Which drugs are safest for moderate to severe depression in adolescents?

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Evidence-based answer

Selective serotonin-reuptake inhibitors (SSRIs) appear to be the safest, given current data.

Major safety concerns—prompting a US Food and Drug administration (FDA) black box label warning—have been raised about increased risk of suicidality (ideation, behavior, and attempts) among adolescents receiving antidepressant therapy. Studies indicate that SSRIs and venlafaxine increase the absolute risk of suicidality by 1% to 2% compared with placebo. However, no suicides occurred during any study. On detailed subanalysis, each SSRI was as safe as placebo, and only venlafaxine demonstrated a statistically significant increase in risk of suicidality (strength of recommendation [SOR]: **A**, meta-analysis).

Information about the safety of tricyclic antidepressants in young people is limited because adverse effects have not been systematically reported in trials (SOR: **A**, meta-analysis).

(For information on the efficacy of antidepressants in adolescents, see the Clinical Inquiry on page 330.)

Clinical commentary

Treat with vigilance

Based on the available evidence, I'm confident in my decision to use SSRIs to treat depressed adolescents. But the FDA black box warning often leaves me with a sense of apprehension as I write the prescription. I consider this a healthy reminder that depression in adolescents is no small matter, and its treatment shouldn't be taken lightly.

In my practice, patient and family education always accompany the use of SSRIs, as does weekly follow-up in the beginning. Of the many patient education resources available on the Internet, my favorite Web sites include:

- www.familydoctor.org,
- www.aacap.org (Facts for Families),
- www.kidshealth.org (features pages for both parents and teenagers), and
- www.medlineplus.gov (handouts in English and Spanish and interactive tutorials).

Finally, no adolescent leaves my office without suicide precautions and phone numbers of local and national suicide prevention hotlines (www.suicidehotlines.com).

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Evidence summary

In 2003, the United Kingdom's Expert Working Group of the Committee on Safety of Medicines (CSM) and the FDA

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TABLE

Risk of suicidality among young people taking antidepressants—Pooled results of 2 meta-analyses[1,4]

DRUG	META-ANALYSIS	OR* (95% CI)
Citalopram, escitalopram	Hammad[3] Dubicka[6]	1.37 (0.53-3.50) 1.21 (0.60-2.45)
Fluoxetine	Hammad Dubicka	1.53 (0.74-3.16) 1.36 (0.65-2.88)
Paroxetine	Hammad Dubicka	2.15 (0.71-6.52) 1.53 (0.61-3.84)
Sertraline	Hammad Dubicka	2.16 (0.48-9.62) 2.47 (0.47-12.9)
Venlafaxine	Hammad Dubicka	8.84 (1.12-69.51) 14.83 (1.93-114.0)

*Includes suicidal ideation, behavior, and attempts.
CI, confidence interval; OR, odds ratio.

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Venlafaxine had the only statistically significant increased risk of suicidality—mostly because of suicidal ideation

conducted a review and meta-analysis, respectively, of the newer antidepressants used in children and adolescents.[1,2] Based on these studies, the FDA mandated that all antidepressant labels carry a black box warning about the increased risk of suicidal thinking and behavior (suicidality) among adolescents taking the medications.

No suicides, but a two-fold increase in suicidality

A recent study that incorporated the FDA meta-analysis analyzed data from 4582 patients. Although no completed suicides were reported in any trial, the drug-treated groups had a two-fold increase in suicidality compared with placebo groups (4% vs 2%; number needed to harm [NNH]=50).[3] A recent Cochrane review confirmed the increase in absolute risk (1.8; 95% confidence interval [CI], 1.19-2.72).[4]

Two subsequent analyses estimated the difference in risk to be 1.6-fold with a 95% CI of 1.0-2.7 (3% vs 2%; NNH=112).[5,6] The lower estimated risk results largely from a statistical reframing rather than any major difference in data analyzed. The analyses used a random-effects model instead of a fixed-effects model to calculate suicidality, assuming heterogeneity in the drugs used, trial designs, and outcome measures.[3,6] All of the analyzed trials excluded patients at high risk for suicide, defined uniquely in the exclusion criteria for each trial.

The **TABLE** summarizes the increased risk of suicidality for each drug. Notably, venlafaxine had the greatest—and only statistically significant—increased risk, mostly because of suicidal ideation (7 of 9 events in 182 treated patients vs none in 179 placebo patients).[6] (For a detailed look at the risk of suicidal ideation, suicidal behavior, or suicide attempt, see **TABLE W1**, available online at www.jfponline.com.)

Data on tricyclics in adolescents are scarce

Evidence concerning the safety of tricyclic antidepressants in adolescents is limited because adverse effects have not been systematically reported. A 2002 Cochrane meta-analysis found a statistically significant increase in rates of vertigo, orthostatic hypotension, tremor, and dry mouth among children and adolescents taking tricyclic antidepressants compared with placebo. The drugs are modestly effective in treating depression in adolescents; concerns about side effects and safety, however, have limited their use.[7]

Recommendations

The FDA encourages patients taking antidepressants and their families to be alert for signs of impulsive behavior or suicidal tendencies and to have a safety plan. The FDA, American Academy of Child and Adolescent Psychiatry, and the Society for Adolescent Medicine endorse close follow-up with periodic objective assessment.[8-10]

The Society for Adolescent Medicine explicitly directs clinicians to consider the FDA black box warning in the context of the need to treat major depressive disorder in adolescents and endorses pharmacotherapy for appropriately selected patients.[10] Similarly, the American

College of Neuropsychopharmacology argues that the risk-to-benefit ratio favors drug treatment for moderate to severe adolescent depression.[11] ■

References

1. US Food and Drug Administration. Relationship between psychotropic drugs and pediatric suicidality: review and evaluation of clinical data. Available at: www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf. Accessed October 29, 2007.
2. Medicines and Healthcare products Regulatory Agency, Committee on Safety of Medicines. Use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents with major depressive disorder (MDD). Available at: www.mhra.gov.uk/. Accessed October 29, 2007.
3. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry.* 2006;63:332-339.
4. Hetrick S, Merry S, McKenzie J, et al. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database Syst Rev.* 2007;(3):CD004851.
5. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA.* 2007;297:1683-1696 (and Web-only content http://jama.ama-assn.org/cgi/content/full/297/15/1683; accessed June 13, 2007).
6. Dubicka B, Hadley S, Roberts C. Suicidal behaviour in youths with depression treated with new-generation antidepressants. *Br J Psychiatry.* 2006;189:393-398.
7. Hazell P, O'Connell D, Heathcote D, et al. Tricyclic drugs for depression in children and adolescents. *Cochrane Database Syst Rev.* 2002;(2):CD002317.
8. US Food and Drug Administration. Medication guide about using antidepressants in children and Teenagers. Revised January 26, 2005. Available at: www.fda.gov/cder/drug/antidepressants/MG_template.pdf. Accessed June 2, 2007.
9. Birmaher B, Brent DA, Benson RS, et al. Summary of the practice parameters for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry.* 1998;37:1234-1238.
10. Lock J, Walker LR, Rickert VI, et al. Suicidality in adolescents being treated with antidepressant medications and the black box label: position paper of the Society for Adolescent Medicine. *J Adolesc Health.* 2005;36:92-93.
11. Mann JJ, Graham E, Baldessarini RJ, et al. ACNP Task Force report on SSRIs and suicidal behavior in youth. *Neuropsychopharmacology.* 2006;31:473-492.