-39 ml/min) and 50% in severe (CrCl Less than or equal to 10 ml/min) renal impairment

- CrCl = creatinine clearance

Table 12: Select non-SSRI Antidepressant Dosage Modifications in Renal Impairment – Monoamine Oxidase Inhibitors

Drug Name	Dosage in Renal Impairment
Isocarboxazid	Contraindicated in severe renal impairment; use cautiously in moderate renal impairment due to potential accumulation of active metabolites
Phenelzine	Contraindicated for use in severe renal impairment
Tranylcypromine	Use cautiously in renal impairment due to potential for cumulative effects

Table 13: Select non-SSRI Antidepressant Dosage Modifications in Renal Impairment – Serotonin and Norepinephrine Reuptake Inhibitors

Drug Name	Dosage in Renal Impairment
Desvenlafaxine	• Moderate renal impairment (CrCl 30-50 ml/min): 50 mg/daySevere renal impairment (CrCl less than 30 ml/min) • ESRD: 25 mg once daily or 50 mg every other day
Duloxetine	Mild to moderate renal impairment: start with lower dose, titrate gradually Severe renal impairment, ESRD: not recommended

Levomilnacipran	• Moderate renal impairment (CrCl 30-59 ml/min):
	  ▸ 80 mg/day
	• Severe renal impairment (CrCl 15-29 ml/min):
	  ▸ 40 mg/day
	• ESRD:
	  ▸ not recommended

Milnacipran	• Moderate renal impairment (CrCl 30-49 ml/min):
	  ▸ use cautiously
	• Severe renal impairment (CrCl 5-29 ml/min):
	  ▸ reduce dose by 50% to 25-50 mg twice daily (based on response and tolerability)
	• ESRD:
	  ▸ not recommended

Drug Name	Dosage in Renal Impairment

Venlafaxine	• Mild to moderate renal impairment (CrCl 30-89 ml/min):
	  ▸ IR: reduce total daily dose by 25%
	  ▸ ER: reduce total daily dose by 25% to 50%
	• Severe renal impairment (CrCl less than 30 ml/min) and hemodialysis:
	  ▸ Reduce total daily dose by 50%
	  ▸ Adjust doses based on response and tolerability due to variability in renal clearance

- CrCl = creatinine clearance
- ESRD = end-stage renal disease
- ER = extended-release
- IR = immediate-release

Table 14: Select non-SSRI Antidepressant Dosage Modifications in Renal Impairment – Other Miscellaneous Agents

Drug Name	Dosage in Renal Impairment
Bupropion	• Administer cautiously in renal impairment due to potential for accumulation and risk for adverse events (e.g., seizures); consider reduced dosage/dosage frequency • Forfivo™ XL: ▸ not recommended in renal impairment as no lower dose available
Trazodone	Use cautiously in patients with CrCl less than 50 ml/min

- CrCl = creatinine clearance

2 Duration of Therapy

There is no basis for limiting antidepressant therapy duration when used to manage MDD, OCD, GAD, PTSD, or PD as these disorders can all be characterized as chronic conditions.

While clinical trials have not evaluated vilazodone use in MDD beyond 8 weeks, it is accepted that vilazodone therapy may exceed 8 weeks, as acute episodes of MDD require extended (several months or longer) drug therapy. Patients should be periodically assessed for continued need for vilazodone treatment.

Duloxetine treatment duration in diabetic NP lasting greater than 6 months has not been evaluated in clinical trials. Additionally, duloxetine efficacy in CMP beyond 13 weeks has not been established in clinical trials.

Duloxetine use lasting greater than 12 months as F therapy has not been evaluated in clinical trials. Recent clinical trials have evaluated milnacipran use for up to one year in F with sustained results in pain management. F patients should be routinely evaluated for treatment effectiveness, with milnacipran therapy tapered and discontinued if positive treatment outcomes are no longer present.

3 Duplicative Therapy

The concurrent use of two antidepressant medications with the same spectrum of activity may not be justified. The concomitant use of two cyclic antidepressants, two MAOIs or two SNRIs will be reviewed.

The concurrent use of three or more antidepressants is not justified. Therefore, the adjunctive use of three or more antidepressants, including MAOIs, SNRIs, SSRIs, cyclic antidepressants, trazodone, bupropion, and nefazodone, will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. The following drug-drug interactions summarized in Table 15 are considered clinically relevant for antidepressants. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 15: Major Drug-Drug Interactions for Non-SSRI Antidepressant Drugs

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
bupropion	systemic corticosteroids	concurrent administration may increase seizure risk as both agents lower seizure threshold	reduce initial doses and titrate doses upward slowly; monitor closely for seizure activity	major (DrugReax) 2-major (CP)
cyclic antidepressants, SNRIs, bupropion, levomilnacipran, milnacipran, nefazodone, trazodone, vilazodone, vortioxetine	monoamine oxidase inhibitors (MAOIs)	increased risk of serotonin syndrome (e.g., mental status changes, hyperpyrexia, restless, shivering, hypertonia, tremor) due to serotonin metabolism inhibition by monoamine oxidase	allow 14 days after MAOI discontinuation before initiating other antidepressant therapy; wait 5 weeks after discontinuing fluoxetine before initiating MAOIs	contraindicated (DrugReax) 1-severe (CP)
fluoxetine	ergot derivatives	increased risk of ergotism due to fluoxetine inhibition of CYP3A4-mediated ergot metabolism	avoid concurrent use	contraindicated (DrugReax) major (CP)
MAOIs	select CNS stimulants (amphetamines, atomoxetine, methylphenidate and derivatives)	increased risk of hypertensive crisis due to additive effects on catecholamine neurotransmitters	avoid concurrent use; allow two weeks between discontinuing MAOIs and initiating CNS stimulant therapy	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
MAOIs	cyclobenzaprine	increased risk of hyperpyretic crisis, seizures and death potentially due to additive adrenergic activity	avoid concurrent use; allow two weeks between discontinuing MAOIs and initiating cyclobenzaprine therapy	contraindicated (DrugReax) 1-severe (CP)
MAOIs	morphine	increased risk of hypotension and enhanced CNS/respiratory depression as MAOIs amplify morphine pharmacologic effects	avoid concurrent use; allow two weeks between discontinuing morphine and initiating MAOI therapy	contraindicated (DrugReax) 1-severe (CP)
MAOIs	sympathomimetics	increased risk of hypertensive crisis as MAOIs increase norepinephrine availability at neuronal storage sites as well as enhance adrenergic effects	avoid concurrent use; allow two weeks between discontinuing sympathomimetics and initiating MAOI therapy	contraindicated (DrugReax) 1-severe (CP)
MAOIs	sympathomimetics	increased risk of hypertensive crisis as MAOIs increase norepinephrine availability at neuronal storage sites as well as enhance adrenergic effects	avoid concurrent use; allow two weeks between discontinuing sympathomimetics and initiating MAOI therapy	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
nefazodone (NZD)	carbamazepine	reduced NZD serum levels/antidepressant effects and increased carbamazepine (CBZ) serum levels and potential for toxicity due to induced CYP3A4-mediated NZD metabolism and inhibited CYP3A4-mediated CBZ metabolism	avoid concurrent use	contraindicated (DrugReax) 1-severe (CP)
NZD	pimozide	enhanced pimozide pharmacologic effects and potential for cardiovascular toxicity due to NZD-mediated CYP3A4 inhibition	avoid concurrent use	contraindicated (DrugReax) 1-severe (CP)
SNRIs, vilazodone, vortioxetine	anticoagulants	co-administration may increase bleeding risk due to impaired platelet aggregation most likely resulting from platelet serotonin depletion	patients should be monitored for signs/symptoms of bleeding (including INR) if combined therapy necessary	major (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
SNRIs, vortioxetine	antiplatelet agents	adjunctive administration may increase bleeding risk due to impaired platelet aggregation most likely resulting from platelet serotonin depletion	patients should be monitored for signs/symptoms of bleeding if combined therapy necessary	major (DrugReax) 3-moderate (CP)
SNRIs, vilazodone, vortioxetine	drugs with serotonergic properties (e.g., antipsychotics, dextromethorphan, tramadol, triptans) or dopamine antagonist properties (e.g., phenothiazines, metoclopramide)	combined use may increase risk of serotonin syndrome or neuroleptic malignant syndrome (NMS)	cautiously administer concurrently and closely observe for signs/symptoms of serotonin syndrome or NMS, especially with treatment initiation or dosage increases	major (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
SNRIs, vortioxetine	tramadol	increased risk of serotonin syndrome and seizures due to increased nervous system serotonin concentrations (additive effects on serotonin, SSRI inhibition of CYP2D6-mediated tramadol metabolism) as well as potential reduced seizure threshold with SNRIs, SSRIs	avoid concurrent use	major (DrugReax) 2-major (CP)
TCAs	pimozide	increased risk of pimozide toxicity including cardiotoxicity (QT prolongation) due to elevated plasma concentrations or additive effects on QT interval	avoid concurrent use	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
TCAs, duloxetine	select phenothiazines (mesoridazine, thioridazine)	increased risk of somnolence, bradycardia and serious cardiotoxicity (QT prolongation, torsades de pointes) due to potential additive effects on QT interval prolongation; increased thioridazine serum concentrations/decreased thioridazine elimination and potential for serious cardiac arrhythmias due to CYP2D6 inhibition by duloxetine, fluoxetine, or paroxetine	avoid concurrent use; if adjunctive use necessary, monitor for increased pharmacologic/toxic effects; adjust dose as necessary	contraindicated (DrugReax) 1-severe (CP)
vilazodone	CYP3A4 inducers	combined administration may result in reduced vilazodone serum levels and decreased pharmacologic effects, as vilazodone is primarily metabolized by CYP3A4	monitor for decreased pharmacologic effects and adjust doses as necessary	3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
vilazodone	CYP3A4 inhibitors	adjunctive administration may result in increased vilazodone serum levels and enhanced pharmacologic/adverse effects, as vilazodone is primarily metabolized by CYP3A4	monitor for increased pharmacologic/adverse effects; reduce vilazodone dose to 20 mg daily when prescribed concurrently with strong (e.g., ketoconazole) CYP3A4 inhibitors; reduce vilazodone dose to 20 mg daily when co-administered with moderate (e.g., erythromycin) CYP3A4 inhibitors and intolerable adverse effects are present	moderate (DrugReax) 2-major (CP)
vortioxetine	strong CYP2D6 inducers	combined administration may result in reduced vortioxetine serum levels and decreased pharmacologic effects, as vortioxetine is primarily metabolized by CYP2D6	monitor for decreased pharmacologic effects; increase the vortioxetine dose (by no more than 3x the recommended dose) if strong CYP2D6 inducer administered concurrently for more than 14 days; reduce vortioxetine dose to original dose within 14 days of CYP2D6 inducer discontinuation	major (DrugReax) 2-major (CP)
vortioxetine	strong CYP2D6 inhibitors	adjunctive administration may result in increased vortioxetine serum levels and enhanced pharmacologic/adverse effects, as vortioxetine is primarily metabolized by CYP2D6	Reduce vortioxetine dose by 50% when administered concurrently with strong CYP2D6 inhibitor; reduce vortioxetine dose to original dose when CYP2D6 inhibitor discontinued	major (DrugReax) 2-major (CP)

- #CP = Clinical Pharmacology
- CNS = central nervous system

- SNRIs = serotonin and norepinephrine reuptake inhibitors
- TCAs = tricyclic antidepressants

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