Texas Vendor Drug Program

Drug Use Criteria: Anti-Depressants, Oral (Other)

Publication History

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

Prepared by:

- Drug Information Service, UT Health San Antonio.
- The College of Pharmacy, The University of Texas at Austin.

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. **Patients of all ages prescribed** antidepressant drugs should be closely monitored for changes in behavior, **clinical worsening, or suicidality**. **When treating elderly patients, caution is indicated when administering these medications due to risk of hyponatremia.**[1-43]

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, and moderate anxiety/agitation/depression.[1-43]

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. Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) - Tricyclic Antidepressants [1-18]

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
			≤ 65 years	*> 65* years
amitriptyline (**generics)**	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg tablets	MDD	150 mg/day	**150 mg/ day divided into three doses**
amoxapine (generics)	25 mg, 50 mg, 100 mg, 150 mg tablets	MDD	**400 mg/day**[*]	300 mg/day*
clomipramine (Anafranil®, generics)	25 mg, 50 mg 75 mg capsules	OCD	250 mg/day	250 mg/day
desipramine (generics)	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg tablets	MDD	300 mg/day	150 mg/day
doxepin (generics)	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg capsules; 10 mg/mL oral concentrate	MDD	mild to moderate illness: 150 mg/day	*mild to moderate illness:* 150 mg/day
			severe illness: 300 mg/day	*severe illness:* 300 mg/day
		anxiety[#]	mild to moderate illness: 150 mg/day	*mild to moderate illness:* 150 mg/day
			severe illness: 300 mg/day	*severe illness:* 300 mg/day
doxepin (Silenor®)	3 mg, 6 mg tablets	I	6 mg/day	6 mg/day
imipramine hydrochloride (Tofranil®, generics)	generics:10 mg, 25 mg, 50 mg tablets Tofranil®: 10 mg, 25 mg tablets	MDD	200 mg/day	100 mg/day[^]
imipramine pamoate (generics)	**75 mg, 100 mg, 125 mg, 150 mg capsules**			
nortriptyline (Pamelor®, generics)	10 mg, 25 mg, 50 mg, 75 mg capsules; 10 mg/5 mL oral solution (generic only)	MDD	150 mg/day**	50 mg/day
protriptyline (generics)	5 mg, 10 mg tablets	MDD	60 mg/day	20 mg/day[+]
trimipramine (generics)	25 mg, 50 mg 100 mg capsules	MDD	200 mg/day	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 ≤ 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.

[#]Doxepin is also recommended for depression and anxiety associated with psychoneurosis, alcoholism, and organic disease.

*[^]May increase to 150 mg/day, if needed; **doses over 200 mg are not recommended**; doses usually do not exceed 100 mg/day in geriatric patients.*

****When doses above 100 mg daily are administered, plasma levels of nortriptyline should be maintained in the optimum range of 50 ng/mL to 150 ng/mL.**

[+]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.

Table 2. Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) - Tetracyclic Antidepressants [1-2, 19-20]

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
			≤ 65 years	*> 65 years*
mirtazapine (Remeron®, generics)	7.5 mg, 15 mg, 30 mg, 45 mg tablets; 15 mg, 30 mg, 45 mg orally disintegrating tablets	MDD	45 mg/day	45 mg/day

MDD = major depressive disorder

Table 3. Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) - Monoamine Oxidase Inhibitors [1-2, 21-25]

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
			≤ 65 years	*> 65 years*
isocarboxazid (Marplan®)	10 mg tablets	MDD	60 mg/day	60 mg/day[•]
phenelzine (Nardil®, generics)	15 mg tablets	**depression***	90 mg/day	90 mg/day[•]
selegiline (EMSAM®) transdermal patch	6 mg/ 24 hours, 9 mg/ 24 hours, 12 mg/ 24 hours transdermal patch	MDD	12 mg/ 24 hours	**6mg/24 hours[•]**
tranylcypromine (Parnate®, generics)	10 mg tablets	MDD[^]	60 mg/day	60 mg/day[•]

MDD = major depressive disorder

·*Use MAOIs cautiously in elderly patients due to a greater risk of morbidity if hypertensive crisis develops.*
***Phenelzine has been found to be effective in depressed patients clinically characterized as "atypical," "nonendogenous," or "neurotic."**
^Indicated for MDD in patients who have not responded adequately to other antidepressants.

Table 4. Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) – Serotonin and Norepinephrine Reuptake Inhibitors [1-2, 26-32]

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
			≤ 65 years	*>65 years*
desvenlafaxine (Pristiq®, generics)	25 mg, 50 mg 100 mg 24-hour ER tablets	MDD	400 mg/day^	400 mg/day^
duloxetine (Cymbalta®, Drizalma Sprinkle®, generics)	30 mg, 60 mg delayed-release capsules **Generic only: 20, 40 mg**	CMP, F, NP	60 mg/day	60 mg/day
		GAD, MDD	120 mg/day#	120 mg/day#
levomilnacipran (Fetzima®)	20 mg, 40 mg 80 mg, 120 mg 24-hour ER capsules	MDD	120 mg/day	120 mg/day
milnacipran (Savella®)	12.5 mg, 25 mg, 50 mg 100 mg tablets	F	200 mg/day	200 mg/day
venlafaxine (generics)	25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg IR tablets	MDD	375 mg/day~	375 mg/day~
venlafaxine (Effexor XR®, generics)	37.5 mg, 75 mg, 150 mg 24-hour ER capsules	GAD, MDD, PD	225 mg/day	225 mg/day
		SAD	75 mg/day	75 mg/day
venlafaxine (generics)	37.5 mg, 75 mg, 150 mg, 225 mg 24-hour ER tablets	MDD	225 mg/day	225 mg/day

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
		SAD	75 mg/day	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 > 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-HT$_{1A}$ Receptor Agonists and SSRIs/5-HT$_{1A}$ Receptor Agonists/5-HT3 Receptor Antagonists [1-2, 33-34]

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
			< 65 years	*>65 years*
vilazodone (Viibryd®)	10 mg, 20 mg, 40 mg tablets	MDD	40 mg/day	40 mg/day
vortioxetine (Trintellix®)	5 mg, 10 mg, 20 mg tablets	MDD	20 mg/day	20 mg/day

MDD = major depressive disorder

Table 6. Adult and Elderly Maximum Recommended Antidepressant Dosages (Monotherapy) – Miscellaneous Agents [1-2, 35-40]

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
			≤ 65 years	*>65 years*
bupropion (generics)	75 mg, 100 mg IR tablets	MDD	450 mg/day	450 mg/day
	150 mg 12-hour ER tablets	SC	300 mg/day	300 mg/day

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
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	MDD	450 mg/day	450 mg/day
bupropion (Wellbutrin SR®, generics)	100 mg, 150 mg, 200 mg 12-hour ER tablets	MDD	400 mg/day	400 mg/day
bupropion (Aplenzin®)	174 mg, 348 mg, 522 mg 24-hour ER tablets	MDD	522 mg/day	522 mg/day
		AD	348 mg/day	348 mg/day*****
bupropion (Wellbutrin XL®, generics)	Wellbutrin XL®, generics: 150 mg, 300 mg 24-hour ER tablets	AD	300 mg/day	300 mg/day
nefazodone (generics)	50 mg, 100 mg, 150 mg, 200 mg, 250 mg tablets	MDD	600 mg/day	600 mg/day
trazodone (generics)	50 mg, 100 mg, 150 mg, 300 mg IR tablets	MDD	*outpatients:* 400 mg/day	*outpatient:* 400 mg/day

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

***300 mg of bupropion HCl extended-release is equivalent to APLENZIN 348 mg**

Table 7. Adult Maximum Recommended Antidepressant Dosages (Combination Therapy) [1-2, 41-42]

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage
chlordiazepoxide/ amitriptyline (generics)	5 mg/ 12.5 mg, 10 mg/25 mg tablets	**Moderate to** severe depression	60 mg/150 mg/day[*]
perphenazine/ amitriptyline (generics)	2 mg/10 mg, 4 mg/10 mg, 2 mg/25 mg, 4 mg/25 mg, 4 mg/50 mg tablets	Anxiety/agitation/depression	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.[1-2]

Maximum recommended doses for non-SSRI antidepressants approved for use as monotherapy in pediatric patients are summarized in Tables 8-10. An additional column reflecting literature-based dosing included in the Texas Health and Human Services Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health (6th Version) is included in Tables 8-11. Dosages exceeding these recommendations will be reviewed.

Table 8. Pediatric Maximum Recommended Antidepressant Drug Dosages (Monotherapy) – Tricyclic Antidepressants [1-2, 3-4, 6-9, 12-18, 44]

Drug Name	Available Dosage Strengths	Treatment Indication	Literature Based Maximum Dosage	FDA Approved Maximum Recommended Dosage
amitriptyline (generics)	generics: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg tablets	MDD	Reviewed but not included/ recommended	**> 12 years of age: 150 mg daily divided into three doses^**
clomipramine (Anafranil®, generics)	25 mg, 50 mg 75 mg capsules	OCD	Age 10-17 years: 3 mg/kg/day or 200 mg/ day, whichever is less	*≥ 10 years of age:* 3 mg/kg/day or 200 mg/day, whichever is less
desipramine (Norpramin®, generics)	generics: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg tablets Norpramin®: 10 mg, 25 mg tablets	MDD	Reviewed but not included/ recommended	*adolescents: 150 mg/day*
imipramine hydrochloride (Tofranil®, generics)#	generics:10 mg, 25 mg, 50 mg tablets Tofranil®: 10 mg, 25 mg, 50 mg tablets	MDD	Reviewed but not included/ recommended	*adolescents: 100 mg/day*
		Nocturnal enuresis		6-11 years of age: 2.5 mg/kg/day up to 50 mg/day ≥ 12 years of age: 2.5 mg/kg/day up to 75 mg/day

Drug Name	Available Dosage Strengths	Treatment Indication	Literature Based Maximum Dosage	FDA Approved Maximum Recommended Dosage
nortriptyline (Pamelor®, generics)	10 mg, 25 mg, 50 mg, 75 mg capsules; 10 mg/5 mL oral solution (generic only)	MDD	Reviewed but not included/ recommended	*adolescents:* 50 mg/day
protriptyline	5 mg, 10 mg tablets	MDD	Reviewed but not included/ recommended	*adolescents:* 30 mg/day*
trimipramine (generics)	25 mg, 50 mg 100 mg capsules	MDD	Reviewed but not included/ recommended	*adolescents:* 100 mg/day

MDD = major depressive disorder; OCD = obsessive-compulsive disorder

^In general, lower dosages are recommended for these patients. Ten milligrams 3 times daily with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher dosages
#imipramine pamoate is not approved for pediatric use
**Adolescents should usually be given lower than average protriptyline doses*

Table 9. Pediatric Maximum Recommended Antidepressant Drug Dosages (Monotherapy)– Monoamine Oxidase Inhibitors [1-2, 21, 24, 44]

Drug Name	Available Dosage Strengths	Treatment Indication	Literature Based Maximum Dosage	FDA Approved Maximum Recommended Dosage
isocarboxazid (Marplan®)	10 mg tablets	MDD	Not reviewed	*≥16 years of age:* 60 mg/day
selegiline (EMSAM®) transdermal patch	6 mg/ 24 hours, 9 mg/ 24 hours, 12 mg/ 24 hours transdermal patch	MDD	*Age ≥ 12 years:* 12 mg per 24 hours	Not approved for pediatric use

MDD = major depressive disorder

Table 10. Pediatric Maximum Recommended Antidepressant Drug Dosages (Monotherapy) – Serotonin and Norepinephrine Reuptake Inhibitors [1-2, 26-28, 44]

Drug Name	Available Dosage Strengths	Treatment Indication	Literature Based Maximum Dosage	FDA Approved Maximum Recommended Dosage
desvenlafaxine (Pristiq®, generics)	25 mg, 50 mg 100 mg 24-hour ER tablets	MDD	Age 7-17 years: 50 mg/day	Not approved for pediatric use

Drug Name	Available Dosage Strengths	Treatment Indication	Literature Based Maximum Dosage	FDA Approved Maximum Recommended Dosage
duloxetine (Cymbalta®, generics)	20 mg, 30 mg, 40 mg 60 mg delayed-release capsules	GAD	Age 7-17 years: 120 mg/day	7-17 years of age: 120 mg/day
		F		13 years of age: 60 mg/ day

F = fibromyalgia; GAD = general anxiety disorder; MDD = major depressive disorder

Table 11. Pediatric Maximum Recommended Antidepressant Drug Dosages (Monotherapy) - Tetracyclic Antidepressants [1-2, 19-20, 44]

Drug Name	Available Dosage Strengths	Treatment Indication	Literature Based Maximum Dosage	FDA Approved Maximum Recommended Dosage
mirtazapine (Remeron®, generics)	7.5 mg, 15 mg, 30 mg, 45 mg tablets; 15 mg, 30 mg, 45 mg orally disintegrating tablets	MDD	Age ≥ 3 years: 45 mg/day	Not approved for pediatric use

MDD = major depressive disorder

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 12-15 summarizes dosage modifications and/or restrictions for specific non-SSRI antidepressant medications.

Table 12. Select non-SSRI Antidepressant Dosage Modifications in Renal Impairment – Tetracyclic Antidepressants [1-2, 19-20]

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 $\leq$ 10 ml/min) renal impairment

CrCl = creatinine clearance

Table 13. Select non-SSRI Antidepressant Dosage Modifications in Renal Impairment – Monoamine Oxidase Inhibitors [1-2, 21-23, 25]

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

Table 14. Select non-SSRI Antidepressant Dosage Modifications in Renal Impairment – Serotonin and Norepinephrine Reuptake Inhibitors [1-2, 26-32]

Drug Name	Dosage in Renal Impairment
Desvenlafaxine	Moderate renal impairment (CrCl 30-50 ml/min): 50 mg/day Severe renal impairment (CrCl < 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 **(GFR<30 ml/min),** ESRD: **avoid use**
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 **mg twice daily or**—50 mg **twice** daily (based on response and tolerability) ESRD: not recommended
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 < 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 15. Select non-SSRI Antidepressant Dosage Modifications in Renal Impairment – Other Miscellaneous Agents [1-2, 35-38, 40]

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 **renal impairment**

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. **NP, CMP, and F are considered chronic conditions and may be used for the duration of the condition.**

While clinical trials have not evaluated vilazodone use in MDD beyond **52** weeks, it is accepted that vilazodone therapy may exceed **52** 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.[33]

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 16 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 16. Major Drug-Drug Interactions for Non-SSRI Antidepressant Drugs [1-43]

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	**Moderate (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** (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 (CP)
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 (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
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 (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 (CP)
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 (CP)
NZD	pimozide	enhanced pimozide pharmacologic effects and potential for cardiovascular toxicity due to NZD-mediated CYP3A4 inhibition	avoid concurrent use	contraindicated (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	**moderate** (CP)
SNRIs, vortioxetine **Vilazodone**	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	**moderate** (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
SNRIs,	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	**contraindicated** (CP)
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). Platelet aggregation may be impaired due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication**	**cautiously administer concurrently and closely observe for signs/symptoms of serotonin syndrome or NMS, especially with treatment initiation or dosage increases**	**Moderate (CP)**
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	**Moderate** (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
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 (CP)
TCAs, duloxetine	select phenothiazines (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 (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	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	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 **as well as QTC prolongation with concurrent use of thioridazine**	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 (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 (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
Amitripityline/ Perphenazine	**cisapride**	**increased risk of QT prolongation and increased risk for arrythmia**	**avoid concurrent use**	**Contraindicated (CP)**

[#]CP = Clinical Pharmacology
CNS = central nervous system; SNRIs = serotonin and norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants

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