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Drugs for Depression

Complete remission of symptoms is the goal of antidepressant therapy; partial response is associated with an increased risk of relapse. Improvement can occur within the first two weeks of drug therapy, but it may take 4-8 weeks to achieve a substantial benefit.[1] Fewer than 50% of patients with depression respond to first-line pharmacotherapy, and the rate of response decreases with each subsequent drug trial.[2] Following remission after a first episode of depression, many experts recommend continuing antidepressant treatment at the same dose for at least 6-12 months to consolidate recovery. For patients with recurrent depressive episodes, long-term maintenance therapy can reduce the risk of recurrence.

SSRIs – Selective serotonin reuptake inhibitors (SSRIs) are generally recommended for first-line treatment of major depression. There is no convincing evidence that any one SSRI is more effective than any other. Fluoxetine has been shown to be effective and is the only SSRI approved by the FDA for treatment of major depressive disorder in children.[3] Fluoxetine and escitalopram are both approved for treatment of major depressive disorder in adolescents.

Adverse Effects – Restlessness and sleep disturbances, particularly vivid dreams, can occur with SSRI treatment. Nausea, diarrhea, headache, dizziness, fatigue, and sexual dysfunction, which can include decreased libido, impaired arousal, delayed orgasm, or anorgasmia, can also occur.[4] An increase in motor activity is common in children. The long-term effects of these drugs on the growth, personality development, and behavior of children are unknown, but after >25 years of use, no clear signal for problems has been detected.

Some patients gain significant amounts of weight with continued use of an SSRI. SSRIs can cause hyponatremia, particularly in elderly patients. They have been associated with a possible increase in the risk of nonvertebral fractures in older women.[5] SSRIs can also increase the risk of bleeding by inhibiting serotonin uptake by platelets. SSRIs vary in their effects on CYP isoenzymes and interact with many other drugs; some of these interactions are summarized in Table 2 (see p. 88). Citalopram and escitalopram can prolong the QT interval.[6]

When SSRIs are stopped abruptly, discontinuation symptoms including nervousness, anxiety, irritability, electric-shock sensations, bouts of tearfulness or crying, dizziness, lightheadedness, insomnia, confusion, trouble concentrating, nausea, and vomiting can occur; these effects are most severe with paroxetine, possibly because of its potent serotonergic effects, and least likely to occur with fluoxetine because of its long half-life.

Pregnancy – The risk of congenital malformations after taking an SSRI during pregnancy appears to be very low, and no increase in perinatal mortality has been demonstrated.[7] An increased risk of cardiovascular and other malformations has been reported in infants born to mothers who took paroxetine in the first trimester.[8] Both untreated maternal depression and SSRI use during pregnancy have been associated with delayed fetal development, preterm birth, and low birth weight.[9] Taking SSRIs in

Recommendations for Treatment of Depression

- An SSRI, an SNRI, bupropion, or mirtazapine could be used for first-line treatment of major depression, but most expert clinicians begin with an SSRI.
- The choice among SSRIs may be determined by adverse effects and potential drug interactions, as well as accessibility and cost.
- Generic sertraline or escitalopram would be a reasonable choice for first-line treatment of depression in adults.
- Generic fluoxetine would be a good choice for treatment of depressed children, adolescents, or young adults, or patients of any age who are not taking medications metabolized by CYP2D6 or 2C19 and who would benefit from a longer half-life, such as those who miss doses.
- When patients show little to no response to an adequate trial of an SSRI (4-8 weeks), many expert clinicians switch to another SSRI or try an antidepressant from a different class. Combining two antidepressants from different classes, such as bupropion and an SSRI, or adding another drug for augmentation, such as an antipsychotic, are additional alternatives.

Table 1. Some Drugs for Depression

Drug	Some Available Formulations	Initial Adult Dosage[1]	Usual Adult Dosage[1]	Cost[2]
SSRIs				
Citalopram – generic	10, 20, 40 mg tabs; 40 mg ODT; 10 mg/5 mL soln	20 mg once/d	40 mg once/d[3]	$4.00[4]
Celexa (Allergan)	10, 20, 40 mg tabs			236.60
Escitalopram – generic	5, 10, 20 mg tabs; 5 mg/5 mL PO soln	10 mg once/d	10-20 mg once/d	6.60
Lexapro (Allergan)				241.60
Fluoxetine – generic	10, 20, 40 mg caps; 10, 20 mg tabs; 20 mg/5 mL soln	10-20 mg once/d	20 mg once/d	4.00[4]
Prozac (Lilly)	10, 20, 40 mg caps			321.60
delayed-release – generic	90 mg caps	90 mg once/wk	90 mg once/wk	130.70
Prozac Weekly				145.20
Paroxetine hydrochloride – generic	10, 20, 30, 40 mg tabs; 10 mg/5 mL susp	20 mg once/d	20 mg once/d	4.00[4]
Paxil (Apotex)				165.30
extended-release – generic	12.5, 25, 37.5 mg tabs	12.5-25 mg once/d	25 mg once/d	139.60
Paxil CR				170.30
Paroxetine mesylate – *Pexeva* (Noven)	10, 20, 30, 40 mg tabs	20 mg once/d	20-50 mg once/d	322.50
Sertraline – generic	25, 50, 100 mg tabs; 20 mg/mL soln	50 mg once/d	50-200 mg once/d	2.90
Zoloft (Pfizer)				243.00
SNRIs				
Desvenlafaxine succinate – generic	25, 50, 100 mg ER tabs	50 mg once/d	50 mg once/d	161.00
Pristiq (Pfizer)				291.20
Desvenlafaxine – generic	50, 100 mg ER tabs	50 mg once/d	50 mg once/d	139.30
Desvenlafaxine base – *Khedezla* (Osmotica)	50, 100 mg ER tabs	50 mg once/d	50 mg once/d	365.30
Duloxetine – generic	20, 30, 60 mg delayed-release caps	30-60 mg once/d	60 mg once/d or divided bid	40.80
Cymbalta (Lilly)				218.10
Venlafaxine – generic	25, 37.5, 50, 75, 100 mg tabs	25 mg tid	75 mg tid	31.50
extended-release – generic	37.5, 75, 150 mg caps; 37.5, 75, 150, 225 mg tabs	37.5 mg once/d	75-225 mg once/d	9.30[5]
Effexor XR (Pfizer)	37.5, 75, 150 mg caps			322.10
Levomilnacipran – *Fetzima* (Allergan)	20, 40, 80, 120 mg ER caps	20 mg once/d x 2d, then 40 mg once/d	40-120 mg once/d	299.20

ODT = orally disintegrating tablet; soln = solution; susp = suspension; ER = extended-release

1. Dosage may need to be adjusted for renal or hepatic impairment or for drug interactions.
2. Approximate WAC for 30 days' treatment at the lowest usual adult daily dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy.
3. According to the FDA, the daily dose should not exceed 40 mg (20 mg in patients >60 years old, patients with hepatic impairment, CYP2C19 poor metabolizers, or those taking a CYP2C19 inhibitor).
4. Cost of generics at some large discount pharmacies.

the third trimester has been associated with a self-limited neonatal behavioral syndrome, treatment in a neonatal intensive care unit, and a possible risk of persistent pulmonary hypertension in the newborn.[10,11]

SNRIs — Serotonin and norepinephrine reuptake inhibitors (SNRIs) are also considered first-line options for treatment of major depression. It is not clear that they offer any advantage in efficacy over SSRIs, and they cause more adverse effects.

Adverse Effects – The adverse effects of venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran are similar to those of SSRIs, but can also include increased sweating, tachycardia, and urinary retention. Severe discontinuation symptoms can occur when these drugs are stopped, especially with venlafaxine and desvenlafaxine because of their short half-lives. SNRIs can cause a dose-dependent increase in blood pressure; blood pressure should be controlled before starting an SNRI and monitored during treatment. False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking venlafaxine or desvenlafaxine.

Pregnancy – Pregnancy studies with SNRIs are limited; fetal malformations are uncommon, but increased risks of neonatal behavioral syndrome and perinatal complications have been reported with use of SNRIs during pregnancy.[12]

BUPROPION — Bupropion can be used as an alternative to an SSRI for depressed patients who do not have severe anxiety or a primary anxiety disorder. Bupropion may improve hypoactive sexual desire disorder and antidepressant-induced sexual dysfunction.[13] It is not sedating and has not been

Table 1. Some Drugs for Depression (continued)

Drug	Some Available Formulations	Initial Adult Dosage[1]	Usual Adult Dosage[1]	Cost[2]
TCAs[6]				
Amitriptyline – generic	10, 25, 50, 75, 100, 150 mg tabs	25-100 mg at bedtime or divided	100-300 mg once/d	$34.30
Desipramine – generic *Norpramin* (Sanofi)	10, 25, 50, 75, 100, 150 mg tabs	25-100 mg once/d or divided	100-300 mg once/d	115.10 175.50
Imipramine – generic *Tofranil* (Mallinckrodt)	10, 25, 50 mg tabs	25-100 mg once/d	100-300 mg once/d	32.20 817.60
Imipramine pamoate – generic	75, 100, 125, 150 mg caps	75 mg once/d	150 mg once/d	672.60
Nortriptyline – generic *Pamelor* (Mallinckrodt)	10, 25, 50, 75 mg caps	50-100 mg once/d or divided	50-150 mg once/d	7.10 1021.70
MAOIs				
Isocarboxazid – *Marplan* (Validus)	10 mg tabs	10 mg bid	30-40 mg/d divided	354.60
Phenelzine – generic *Nardil* (Pfizer)	15 mg tabs	15 mg tid	30 mg bid	78.90 221.30
Selegiline – *Emsam* (Somerset)	6, 9, 12 mg/24 hr patches	6 mg/24 hr	6, 9, 12 mg/24 hr	1513.40
Tranylcypromine – generic *Parnate* (Covis)	10 mg tabs	10 mg once/d	20-30 mg bid	323.00 438.00
Other				
Bupropion – generic extended-release (12 hour) – generic *Wellbutrin SR* (GSK) *Aplenzin* (Valeant) extended-release (24 hour) – generic *Wellbutrin XL* *Forfivo XL* (Edgemont)	75, 100 mg tabs 100, 150, 200 mg tabs 174, 348, 522 mg ER tabs 150, 300 mg tabs 450 mg ER tabs	100 mg bid 150 mg once/d 174 mg once/d 150 mg once/d See footnote 7	100 mg tid 150 mg bid 348 mg once/d 300 mg once/d 450 mg once/d	63.00 19.00 377.70 1444.20 78.30 1427.80 360.00
Mirtazapine – generic *Remeron* (Organon) orally disintegrating – generic *Remeron SolTab*	7.5, 15, 30, 45 mg tabs 15, 30, 45 mg tabs 15, 30, 45 mg ODT	15 mg once/d at hs	30-45 mg once/d	11.30 163.20 60.20 130.00
Nefazodone[8] – generic	50, 100, 150, 200, 250 mg tabs	100 mg bid	200 mg bid	82.30
Trazodone – generic extended-release – *Oleptro* (Labopharm)	50, 100, 150, 300 mg tabs 150, 300 mg tabs	75 mg bid 150 mg once/d	300 mg divided bid 150-375 mg once/d	10.80 96.00
Vilazodone – *Viibryd* (Allergan)	10, 20, 40 mg tabs	10 mg once/d	40 mg once/d	208.30
Vortioxetine – *Trintellix* (Takeda/Lundbeck)	5, 10, 20 mg tabs	10 mg once/d	10-20 mg once/d	318.20

5. Cost of capsules. The cost for tablets is $115.30.
6. Therapeutic serum concentrations are: amitriptyline 100-250 ng/mL; desipramine 150-300 ng/mL; imipramine 150-300 ng/mL; nortriptyline 50-150 ng/mL.
7. Initiate treatment with another bupropion formulation.
8. Brand name nefazodone was withdrawn from the market due to hepatotoxicity.

associated with weight gain, sexual dysfunction, or an increased risk of bleeding.

Adverse Effects – Bupropion can cause agitation, anxiety, insomnia, headache, nausea, anorexia, and hypersensitivity reactions. Dose-related seizures may occur; the drug is contraindicated in patients with seizure disorders. It is also contraindicated in patients with eating disorders because these patients have had a higher incidence of seizures when treated with high doses of bupropion. The safety of bupropion during pregnancy has not been established.[14]

MIRTAZAPINE — Mirtazapine may be useful when insomnia is prominent, and its appetite-stimulating and weight-gain-promoting properties may be helpful in depressed patients with marked anorexia.

Adverse Effects – Mirtazapine can cause sedation, increased appetite, weight gain, dizziness, dry mouth, and constipation; neutropenic fevers have occurred rarely. Pregnancy studies with mirtazapine are limited; the risk of congenital malformations appears to be low.[15]

OTHER DRUGS — Trazodone, which is also sedating, is seldom used as monotherapy, but is commonly used in low doses as an adjunct to an SSRI in patients with insomnia.[16] Trazodone can cause drowsiness, orthostatic hypotension, myocardial irritability, and priapism. **Nefazodone**, which is structurally similar to trazodone, has been withdrawn from the market in some countries because of rare severe hepatotoxicity.

Vilazodone is an SSRI and partial serotonin 1a receptor agonist; it appears to be an effective antidepressant, but there is no acceptable evidence for claims that it acts more rapidly than SSRIs.[17] Vilazodone has an adverse effect profile similar to that of SSRIs; limited

Table 2. Some SSRI and SNRI Drug Interactions

Drug	CYP	Comments
Citalopram	Metabolized by 2C19[1] and 3A4	Maximum dose of 20 mg/day in 2C19 poor metabolizers or with inhibitors of 2C19; higher serum concentrations increase the risk of QT prolongation; avoid use with other drugs that prolong the QT Interval
Desvenlafaxine	Metabolized by 3A4 Weak inhibitor of 2D6	Low potential for interactions; reduce dose of 2D6 substrates if administered with 400 mg of desvenlafaxine
Duloxetine	Metabolized by 1A2[1] and 2D6 Moderate inhibitor of 2D6	Avoid strong inhibitors of 1A2; 2D6 inhibitors can increase duloxetine concentrations; duloxetine increases concentrations of drugs that are substrates of 2D6
Escitalopram	Metabolized by 2C19[1] and 3A4	Low potential for interactions; dose adjustments may be needed with 2C19 inhibitors; may prolong the QT interval
Fluoxetine	Metabolized by 2D6[1] and 2C9 Strong inhibitor of 2D6 Moderate inhibitor of 2C19	May decrease efficacy of tamoxifen; may increase concentrations of 2D6 substrates; long half-life is a problem when interactions occur
Levomilnacipran	Metabolized by 3A4[1]	Dose adjustment needed when administered with strong 3A4 inhibitors
Paroxetine	Metabolized by 2D6 Strong inhibitor of 2D6	May decrease efficacy of tamoxifen; may increase concentrations of 2D6 substrates; lower doses of paroxetine may be needed with 2D6 inhibitors
Sertraline	Metabolized by 2C19 Moderate inhibitor of 2D6	Low potential for interactions
Venlafaxine	Metabolized by 2D6[1] and 3A4	Low potential for interactions; serum concentrations may be increased by 3A4 inhibitors

1. Primary pathway

data exist to support claims that it causes less sexual dysfunction or weight gain than SSRIs.[18]

Vortioxetine, which inhibits reuptake of serotonin and acts as an agonist or antagonist at various serotonin receptors, is FDA-approved for treatment of major depressive disorder.[19] Vortioxetine has an adverse effect profile similar to that of SSRIs.

Tricyclic antidepressants (TCAs) and **monoamine oxidase inhibitors** (MAOIs) remain valuable alternatives for patients with moderate to severe treatment-resistant depression. TCAs have a narrow therapeutic index and serum levels should be monitored. TCAs commonly cause anticholinergic effects (urinary retention, constipation, dry mouth, blurred vision, memory impairment, confusion), orthostatic hypotension, weight gain, sedation, and sexual dysfunction. They can cause cardiac conduction delays which can lead to arrhythmias and death when taken in overdose. TCAs must be used with caution in patients with ischemic heart disease. TCA use during pregnancy has been associated with jitteriness and convulsions in newborns.

MAOIs are contraindicated for use with serotonergic drugs (SSRIs) or other drugs that increase monoamines (noradrenergic, dopaminergic), and their use requires strict adherence to a low tyramine diet to avoid life-threatening drug interactions. Interactions with serotonergic drugs, sympathomimetics, and tyramine-rich foods can result in serotonin syndrome or a hypertensive crisis, either of which can be fatal. These interactions have not been reported with transdermal selegiline 6 mg/day.[20] The enzyme-inhibiting effects of MAOIs can persist for up to 2 weeks after the drug is stopped (during which period of time other serotonergic medications are contraindicated). Adverse effects of MAOIs include sleep disturbances, orthostatic hypotension, sexual dysfunction, and weight gain. Some expert clinicians do not recommend use of MAOIs during pregnancy because of the risk of drug or food interactions causing a hypertensive crisis.

A single IV infusion of the anesthetic agent **ketamine**, which can have hallucinogenic effects, has been found to be effective for treatment of depression in several trials, but it is not recommended because it lacks FDA approval for use in depression and has a potential for abuse.[21]

OTHER ADVERSE EFFECTS – Suicidality – All FDA-approved antidepressants have a boxed warning in their labels regarding an increased risk of suicidal thinking and behavior in children, adolescents, and young adults. An FDA analysis of placebo-controlled antidepressant studies found an increased risk of suicidal thinking or behavior in patients ≤24 years old being treated with an antidepressant and a decreased risk in those ≥65 years old. Several other reviews have also suggested that antidepressant use can increase the risk of aggression and suicidality in children, adolescents, and young adults.[22,23] No increase in completed suicide was documented among patients treated with antidepressants. In one randomized controlled trial in

adolescents with depression, fluoxetine significantly improved suicidal thinking, compared to placebo.[24] One study of early adolescent suicide found that more SSRI prescriptions were associated with lower suicide rates.[25] All depressed children, adolescents, and adults should be monitored for suicidal ideation and behavior.

Mania – All antidepressants can induce mania, most often in patients with undetected or undiagnosed bipolar disorder. Patients should be screened for personal or first-degree-relative history of mania, hypomania, or other evidence of bipolar disorder before starting antidepressant therapy. Patients starting antidepressant therapy should be followed closely in the first weeks to months of treatment.

Serotonin Syndrome – All serotonergic drugs can cause serotonin syndrome, a rare but potentially life-threatening condition characterized by altered mental status, fever, tachycardia, hypertension, agitation, tremor, myoclonus, hyperreflexia, ataxia, incoordination, diaphoresis, shivering, and gastrointestinal symptoms.[26] It occurs only very rarely with SSRI monotherapy at recommended doses. Serotonin syndrome occurs most commonly as a result of interactions with other drugs. Serotonergic drugs and MAOIs should not be used concurrently or within 2 weeks of each other; up to 5 weeks may be required with fluoxetine. Some drugs with MAOI activity, such as the antimicrobial agent linezolid (*Zyvox*, and generics), and some drugs that may not be recognized as serotonergic, such as dextromethorphan, sumatriptan (*Imitrex*, and generics), tramadol (*Ultram*, and generics), methadone, and St. John's wort, can cause serotonin syndrome when taken concurrently with an SSRI or SNRI.[27]

SECOND-LINE TREATMENT — When patients show little to no response to an adequate trial of an SSRI (4-8 weeks), many expert clinicians switch to another SSRI or try an antidepressant from a different class. Combining two antidepressants from different classes, such as bupropion and an SSRI, or adding another drug for augmentation are additional alternatives.[1,28,29] Augmentation with second-generation **antipsychotic drugs** has been effective, but it can cause weight gain, metabolic adverse effects, and akathisia.[30,31] Extended-release **quetiapine**, **aripiprazole,** and **brexpiprazole**[32] are FDA-approved for adjunctive treatment of major depressive disorder. A fixed-dose combination of **olanzapine and fluoxetine** *(Symbyax)* is FDA-approved for treatment-resistant depression. Augmentation with **liothyronine** has been reported to be effective, but thyroid function must be monitored.[33] Augmentation with low doses of **lithium** has been reported to be effective with both TCAs and newer antidepressants.[34] Augmentation with the anti-anxiety agent **buspirone**, once widely used, appears to be ineffective.[28,29,35]

NON-DRUG THERAPY — Psychotherapy, particularly **cognitive-behavioral therapy** (CBT) and **interpersonal therapy**, is an effective treatment for mild to moderately severe, nonpsychotic depression. **Electroconvulsive therapy** (ECT) is highly effective for severe depression, depression with psychosis, bipolar depression, and depression refractory to medications.[36] **Transcranial magnetic stimulation** (TMS) and **vagus nerve stimulation** (VNS) are FDA-approved for treatment-resistant depression. TMS, unlike ECT, does not require anesthesia and does not appear to have cognitive side effects. Studies of TMS have demonstrated response and remission rates similar to those with antidepressants[37]; it may be a reasonable treatment option when patients are unable to tolerate or do not respond to antidepressants. **Deep brain stimulation** has been effective in a small number of patients with treatment-resistant depression,[38] but was not found to be superior compared to sham treatment in clinical trials.[39] ■

1. American Psychiatric Association, 2010. Treating major depressive disorder: a quick reference guide. Practice guideline for the treatment of patients with major depressive disorder, third edition. Available at psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd-guide.pdf. Accessed June 23, 2016.
2. D Warden et al. The STAR*D Project results: a comprehensive review of findings. Curr Psychiatry Rep 2007; 9:449.
3. A Cipriani et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. Lancet 2016 Jun 7 (epub).
4. MD Waldinger. Psychiatric disorders and sexual dysfunction. Handb Clin Neurol 2015; 130:469.
5. V Rabenda et al. Risk of nonvertebral fractures among elderly postmenopausal women taking antidepressants. Bone 2012; 51:674.
6. Citalopram, escitalopram and the QT interval. Med Lett Drugs Ther 2013; 55:59.
7. O Stephansson et al. Selective serotonin reuptake inhibitors during pregnancy and risk of stillbirth and infant mortality. JAMA 2013; 309:48.
8. A Bérard et al. Paroxetine use during pregnancy and perinatal outcomes including types of cardiac malformations in Quebec and France: a short communication. Curr Drug Saf 2012; 7:207.
9. H Malm et al. Pregnancy complications following prenatal exposure to SSRIs or maternal psychiatric disorders: results from population-based national register data. Am J Psychiatry 2015; 172:1224.
10. S Gentile. On categorizing gestational, birth, and neonatal complications following late pregnancy exposure to antidepressants: the prenatal antidepressant exposure syndrome. CNS Spectr 2010; 15:167.
11. CD Chambers et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 2006; 354:579.
12. C Bellantuono et al. The safety of serotonin-noradrenaline reuptake inhibitors (SNRIs) in pregnancy and breastfeeding: a comprehensive review. Hum Psychopharmacol 2015; 30:143.
13. VM Pereira et al. Bupropion in the depression-related sexual dysfunction: a systematic review. CNS Neurol Disord Drug Targets 2014; 13:1079.

14. NE De Long et al. Is it safe to use smoking cessation therapeutics during pregnancy? Expert Opin Drug Saf 2014; 13:1721.
15. U Winterfeld et al. Pregnancy outcome following maternal exposure to mirtazapine: a multicenter, prospective study. J Clin Psychopharmacol 2015; 35:250.
16. Extended-release trazodone (Oleptro) for depression. Med Lett Drugs Ther 2010; 52:91.
17. Vilazodone (Viibryd) – a new antidepressant. Med Lett Drugs Ther 2011; 53:53.
18. AH Clayton et al. Sexual dysfunction during treatment of major depressive disorder with vilazodone, citalopram, or placebo: results from a phase IV clinical trial. Int Clin Psychopharmacol 2015; 30:216.
19. Vortioxetine (Brintellix/Trintellix) for depression. Med Lett Drugs Ther 2013; 55:93.
20. Transdermal selegiline (Emsam). Med Lett Drugs Ther 2006; 48:41.
21. C Caddy et al. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst Rev 2015; 9:CD011612.
22. SE Hetrick et al. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev 2012; 11:CD004851.
23. T Sharma et al. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016 Jan 27 (epub).
24. J March et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA 2004; 292:807.
25. RD Gibbons et al. The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry 2006; 163:1898.
26. NA Buckley et al. Serotonin syndrome. BMJ 2014 Feb 19 (epub).
27. EW Boyer and M Shannon. The serotonin syndrome. N Engl J Med 2005; 352:1112.
28. KR Connolly and ME Thase. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. Drugs 2011; 71:43.
29. MH Trivedi et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006; 354:1243.
30. Adjunctive antipsychotics for major depression. Med Lett Drugs Ther 2011; 53:74.
31. BM Wright et al. Augmentation with atypical antipsychotics for depression: a review of evidence-based support from the medical literature. Pharmacotherapy 2013; 33:344.
32. Brexpiprazole (Rexulti) for schizophrenia and depression. Med Lett Drugs Ther 2015; 57:116.
33. R Cooper-Kazaz and B Lerer. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. Int J Neuropsychopharmacol 2008; 11:685.
34. JC Nelson et al. A systematic review and meta-analysis of lithium augmentation of tricyclic and second generation antidepressants in major depression. J Affect Disord 2014; 168:269.
35. MH Trivedi et al. Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. Arch Gen Psychiatry 2004; 61:669.
36. PE Holtzheimer and HS Mayberg. Neuromodulation for treatment-resistant depression. F1000 Med Rep 2012; 4:22.
37. Health Quality Ontario. Repetitive transcranial magnetic stimulation for treatment-resistant depression: A systematic review and meta-analysis of randomized controlled trials. Ont Health Technol Assess Ser 2016; 16:1.
38. IO Bergfeld. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry 2016; 73:456.
39. DD Dougherty. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry 2015; 78:240.

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