Texas Vendor Drug Program

Drug Use Criteria: Antidepressant Drugs – Selective Serotonin Reuptake Inhibitors

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 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.

Selective serotonin reuptake inhibitor (SSRI) antidepressant drugs are FDA-approved for use in major depressive disorder (MDD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder (PD), premenstrual dysphoric disorder (PMDD), and posttraumatic stress disorder (PTSD). Recently, paroxetine has been approved to manage moderate to severe vasomotor symptoms associated with menopause (VMS). Combination therapy is FDA-approved for bipolar I disorder (BD) and treatment-resistant depression (TRD).

Maximum recommended daily doses for SSRI antidepressant drugs in adults, including the elderly population, are summarized in Tables 1 and 2 for both monotherapy and SSRI combination therapy, respectively. However, in all patients, the lowest effective antidepressant dose should be utilized to minimize unwanted adverse effects. Patient profiles with SSRI antidepressant dosages exceeding these recommendations will be reviewed.

Table 1. Oral SSRI Medications - Adult Maximum Recommended Dosages – Monotherapy

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage (Less than or Equal to 65 years)	Maximum Recommended Dosage (Greater than 65 years)
MDD	citalopram (Celexa®, generics)	10 mg, 20 mg, 40 mg tablets; 10 mg/ 5 mL oral solution	40 mg/day	20 mg/day
GAD, MDD	escitalopram (Lexapro®, generics)	5 mg, 10 mg, 20 mg tablets; 5 mg/5 mL oral solution	20 mg/day20 mg/day	10 mg/day
MDD, OCD	fluoxetine (Prozac®, generics)	10 mg, 20 mg, 40 mg capsules; 10 mg, 20 mg, 40 mg, 60 mg tablets; 20 mg/5 mL solution	80 mg/day	80 mg/day
BN, PD			60 mg/day	60 mg/day
MDD	fluoxetine (Prozac® Weekly, generics)		90 mg/week	90 mg/week
PMDD	fluoxetine (Sarafem®, generics)	10 mg, 20 mg capsules	80 mg/day	---
OCD	fluvoxamine (generics)	IR: 25 mg, 50 mg, 100 mg tablets ER: 100 mg, 150 mg 24-hour ER capsules	300 mg/day*	300 mg/day*
GAD, MDD	paroxetine (Paxil®, Pexeva®, generics)	10 mg, 20 mg, 30 mg, 40 mg tablets	50 mg/day	40 mg/day
OCD, PD			60 mg/day	40 mg/day
SAD	paroxetine (Paxil®, generics)	10 mg, 20 mg, 30 mg, 40 mg tablets	60 mg/day++	40 mg/day
PTSD			50 mg/day++	40 mg/day
MDD	paroxetine (Paxil CR®, generics)	12.5 mg, 25 mg, 37.5 mg 24-hour ER tablets	62.5 mg/day	50 mg/day
PD			75 mg/day	50 mg/day
SAD			37.5 mg/day	50 mg/day
PMDD			25 mg/day	---

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage (Less than or Equal to 65 years)	Maximum Recommended Dosage (Greater than 65 years)
VMS	paroxetine (Brisdelle®)	7.5 mg capsule	7.5 mg/day at bedtime	7.5 mg/day at bedtime
MDD, OCD, PD, SAD, PTSD	sertraline (Zoloft®, generics)	25 mg, 50 mg, 100 mg tablets; 20 mg/mL oral concentrate	200 mg/day	200 mg/day
PMDD			150 mg/day	---

- ER = extended-release
- GAD = generalized anxiety disorder
- IR = immediate-release
- MDD = major depressive disorder
- OCD = obsessive-compulsive disorder
- PD = panic disorder
- PMDD = premenstrual dysphoric disorder
- PTSD = posttraumatic stress disorder
- SAD = social anxiety disorder
- VMS = vasomotor symptoms associated with menopause
- *Fluvoxamine IR doses greater than 100 mg daily should be administered in divided doses.
- ++Data do not confirm that paroxetine doses greater than 20 mg/day are more effective.
- +Lower doses may be required in elderly patients

Table 2. Oral SSRI Medications - Adult Maximum Recommended Dosages – Combination Therapy

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage (Less than or equal to 65 years)	Maximum Recommended Dosage (Greater than 65 years)
BD, TRD	olanzapine/ fluoxetine (Symbyax®, generics)	3 mg/ 25 mg, 6 mg/ 25 mg, 12 mg/25 mg, 6 mg/ 50 mg, 12 mg/ 50 mg capsules	18 mg/ 75 mg per day	18 mg/ 75 mg per day

- BD = bipolar I disorder
- TRD = treatment-resistant depression

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.

Citalopram and paroxetine are not FDA-approved for use in pediatric patients as safety and effectiveness in this age group have not been well established. The olanzapine/fluoxetine combination is FDA-approved in pediatric patients.

Maximum pediatric recommended doses for SSRI antidepressants approved for use as monotherapy and combination therapy are summarized in Tables 3 and 4, respectively. Dosages exceeding these recommendations will be reviewed.

Table 3. Recommended SSRI Antidepressant Drug Dosages for Pediatric Patients – Monotherapy

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
MDD	escitalopram (Lexapro®, generics)	5 mg, 10 mg, 20 mg tablets; 5 mg/5 mL oral solution	12 to 17 years of age: 20 mg once daily
MDD	fluoxetine (Prozac®, generics)	10 mg, 20 mg, 40 mg capsules; 10 mg, 20 mg, 40 mg, 60 mg tablets; 20 mg/5 mL solution	8 to 17 years of age: 20 mg/day
OCD			7 to 17 years of age: • lower weight children: 30 mg/day • higher weight children: 60 mg/day
OCD	fluvoxamine (generics)	IR: 25 mg, 50 mg, 100 mg tablets	8-11 years of age: 200 mg/day# 12 to 17 years of age: 300 mg/day#
OCD	sertraline (Zoloft®, generics)	25 mg, 50 mg, 100 mg tablets; 20 mg/mL oral concentrate	6 to 17 years of age: 200 mg/day

- IR = immediate-release
- MDD = major depressive disorder
- OCD = obsessive-compulsive disorder
- #Fluvoxamine IR doses greater than 50 mg daily should be administered in divided doses

Table 4. Recommended SSRI Antidepressant Drug Dosages for Pediatric Patients – Combination Therapy

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
BD	olanzapine/ fluoxetine (Symbyax®, generics)	**3 mg/ 25 mg, 6 mg/ 25 mg, 12 mg/25 mg, 6 mg/ 50 mg, 12 mg/ 50 mg capsules**	*10 to 17 years of age:* 12 mg/50 mg per day

BD = bipolar I disorder

1.3 Renal Impairment

Many antidepressants do not require significant dosage modifications in renal impairment. However, dosage guidelines for select SSRIs in renal impairment are available. Table 5 summarizes dosage modifications and/or restrictions for specific SSRI antidepressant medications.

Table 5. Select SSRI Antidepressant Dosage Modifications in Renal Impairment

Drug Name	Dosage in Renal Impairment
Citalopram	Severe renal impairment (creatinine clearance less than 20 mL/min): use cautiously, as potential exists for active metabolites to accumulate with associated adverse effects
Escitalopram	Severe renal impairment (creatinine clearance less than 20 mL/min): use cautiously, as specific dosage guidelines not available
Paroxetine (Paxil®, Pexeva®, Paxil CR®)	Serum levels, AUC increase as renal function declines; therefore, maximum doses when creatinine clearance less than 30 mL/min are: • IR: 40 mg/day • CR: 50 mg/day

- CR = controlled-release
- IR = immediate-release

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.

Clinical trials have documented fluoxetine efficacy in BN management for up to 52 weeks. Fluoxetine has demonstrated efficacy in PMDD for up to 6 months when administered continuously and up to 3 months when administered intermittently. Paroxetine and sertraline have demonstrated efficacy in PMDD for up to 6 months and 12 months, respectively, in clinical trials. Patients should be assessed periodically to determine need for continued treatment. However, the potential exists for PMDD symptoms to worsen with advancing age until patients reach menopause. Patients responding to fluoxetine, paroxetine or sertraline therapy for PMDD may benefit from chronic administration.

Paroxetine treatment for VMS exceeding 24 weeks has not been evaluated in clinical trials. Additionally, paroxetine dosages used to manage VMS are not FDA-approved to manage psychiatric conditions, as the dose contained in Brisdelle® is lower than the recommended doses used to manage psychiatric disorders. Patients requiring paroxetine for psychiatric disorders should discontinue Brisdelle® and initiate therapy with a paroxetine formulation FDA-approved for psychiatric use.

3 Duplicative Therapy

The concurrent use of two SSRI antidepressant medications with the same spectrum of activity may not be justified and 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 6 are considered clinically relevant for SSRI 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 6. Major Drug-Drug Interactions for SSRI Antidepressant Drugs

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
fluoxetine	ergot derivatives	increased risk of ergotism due to fluoxetine inhibition of CYP3A4-mediated ergot metabolism	avoid concurrent use	contraindicated (DrugReax) major (CP)
SSRIs	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)
SSRIs	drugs with serotonergic properties (e.g., antipsychotics, 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)
SSRIs	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)
SSRIs	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)
SSRIs	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#
SSRIs	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)

- MAOI = monoamine oxidase inhibitor
- SNRI = serotonin-norepinephrine reuptake inhibitor
- SSRI= selective serotonin reuptake inhibitor
- #CP = Clinical Pharmacology

5 References

1. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at www-micromedexsolutions-com.libproxy.uthscsa.edu/ (cited: March 21, 2019).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: http://clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed March 21, 2019.
3. Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; March 21, 2019.
4. AHFS Drug Information 2019. Jackson, WY: Teton Data Systems, Version 8.10.1, 2019. Stat!Ref Electronic Medical Library. Available at: http://online-statref-com.libproxy.uthscsa.edu/. Accessed March 21, 2019.
5. Fluoxetine capsules, delayed-release capsules (Prozac®, Prozac® Weekly™) package insert. Eli Lilly and Company, March 2017.
6. Paroxetine tablets (Pexeva®) package insert. Sebela Pharmaceuticals, Inc., January 2017.
7. Paroxetine capsules (Brisdelle®) package insert. Sebela Pharmaceuticals Inc., April 2017.

8. Olanzapine and fluoxetine (Symbyax®) package insert. Eli Lilly and Company, March 2018.
9. U.S. Food and Drug Administration. FDA drug safety communication: revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm. Accessed March 21, 2019.
10. American Psychiatric Association. Work Group on Major Depressive Disorder. Practice guideline for the treatment of patients with major depressive disorder Practice guideline for the treatment of patients with major depressive disorder, 3rd edition; 2010. Available at psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed March 21, 2019.
11. Zuckerbrot RA, Cheung A, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): Part I. Practice preparation, identification, assessment, and initial management. Pediatrics. 2018;141(3):e20174081.
12. Cheung AH, Zuckerbrot RA, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD- PC): Part II. Treatment and ongoing management. Pediatrics. 2018;141(3): e20174082.
13. Freeman EW, Rickels K, Sammel MD, et al. Time to relapse after short- or long-term treatment of severe premenstrual syndrome with sertraline. Arch Gen Psychiatry. 2009; 66(5):537-44.
14. Steiner M, Ravindran AV, LeMelledo JM, et al. Luteal phase administration of paroxetine for the treatment of premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled trial in Canadian women. J Clin Psychiatry. 2008;69(6):991-8.
15. Busti AJ, Lehew DS, Nuzum DS, Daves BJ. Part 1: How does the opioid analgesic tramadol (Ultram®; Ultram ER®, Ultracet®) increase the risk for developing serotonin syndrome in patients taking SSRI antidepressant medications? Pharmacol Wkly. 2009;1(9):1-4.
16. Taylor WD. Depression in the elderly. N Engl J Med. 2014; 371:1228-36.
17. Clark MS, Jansen KL, Cloy JA. Treatment of childhood and adolescent depression. Am Fam Physician. 2012;86(5):442-8.
18. Bentley SM, Pagalilauan GL, Simpson SA. Major depression. Med Clin N Am. 2014; 98:981-1005.
19. Kovich H, DeJong A. Common questions about the pharmacologic management of depression in adults. Am Fam Physician. 2015;92(2):94-100.