FAQ– Winter 2014-15

IN THIS ISSUE: Suicidality Risk with Antidepressants in Pediatric Patients

The subject of suicidality, antidepressants, and pediatrics is full of dichotomous opinions and data. For example, the 2004 FDA black box warning update for all antidepressants states "antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults…" and the 2007 FDA News release says "the proposed warning statements emphasize that depression and certain other serious psychiatric disorders are themselves the most important causes of suicide." The FDA data showed a small increase (4% versus 2%) in suicidal thoughts and behaviors in antidepressant versus placebo groups of pediatric patients. There were no completed suicides. Of interest, at the time of the FDA advisory, the rate of suicide in children had been steadily declining for at least 10 years, along with a steadily increasing use of antidepressants. Since that same time, a measurable decrease in prescribing of antidepressants has been noted in the US (18-29%) along with other countries (UK, Canada, Australia, and Sweden) accompanied by a measurable increase in suicides among young people in the same countries (18% in the US) except the UK (Hamilton 2005, Isacsson, 2014, Nemeroff 2007). It is unknown if the decrease in antidepressant use is the cause for these noted increases in suicide rate.

A 2007 meta-analysis of pediatric trials (Bridge et al, 2007) including mostly use of selective serotonin reuptake inhibitors (SSRIs) found a non-significant 1% difference in suicidal thoughts/behaviors when comparing antidepressants to placebo (3% vs. 2%, p=0.08) in the treatment of major depression, corresponding to a Number Needed to Harm (NNH) of 112. NNH in obsessive compulsive disorder (OCD) trials was 200, and that in non-OCD anxiety trials was 143. Antidepressants were more efficacious than placebo for the treatment of depression, OCD, and non-OCD anxiety disorders, with a Number Needed to Treat (NNT) of 10, 6, and 3 respectively. For children younger than 12 years with depression, only fluoxetine showed benefit as compared to placebo. It was concluded that "benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions." Of note, not all antidepressants have FDA-approved pediatric indications.

The FDA black box warning has placed prescribers in a difficult position. Overall, treatment with certain SSRIs has been shown to improve depression and reduce suicidality. However, some studies indicate that a few patients may experience worsening or new-onset suicidality with antidepressant treatment. Regardless of the cause, the possible increase in suicidal thoughts and behaviors cannot be discounted so communication between the parent, child, and prescriber is critical. The American Academy of Child and Adolescent Psychiatry (AACAP) recommends that parents and children be educated about the suicide risk in psychiatric disorders in youth, as well as about the risks and benefits of medication treatments (Birmaher et al, 2007). Families should be provided contact information for the suicide hotline or mental health crisis response team (AAP 2010). Parents should be informed, away from the child, about risk reduction by limiting access to lethal means (Kruesi et al, 1999). AACAP recommends that "during all treatment phases, clinicians should arrange frequent follow-up encounters that allow sufficient time to monitor the subject's clinical status, environmental conditions, and, if appropriate, medication side effects." AACAP suggests using rating scales to assess depressive symptoms and functional status, including careful monitoring for suicidal thoughts and behavior in all patients who receive antidepressants. Parents, children and prescribers should always be alert for the appearance or worsening of anxiety, agitation, insomnia, irritability, hostility, impulsivity, restlessness, and mania. Although research has not yet linked these symptoms to suicidal thoughts, urges, or behaviors, consideration should be given to changing or discontinuing the antidepressant medication should they occur. The FDA recommends that depressed youth be seen every week for the first 4 weeks, and biweekly thereafter, although there are no controlled studies to support this monitoring schedule. Patients at increased risk for suicide may require closer follow-up (Birmaher et al, 2007). Risk factors in depressed youths include higher levels of suicidality at baseline, family conflict, drug or alcohol use, and peer conflict (Adegbite-Adeniyi et al, 2012). Other risk factors that may increase the risk of suicide in the general adolescent population include a family history of suicide, exposure to the suicidal behavior of others, easy access to lethal methods, and stressful life event or loss (CDC 2012). It is important to note that having these risk factors does not mean suicide will always occur, but it is important to recognize these risk factors.

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SUMMARY OF EVENTS LEADING TO BLACK BOX WARNING

Date	Results/Comments
June 2003	Placebo-controlled data suggest an association between paroxetine and suicidality in pediatric patients per GlaxoSmithKline.
June 2003	UK MHRA advised doctors not to prescribe paroxetine to patients under 18 years due to increased suicidality risk.
June 2003	FDA requests original study data from pharmaceutical manufacturers to reclassify and further analyze suicide-related events.
December 2003	After reviewing reports from controlled trials submitted by pharmaceutical companies and/or published reports, CSM in the UK warns that SSRIs and venlafaxine are not suitable for use in patients under 18 years. CSM concluded that, except for fluoxetine, the benefits of SSRIs and venlafaxine do not outweigh the risks. MHRA subsequently banned their use (except for fluoxetine) in pediatric patients.
March 2004	After reclassification of suicide-related events (using C-CASA), FDA meta-analysis (did not include TADS) showed a RR 1.41 (95% CI 0.84-2.37) for definite suicidal behavior and ideation (excluding non-suicidal self-harm) for all SSRI trials in MDD, and RR 1.71 (95% CI 1.05-2.77) when venlafaxine, mirtazapine and nefazodone were also included. The risk was higher for non-MDD trials (RR 2.17, 95% CI 0.72-6.48).
October 2004	FDA requested labeling changes for all antidepressants to include a black box warning regarding suicidality risk in pediatric patients based on their meta-analysis.
March 2006	Publication of FDA meta-analysis (Hammad et al, 2006).
December 2006	FDA raised age for black box warning from 18 to 24 years old.
May 2007	Black box warning expanded to recommend close monitoring of all patients starting an antidepressant.

Key: C-CASA = Columbia Classification Algorithm of Suicide Assessment; CSM = Committee on Safety of Medicines; FDA = Food and Drug Administration; MDD = Major depressive disorder; MHRA = Medicines and Healthcare Products Regulatory Agency; NIMH = National Institute of Mental Health; RR = Relative risk; TADS = Treatment for Adolescents with Depression Study

References

- Adegbite-Adeniyi C, Gron B, Rowles BM, et al. An update on antidepressant use and suicidality in pediatric depression. Expert Opin Pharmacother 2012;13:2119-2130.
- Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit. Copyright © 2010 American Academy of Pediatrics.
- Birmaher B, Brent D, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry 2007;46:1503-1526.
- 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.
- Centers for Disease Control and Prevention. Suicide Prevention: Youth Suicide. Atlanta, GA: CDC. Last updated August 15, 2012. Available at: http://www.cdc.gov/violenceprevention/pub/youth_suicide.html. Accessed May 20, 2013.
- Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332-339.
- Hamilton BE, Minino AM, Martin JA, et al. Annual summary of vital statistics. Pediatrics 2005;119:345-360.
- Isacsson G, Rich CL. Antidepressant drugs and the risk of suicide in children and adolescents. Pediatr Drugs 2014;16:115-122.
- Kruesi MJP, Grossman J, Pennington JM, Woodward PJ, Duda D, Hirsch JG. Suicide and Violence Prevention: Parent Education in the Emergency Department. J Am Acad Child Adol Psychiatry 1999:38(3)250-255.
- Nemeroff CB, Kalali A, Keller MB, et al. Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States. Arch Gen Psychiatry 2007;64:466-472.