Antidepressants and Suicidality

David A. Brent, MD

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

Western Psychiatric Institute & Clinic, 3811 O'Hara Street, BFT 311, Pittsburgh, PA 15213, USA
E-mail address: brentda@upmc.edu

Psychiatr Clin N Am 39 (2016) 503–512
http://dx.doi.org/10.1016/j.psc.2016.04.002 psych.theclinics.com
0193-953X/16/$ – see front matter

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]

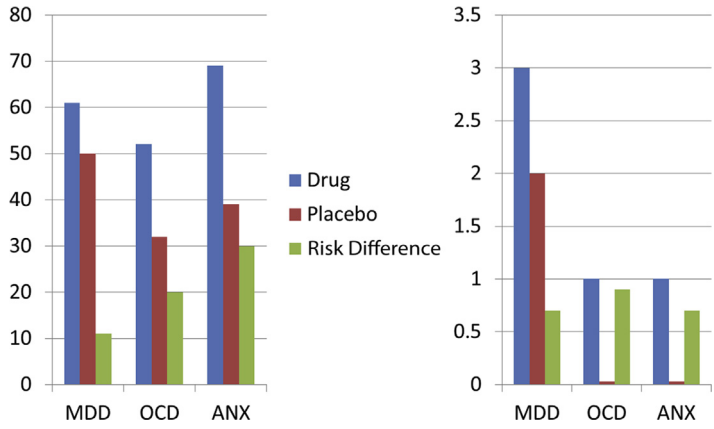

Fig. 1. Risks and benefits of antidepressants by indication in youth. (*Data from* Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 2007;297(15):1683–96.)