# Antidepressants and Suicidality

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**KEYWORDS**

• Depression • Antidepressant • Suicide • Suicidal events • Adolescents
• Young adults • Clinical trials

**KEY POINTS**

- Second-generation antidepressants are associated with a slightly increased risk for suicidal events compared with placebo in randomized clinical trials (RCTs) in youth.
- Four to eleven times more depressed youth benefit from antidepressants than experience a suicidal event.
- Pharmacoepidemiologic studies, which are much larger and more representative of patient populations than RCTs, show a protective effect of regional antidepressant use on suicide.
- Youth most likely to experience a suicidal event have high baseline suicidal ideation, family conflict, alcohol and substance use, nonsuicidal self-injury, and non-response to treatment.
- The clinician can mitigate suicidal risk in depressed youths through education, a safety plan, close clinical monitoring, targeting of suicidal risk factors, and rational dosing.

## DEFINITIONS OF SELF-HARM

The definitions of self-harm used in this article are provided in **Table 1**.[1]

## META-ANALYSES OF RANDOMIZED CLINICAL TRIALS

Hammad and colleagues[2] first reported, in a meta-analysis of 24 randomized clinical trials (RCTs) (20 of which had data on suicidal events), that antidepressant use was associated with an increased risk for suicidal events in depressed youth (odds ratio [OR] = 1.66) and across indications (OR = 1.95). A subsequent meta-analysis of RCTs registered by the Food and Drug Administration (FDA) across the life span showed an increased rate of suicidal events in adults younger than 25 (OR = 1.62), but a protective effect in those aged 25 to 64 (OR = 0.87) and older than 65 (OR = 0.37).[3] A meta-analysis of 27 youth antidepressant RCTs found an increased rate of suicidal events with a risk-difference of 0.7% (meaning the rate of suicidal events in the medication group was higher than the placebo group by

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**Table 1**
**Definitions of self-harm outcomes**

| Type of Self-Harm | Definition |
|---|---|
| Suicidal ideation | Thoughts of death, thoughts of one's own death, with or without intent or a plan |
| Suicide attempt | Self-destructive behavior with explicit or inferred intent to die |
| Nonsuicidal self-harm | Self-destructive behavior with an aim to modify negative affect, punish self, or escape, but without any suicidal intent |
| Suicide | Suicide attempt that results in a fatality |
| Suicidal event | New-onset or worsened suicidal ideation or suicidal behavior |

*Adapted from* Posner K, Oquendo MA, Gould M, et al. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007;164(7):1035–43.

0.7%), with a 1.7-fold increase in suicidal events (Fig. 1).[4] In addition, 11 times more depressed adolescents responded to an antidepressant than experienced a suicidal event, with even higher benefit-risk ratios for those with obsessive compulsive or anxiety disorders. A Cochrane review of adolescent depression RCTs found similarly increased risks for suicidal events (OR = 1.6), with approximately 4.5 times the number of youth attaining clinical remission as experienced suicidal events.[5]

## WHY IS THERE AN INCREASED RISK FOR SUICIDAL EVENTS FOUND IN THOSE YOUNGER THAN 25?

1. There are no proven explanations, but the following are commonly offered: Antidepressant treatment in the young is more likely to uncover a proclivity to bipolar disorder, induce a possible mixed state, and thereby increase the risk for suicide.[6] The younger the patient treated with an antidepressant, the higher the risk for antidepressant-associated mania (Fig. 2).[7] One meta-analysis estimated that the risk of mania in depressed youth treated with an antidepressant versus placebo was 10% versus 0.45%.[8]

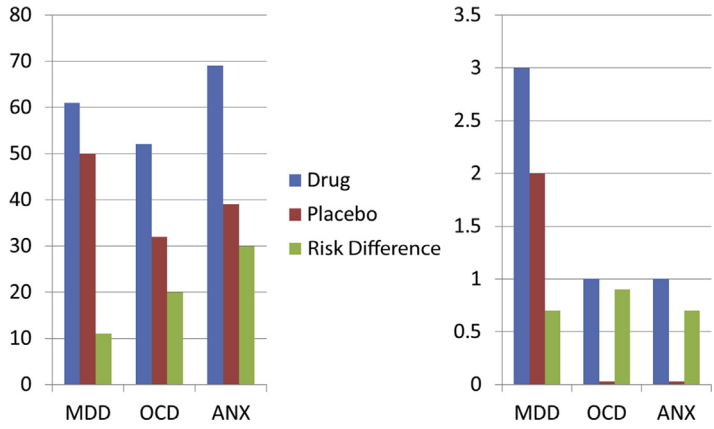


**Fig. 1.** Risks and benefits of antidepressants by indication in youth. (*Data from* Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 2007;297(15):1683–96.)

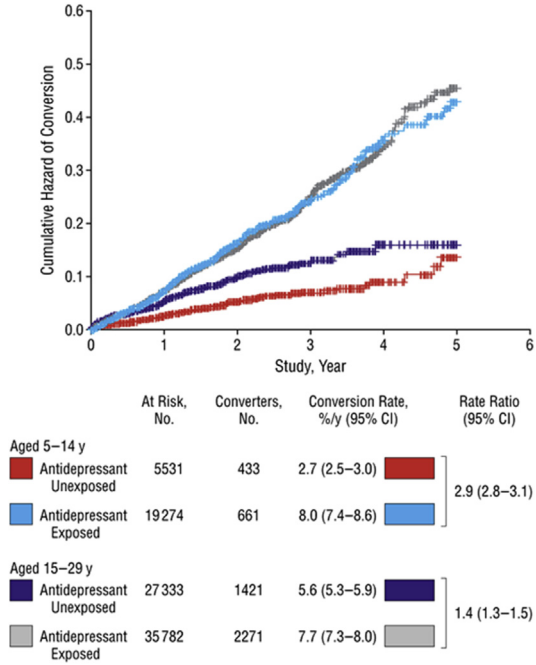


**Fig. 2.** Risk of mania and antidepressant treatment by age. CI, confidence interval. (*From* Martin A, Young C, Leckman JF, et al. Age effects on antidepressant-induced manic conversion. Arch Pediatr Adolesc Med 2004;158(8):777; with permission.)

2. Developmental differences associated with the transition from adolescence to adulthood may explain the differential adverse effects of antidepressants. A lack of maturity in prefrontal myelination that could predispose to impulsivity,[9] and higher densities of 5HT1A and 5HT2A serotonergic receptors have been reported in younger individuals.[10,11] Higher density of 5HT1A receptors is associated with higher lethality suicide attempts[12] and nonresponse to a selective serotonin reuptake inhibitor (SSRI),[13] whereas greater 5HT2A density has been associated with impulsive aggression,[14] a key risk factor for youth suicide.[15]
3. Younger patients metabolize antidepressants more quickly. For example, at lower doses of sertraline, its half-life is much shorter in adolescents than in adults.[16] This may be important because greater drug concentration may be related to a greater likelihood of response, and in drugs with shorter half-lives, lower doses in adolescents may be associated with experience of withdrawal symptoms.[17] Among 7 antidepressants studied in adolescent depression, there is a high inverse correlation (rho = −0.79) between the half-life of the drug and the rate of suicidal events in those studies.[18] However, suicidal events are also seen in patients treated with fluoxetine, which has a half-life of approximately 5 days and whose active metabolite, norfluoxetine, has a half-life of approximately 15 days.
4. Suicidal events are more tightly tied to depression in older adults, whereas in younger individuals, substance abuse and impulsive aggression make a stronger contribution.[15] In meta-analyses of RCTs of fluoxetine, a similar decline in depressive symptoms is seen in adolescents and in adults, but a decline in suicidal ideation, and its correlation with a decline in depression was observed only in adults.[19]

This may explain why antidepressants are found to be protective against suicidal events only in older adults.[3]

5. Antidepressants may worsen sleep.[20] Insomnia is one of the most potent risk factors for suicidal behavior.[21]

## WHAT IS THE CLINICAL SIGNIFICANCE OF SUICIDAL EVENTS?

Every increase in suicidal ideation should be taken seriously, but to provide clinical context, in adolescent RCTs of adolescent depression, of 80 suicidal events, most (46/80, 57.5%) were increases in suicidal ideation, rather than preparatory behavior for a suicide attempt, or actual attempts. Moreover, in nearly all RCTs, suicidal events were assessed by spontaneous report from patients, rather than by systematic assessment, a method that underestimates the number of true events by more than twofold.[22] It has been posited that suicidal events in patients treated with medication may be more likely to come to clinical attention than those treated with placebo, because medication-treated patients may have other adverse effects that result in greater clinical scrutiny.[23]

## PHARMACOEPIDEMIOLOGIC STUDIES

Most pharmacoepidemiologic studies find a relationship between greater number of sales or prescriptions of antidepressants and a lower suicide rate. An inverse relationship between sales of SSRIs and suicide has been found in 24 countries, with the strongest findings among youth younger than 25 (**Fig. 3**).[24] There is also an inverse relationship between prescriptions of SSRIs and suicide in a county-by-county analysis in the United States.[25] This relationship was found only for SSRI prescriptions; the higher the proportion of tricyclic antidepressant prescriptions of the total antidepressants prescribed, the higher the suicide rate.[25] In the period from 1990 to 2000, it was found that for every 1% increase in antidepressant prescriptions, there was a drop in the suicide rate of 0.23 per 100,000.[26] A propensity-matching study in 24,119 depressed adolescents found no increased risk for a suicide attempt in those who started taking an antidepressant, and found that longer duration of treatment (>180 days) was protective against suicide attempts relative to shorter treatment (<55 days).[27] A prospective follow-up of a Finnish cohort of 15,390 hospitalized suicide attempters found that SSRI use was associated with a higher rate of suicide

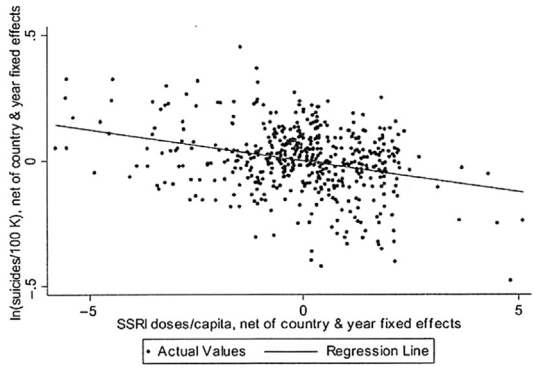


**Fig. 3.** Antidepressants, suicides, and drug regulation. (*From* Ludwig J, Marcotte DE. Anti-depressants, suicide, and drug regulation. J Policy Anal Manage 2005;24(2):259; with permission.)

attempts but a lower rate of suicide in both adolescents and adults.[28] A longitudinal study of antidepressant prescription in a Dutch sample found no overall association between prescriptions and suicidal behavior, although there was an increased rate of suicide on the first day of initiation of medication and in the fourth week of treatment.[29]

Some of the association between antidepressant use and suicide attempt in cross-sectional studies may be due to confounding of indication and treatment. In a large group health maintenance organization (HMO), the most common event *preceding* the initiation of an antidepressant was a suicide attempt.[30] The rate of attempts subsequent to the initiation of an antidepressant was much lower than the rate before the initiation (**Fig. 4**). Similarly, one large propensity-matching study of 221,028 adolescents found that there was a strong association between antidepressant use and suicide attempt that disappeared after adjustment for clinical confounders.[31] One propensity-matched, prospective case-control study has found an increased risk of suicide and suicide attempt in young individuals associated with antidepressant treatment.[32] However, this finding is inconsistent with the very low rate (<10%) of positive toxicologies for antidepressants found in adolescent suicide postmortem samples.[33] Other studies have found an association with the use of higher doses of antidepressants and suicidal behavior regardless of age, although these associations could be explained by the use of higher doses in those with more refractory conditions.[34,35]

## WHY ARE THE FINDINGS OF PHARMACOEPIDEMIOLOGIC STUDIES SO DIFFERENT FROM THOSE OF RCTs?

First, RCTs routinely exclude those at high suicidal risk, such as those patients with a recent suicide attempt. Conversely, a suicide attempt is one of the most common reasons to initiate antidepressants.[30,31] Therefore, RCTs are not informative about the effect of antidepressants on patients at high suicidal risk. Second, the sample size of pharmacoepidemiologic studies is much larger, and the time frame much

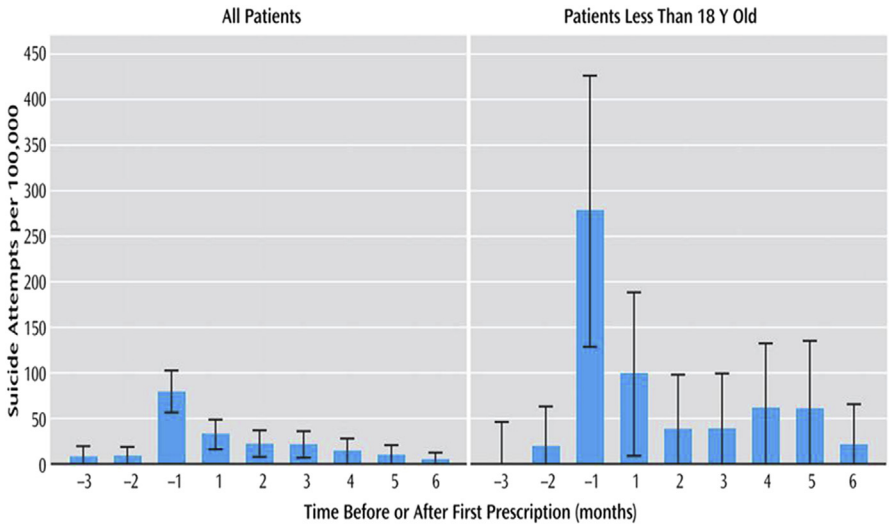


**Fig. 4.** Rates of suicide attempts during the 3 months before and the 6 months after initial antidepressant prescription. (*From* Simon GE, Savarino J, Operskalski B, et al. Suicide risk during antidepressant treatment. Am J Psychiatry 2006;163(1):44; with permission.)

longer compared with RCTs, providing sufficient power to detect differences in completed suicide rather than just effects on suicidal events. Third, although RCTs allow for tight experimental control and comparability of those treated with medication versus placebo, pharmacoepidemiologic studies can use propensity matching or statistical adjustment for confounders to avoid confounding indication with outcome.

## THE BLACK BOX WARNING AS NATURAL EXPERIMENT

In 2004, the FDA issued a warning affixed to all antidepressants about the risk of suicidal events associated with antidepressants in youth. In comparing the period before versus after the so-called Black Box Warning, there were drops in antidepressant prescriptions for youth in the Netherlands, the United States, Canada, and the United Kingdom,[36–39] accompanied by decline in the rate of diagnosis of depressive disorders (**Fig. 5**),[37] number of visits for the treatment of depressive disorders,[38] and increases in suicide in all the previously noted countries but the United Kingdom.[36,38–40] Trends before and after the Black Box Warning in one large group HMO, found a decline in antidepressant use of 31.0% in adolescents and 24.3% in young adults, with a similar magnitude of increase in psychotropic drug overdoses. The study has been criticized insofar as overdoses of psychotropic agents do not include all of suicidal behavior and could be confounded by the presence of psychiatric disorder in patients or their family members. However, if antidepressants were a true risk factor for suicidal behavior, one might have expected a *decline* in overdoses, not an increase.

## IN WHOM ARE SUICIDAL EVENTS MOST LIKELY TO OCCUR?

In the major RCTs for adolescent depression, suicidal events were most likely to occur in those who showed nonsuicidal self-injury, high suicidal ideation, family conflict, drug or alcohol abuse, and treatment nonresponse.[22,40,41] The addition of cognitive behavior therapy (CBT) to antidepressant treatment was protective against suicidal events in some, but not other studies.[42] Starting depressed adolescents or young

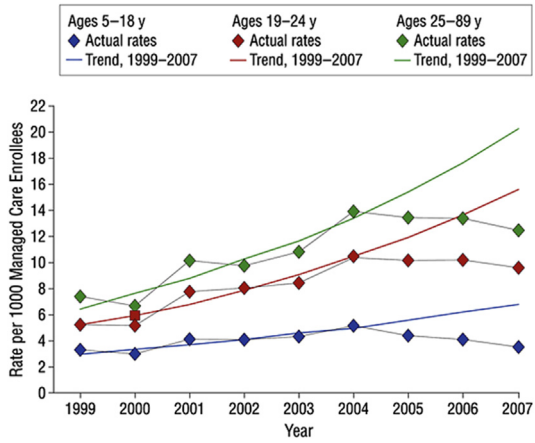


**Fig. 5.** PHARMetrics patient-centric database population rates of major depressive disorder (actual and predicted) by age group (male and female individuals combined). (*From* Libby AM, Orton HD, Valuck RJ. Persisting decline in depression treatment after FDA warnings. Arch Gen Psychiatry 2009;66(6):635; with permission.)

adults at a higher than usual antidepressant dose (eg, the equivalent of fluoxetine 40 mg/d) may also increase the risk of self-harm.[43] In children and adolescents, the extant trials do not provide sufficient power to determine if suicidal events are more commonly associated with specific antidepressants. The risk-difference (% difference in rate of suicidal events on drug vs placebo) for suicidal events was highest in venlafaxine (4), intermediate for fluoxetine (2), and lower for mirtazapine (1), escitalopram (0), and citalopram (−1).[4] Larger studies that include young adults, but not adolescents have found no difference in the rates of suicidal events across SSRIs,[35,44] but higher rates of suicide in mirtazapine relative to citalopram, and higher rates of suicide attempt and self-harm in venlafaxine, mirtazapine, and trazodone, relative to citalopram.[35] In the latter study, the differential effects of these drugs on suicide and suicidal behavior appeared to be stronger in older subgroups.

## HOW CAN CLINICIANS MINIMIZE THE RISK FOR SUICIDAL EVENTS WHEN USING ANTIDEPRESSANTS?

### *Education*

Clinicians should educate patients younger than 25, and the parents of children and adolescents, about the possible adverse effects of antidepressants, such as mania, agitation, akathisia, sleep difficulties, and withdrawal symptoms, all of which could increase the risk for suicidal ideation and behavior. Clinicians should elicit sources of hopelessness about the effects of treatment, and instill realistic hope about the likelihood of achieving symptomatic relief. In addition, clinicians should explain to families that there is a small, but real increased risk for suicidal ideation and behavior in clinical trials, but that the number of youth who benefit from treatment is much greater than the number who experience events.[45]

### *Close Monitoring During Initiation of Treatment and Dose Changes*

Suicidal events tend to occur early in treatment.[22] Patients younger than 25 should be seen weekly for the first 4 weeks after initiation of treatment. Although less than ideal, patients can be monitored by phone if weekly appointments are impractical. Adherence should be monitored by use of a pill-count remainder, as nonadherence is associated with nonresponse,[46] and may also result in withdrawal symptoms that could precipitate suicidal behavior.

### *Strongly Consider Stopping the Antidepressant or Lowering the Dose in the Event of Adverse Effects*

The occurrence of mania, agitation, akathisia, worsening of depression, severe anxiety, or new-onset suicidal ideation or behavior associated with initiation or a dose change should be taken seriously. Unless there are clear other reasons for these adverse events, the antidepressant dose should be lowered, or discontinued.

### *Rational Dosing*

Start an antidepressant for the first week at half the initial target dose (ie, 10 mg fluoxetine). Starting at a high dose is associated with a higher risk of self-harm in adolescents and young adults.[43] Some studies find this association between a higher dose and higher risk of self-harm across the age span, rather than just in adolescence.[34,35] However, in patients who do not respond at a given dose may benefit from a dose increase.[17]

### *Identify and Target Risk Factors for Suicidal Events and Treatment Resistance*

Clinicians should develop a safety plan for the adolescent and family, teach the patient distress tolerance (especially because depressive feelings are not likely to lift immediately after starting an antidepressant), and address sources of family discord.[47,48]

### *Try to Achieve as Rapid a Response in Treatment as Possible*

There is some evidence that combination of medication and CBT will result in more rapid declines in suicidal ideation and depression.[49]

## REFERENCES


1. Posner K, Oquendo MA, Gould M, et al. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007;164(7):1035–43.
2. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63(3):332–9.
3. Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 2009;339:b2880.
4. 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(15):1683–96.
5. Hetrick SE, McKenzie JE, Cox GR, et al. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev 2012;(11):CD004851.
6. Berk M, Dodd S. Are treatment emergent suicidality and decreased response to antidepressants in younger patients due to bipolar disorder being misdiagnosed as unipolar depression? Med Hypotheses 2005;65(1):39–43.
7. Martin A, Young C, Leckman JF, et al. Age effects on antidepressant-induced manic conversion. Arch Pediatr Adolesc Med 2004;158(8):773–80.
8. Offidani E, Fava GA, Tomba E, et al. Excessive mood elevation and behavioral activation with antidepressant treatment of juvenile depressive and anxiety disorders: a systematic review. Psychother Psychosom 2013;82(3):132–41.
9. Casey BJ, Jones RM, Levita L, et al. The storm and stress of adolescence: insights from human imaging and mouse genetics. Dev Psychobiol 2010;52(3):225–35.
10. Tauscher J, Verhoeff NP, Christensen BK, et al. Serotonin 5-HT1A receptor binding potential declines with age as measured by [11C]WAY-100635 and PET. Neuropsychopharmacology 2001;24(5):522–30.
11. Moses-Kolko EL, Price JC, Shah N, et al. Age, sex, and reproductive hormone effects on brain serotonin-1A and serotonin-2A receptor binding in a healthy population. Neuropsychopharmacology 2011;36(13):2729–40.
12. Sullivan GM, Oquendo MA, Milak M, et al. Positron emission tomography quantification of serotonin(1A) receptor binding in suicide attempters with major depressive disorder. JAMA Psychiatry 2015;72(2):169–78.
13. Miller JM, Hesselgrave N, Ogden RT, et al. Brain serotonin 1A receptor binding as a predictor of treatment outcome in major depressive disorder. Biol Psychiatry 2013;74(10):760–7.

14. Oquendo MA, Russo SA, Underwood MD, et al. Higher postmortem prefrontal 5-HT2A receptor binding correlates with lifetime aggression in suicide. Biol Psychiatry 2006;59(3):235–43.
15. McGirr A, Renaud J, Bureau A, et al. Impulsive-aggressive behaviours and completed suicide across the life cycle: a predisposition for younger age of suicide. Psychol Med 2008;38(3):407–17.
16. Axelson DA, Perel JM, Birmaher B, et al. Sertraline pharmacokinetics and dynamics in adolescents. J Am Acad Child Adolesc Psychiatry 2002;41(9): 1037–44.
17. Sakolsky DJ, Perel JM, Emslie GJ, et al. Antidepressant exposure as a predictor of clinical outcomes in the Treatment of Resistant Depression in Adolescents (TORDIA) study. J Clin Psychopharmacol 2011;31(1):92–7.
18. Smith EG. Association between antidepressant half-life and the risk of suicidal ideation or behavior among children and adolescents: confirmatory analysis and research implications. J Affect Disord 2009;114(1–3):143–8.
19. Gibbons RD, Brown CH, Hur K, et al. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. Arch Gen Psychiatry 2012;69(6):580–7.
20. Wichniak A, Wierzbicka A, Jernajczyk W. Sleep and antidepressant treatment. Curr Pharm Des 2012;18(36):5802–17.
21. Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. J Clin Psychiatry 2012;73(9):e1160–1167.
22. Brent DA, Emslie GJ, Clarke GN, et al. Predictors of spontaneous and systematically assessed suicidal adverse events in the treatment of SSRI-resistant depression in adolescents (TORDIA) study. Am J Psychiatry 2009;166(4):418–26.
23. Mann JJ, Emslie G, Baldessarini RJ, et al. ACNP Task Force report on SSRIs and suicidal behavior in youth. Neuropsychopharmacology 2006;31(3):473–92.
24. Ludwig J, Marcotte DE. Anti-depressants, suicide, and drug regulation. J Policy Anal Manage 2005;24(2):249–72.
25. Gibbons RD, Hur K, Bhaumik DK, et al. The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry 2005;62(2):165–72.
26. Olfson M, Shaffer D, Marcus SC, et al. Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry 2003; 60(10):978–82.
27. Valuck RJ, Libby AM, Sills MR, et al. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. CNS Drugs 2004;18(15):1119–32.
28. Tiihonen J, Lonnqvist J, Wahlbeck K, et al. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry 2006;63(12):1358–67.
29. Wijlaars LP, Nazareth I, Whitaker HJ, et al. Suicide-related events in young people following prescription of SSRIs and other antidepressants: a self-controlled case series analysis. BMJ Open 2013;3(9):e003247.
30. Simon GE, Savarino J, Operskalski B, et al. Suicide risk during antidepressant treatment. Am J Psychiatry 2006;163(1):41–7.
31. Gibbons RD, Coca Perraillon M, Hur K, et al. Antidepressant treatment and suicide attempts and self-inflicted injury in children and adolescents. Pharmacoepidemiol Drug Saf 2015;24(2):208–14.
32. Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and suicide in severely depressed children and adults: a case-control study. Arch Gen Psychiatry 2006;63(8):865–72.

33. Leon AC, Marzuk PM, Tardiff K, et al. Paroxetine, other antidepressants, and youth suicide in New York City: 1993 through 1998. J Clin Psychiatry 2004; 65(7):915–8.
34. Courtet P, Lopez-Castroman J, Jaussent I, et al. Antidepressant dosage and suicidal ideation. JAMA Intern Med 2014;174(11):1863–5.
35. Coupland C, Hill T, Morriss R, et al. Antidepressant use and risk of suicide and attempted suicide or self-harm in people aged 20 to 64: cohort study using a primary care database. BMJ 2015;350:h517.
36. Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007;164(9):1356–63.
37. Libby AM, Orton HD, Valuck RJ. Persisting decline in depression treatment after FDA warnings. Arch Gen Psychiatry 2009;66(6):633–9.
38. Katz LY, Kozyrskyj AL, Prior HJ, et al. Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. CMAJ 2008;178(8):1005–11.
39. Wheeler BW, Gunnell D, Metcalfe C, et al. The population impact on incidence of suicide and non-fatal self-harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. BMJ 2008;336(7643):542–5.
40. Wilkinson P, Kelvin R, Roberts C, et al. Clinical and psychosocial predictors of suicide attempts and nonsuicidal self-injury in the adolescent depression antidepressants and psychotherapy trial (ADAPT). Am J Psychiatry 2011;168(5):495–501.
41. Asarnow JR, Porta G, Spirito A, et al. Suicide attempts and nonsuicidal self-injury in the treatment of resistant depression in adolescents: findings from the TORDIA study. J Am Acad Child Adolesc Psychiatry 2011;50(8):772–81.
42. March JS, Silva S, Petrycki S, et al. The treatment for adolescents with depression study (TADS): long-term effectiveness and safety outcomes. Arch Gen Psychiatry 2007;64(10):1132–43.
43. Miller M, Swanson SA, Azrael D, et al. Antidepressant dose, age, and the risk of deliberate self-harm. JAMA Intern Med 2014;174(6):899–909.
44. Schneeweiss S, Patrick AR, Solomon DH, et al. Variation in the risk of suicide attempts and completed suicides by antidepressant agent in adults: a propensity score-adjusted analysis of 9 years' data. Arch Gen Psychiatry 2010;67(5): 497–506.
45. American Academy of Child & Adolescent Psychiatry. Information for patients and their families. Available at: http://www.aacap.org/AACAP/Resources_for_Primary_Care/Information_for_Patients_and_Their_Families/Home.aspx?hkey=bce12396-b276-4fed-8430-ca8628eb1a2b. Accessed March 1, 2016.
46. Woldu H, Porta G, Goldstein T, et al. Pharmacokinetically and clinician-determined adherence to an antidepressant regimen and clinical outcome in the TORDIA trial. J Am Acad Child Adolesc Psychiatry 2011;50(5):490–8.
47. Maalouf FT, Atwi M, Brent DA. Treatment-resistant depression in adolescents: review and updates on clinical management. Depress Anxiety 2011;28(11):946–54.
48. Stanley B, Brown G, Brent DA, et al. Cognitive-behavioral therapy for suicide prevention (CBT-SP): treatment model, feasibility, and acceptability. J Am Acad Child Adolesc Psychiatry 2009;48(10):1005–13.
49. March J, Silva S, Petrycki S, 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(7): 807–20.