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Which drugs are most effective for moderate to severe depression in adolescents?

Evidence-based answer

Fluoxetine is the only selective serotonin-reuptake inhibitor (SSRI) approved by the US Food and Drug Administration (FDA) to treat depression in children 8 years of age and older; it also has the most favorable benefit-to-risk profile compared with placebo in trials lasting up to 12 weeks (strength of recommendation [SOR]: **A**, meta-analysis). Fluoxetine combined with cognitive behavioral therapy (CBT) is superior to fluoxetine alone, CBT alone, or placebo (SOR: **B**, single well-done randomized controlled trial [RCT]).

Further research is needed to address the long-term efficacy of fluoxetine treatment.

Tricyclic antidepressants, citalopram, escitalopram, venlafaxine, and sertraline are minimally effective in treating depression in adolescents (SOR: **A**, meta-analysis). Head-to-head trials are needed to compare the efficacy of antidepressants.

(For information on the safety of antidepressants in adolescents, see the Clinical Inquiry on page 327.)

Clinical commentary

Fluoxetine: A valuable tool

Two studies—the Treatment for Adolescents with Depression Study (TADS)¹ and the recently published Adolescent Depression, Antidepressants, and Psychotherapy Trial (ADAPT)²—both based on validated survey tools available in primary care, clearly demonstrate the effectiveness of SSRIs—particularly fluoxetine—for alleviating depressive symptoms.

In my clinical practice, fluoxetine is a valuable tool to rapidly improve depression and common comorbid conditions such as

bulimia nervosa, anorexia nervosa, binge-eating disorder not otherwise specified, panic disorder, and obsessive-compulsive disorder. The recent ADAPT trial provides further convincing and consistent data that SSRI therapy should be considered first-line therapy for adolescent depression.

Obviously, prudence mandates close follow-up of your teenage patients and thorough discussion of the risk of increased suicidality with both the patient and parent or guardian.

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Consider SSRIs as first-line therapy for adolescent depression

Evidence summary

Fifteen well-designed trials have examined the efficacy of antidepressants for

treating major depressive disorder in youth. All reported the changes in total scores on standard depression scales: the

Children's Depression Rating Scale-Revised, Clinical Global Impressions, Hamilton Rating Scale for Depression, or Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children. The **TABLE** summarizes the findings for SSRIs and venlafaxine based on a meta-analysis of the 15 trials.³ (For more on the characteristics and efficacy of venlafaxine and SSRIs in young people, see **TABLE W1**, available online at www.jfponline.com.)

The best bet: Fluoxetine plus CBT

The landmark Treatment for Adolescents with Depression Study, which was included in the meta-analysis, comprised 4 treatment arms: fluoxetine alone, CBT alone, fluoxetine with CBT, and placebo. Only the combination therapy group showed a statistically significant improvement compared with placebo in the primary outcome (improved Children's Depression Rating Scale-Revised). Improvement in the Clinical Global Impressions score, a subjective measure, was statistically significant in 71% of patients receiving combination therapy and 60.6% of those treated with fluoxetine compared with placebo (34.8%) or CBT alone (43.2%).¹

Two RCTs showed that sertraline was slightly, but statistically significantly, better than placebo when the 2 identically designed trials were combined.⁴ Pooled results of 3 RCTs demonstrated that paroxetine was no better than placebo.³ Two RCTs of citalopram and 1 RCT of escitalopram showed marginally significant benefit over placebo only when pooled.³ A post hoc subgroup analysis of 2 combined RCTs comparing extended-release venlafaxine with placebo showed modest, statistically significant improvement in depressive symptoms in adolescents, but not children.⁵ A 2007 Cochrane review supports the use of SSRIs to treat major depressive disorder in adolescents, reporting efficacy as 1.28 times that of placebo (95% confidence interval, 1.17-1.41).⁶

Quality of available clinical evidence is limited. Statistical significance was demonstrated in meta-analyses only when data from smaller trials were combined. Fluoxetine was the only antidepressant studied in nonindustry-sponsored trials for major depressive disorder in adolescents. Moreover, results are not often reported separately for children (5-12 years of age) and adolescents (12-18 years of age).

Side effects are an issue for tricyclics

A 2002 Cochrane meta-analysis reported marginal evidence to support using tricyclic antidepressants for treating adolescents. However, these drugs have significantly more side effects than placebo.⁷ No placebo-controlled RCTs of bupropion, duloxetine, mirtazapine, or St. John's wort for treating major depressive disorder in adolescents were identified.

Recommendations

A 1998 practice parameter published by The American Academy of Child and Adolescent Psychiatry (AACAP) strongly favors psychotherapy alone or in combination with medication. The guideline recommends treatment throughout the acute and continuation phase of illness—at least 6 months—with possible active treatment during the maintenance phase (which begins after 6 months to 1 year without symptoms and may extend indefinitely). AACAP advocates using SSRIs as first-line therapy without endorsing a specific medication.⁸

The Society for Adolescent Medicine supports pharmacotherapy for depressed adolescents, stating that “data supporting the effectiveness of selective serotonin-reuptake inhibitors for adolescents with major depressive disorder, particularly for fluoxetine, is compelling.”⁹ Similarly, the American College of Neuropsychopharmacology notes that the risk-to-benefit ratio favors drug therapy for moderate to severe depression in adolescents and recommends fluoxetine as an effective treatment for major depression in youth; RCTs

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**Fluoxetine
combined with
cognitive
behavioral therapy
is superior
to fluoxetine alone**

TABLE

Efficacy of SSRIs and venlafaxine in young people

DRUG	ABSOLUTE RISK REDUCTION %* (95% CI)	NNT (95% CI)
Citalopram/escitalopram [†]	8 (1 to 16)	13 (7 to 200)
Fluoxetine ^{† ‡}	20 (11 to 29)	6 (4 to 10)
Sertraline [§]	10 (0 to 20)	10 (6 to 500)
Paroxetine [†]	5 (-3 to 13)	NA
Venlafaxine [‡]	11 (1 to 21)	10 (5 to 112)

CI, confidence interval; NNT, number needed to treat; SSRIs, selective serotonin-reuptake inhibitors.

* Absolute risk reduction is the risk difference when comparing agent to placebo using differences in measures of standardized depression scales before and after therapy (Hamilton Rating Scale for Depression, Clinical Global Impressions, Children's Depression Rating Scale-Revised, or Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children).

[†] Estimates from pooled data.

[‡] NNT represents average of NNT of individual trials pooled.

[§] 2 randomized controlled trials combined.

Source: Bridge JA et al.³

comparing other SSRIs with fluoxetine are needed to establish the efficacy of these drugs.¹⁰ ■

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The Society for Adolescent Medicine notes that the evidence for SSRIs—particularly for fluoxetine—is compelling

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