5 COMMON QUESTIONS WHEN TREATING DEPRESSION

Do Antidepressants Increase the Possibility of Suicide?

Will I Accidentally Induce Mania if I Prescribe an SSRI?

Are Depression Medications Safe and Effective in Young Children?

What Dose Do I Start and How Quickly Should I Titrate?

How Long Should Patients Expect to Stay on the Medication?

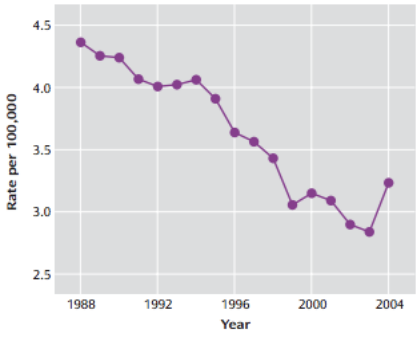
THE BLACK BOX?

Do Antidepressants Increase the Possibility of Suicide?

Important Points

- All antidepressants have a black box warning for increased suicidality (4% vs 2% for placebo)
- Studies conducted since development of Columbia Suicide Severity Rating Scale (see TADS study) have not supported this increased risk.
- Fluoxetine is the best studied medication and seems to have the most favorable risk/benefit profile in this regard
- The black box warning has *not* reduced suicide rates. In fact, rates seemed to increase after the warning (below)

FIGURE 2. Suicide Rate in Children and Adolescents (Ages 5–19 Years) in the United States, 1988–2004



Am J Psychiatry 2007; 164:1356–1363)

History

In October 2003, the U.S. Food and Drug Administration (FDA) issued a public health advisory regarding several reports of children and teenagers taking antidepressants who attempted or committed suicide. In February 2004, the FDA issued a public health advisory providing further caution to physicians, patients, and families about a possible link between suicide and antidepressants. In October 2004, the FDA ordered pharmaceutical companies to add a black box warning to the labeling of all antidepressants used with pediatric patients regarding a possible increased risk of suicidality in pediatric patient taking antidepressants (Am J Psychiatry 2007; 164:1356–1363)

Research in this area always has a number of limitations. For one, suicide is a relatively rare occurrence, and controlled studies usually lack the power to assess this. Observational studies don't establish causality, and suicidal thinking is a common occurrence in both treated and untreated depression. Much has been researched and written on this subject since 2003, both confirming or refuting the stated risk.

The American College of Neuropsychopharmacology (ACNP), American Academy of Child & Adolescent Psychiatry (AACAP) and the Society for Adolescent Medicine (SAM) strongly support the continued use of fluoxetine as an effective and readily available treatment for major depression in children and adolescents, with consideration of alternate antidepressants when necessary due to poor tolerability.

Note: Escitalopram (Lexapro) was approved for treatment of depression (2009) after the above policy statements were issued and is likely a good alternate.

IS IT BIPOLAR?

Will I Accidentally Induce Mania if I Prescribe an SSRI?

Important Points

- The question as to whether antidepressants *ever* induce mania is far from settled
- Bipolar Disorder is rare in adolescents (1%) and almost never diagnosed prior to puberty
- The rare possibility of a manic "switch" should generally not deter a clinician from treating depression

"Activation"

Note that a fair number of children become "activated" as a side effect on SSRIs, leading to hyperactivity, restlessness and/or insomnia. This happens more in younger children, early in the course of treatment, or following a dose increase. Reduce the dose or consider switch and add therapy for residual symptoms. Activation is a side effect, **not** a sign or risk factor for bipolar.

The only major study looking at this in children and adolescents is a 2004 study (*Arch Pediatr Adolesc Med.* 2004 Aug;158(8):773-80.) that utilized secondary data analysis to look at "conversion" to mania - defined when a working diagnosis of depression was changed to bipolar disorder during the course of treatment. The SSRI treated group seemed to have a higher rate of conversion (hazard ratio 2.1) than placebo and it appeared that age was an effect modifier and that peripubertal children (10-14 year olds) "converted" at the highest rate.

Although this study is often referenced, the data are far from definitive. It is a notable limitation that the data were administrative rather than clinical and therefore without specific information about what criteria were used to diagnose bipolar disorder, something of considerable controversy over the past decade. Additionally there was no randomization, no information on medication adherence, and potential problems with confounding by indication.

Remember that the prevalence of Bipolar Disorder in adolescents is probably around 1%, and that most studies examining manic "switch" in adults *already known to have bipolar disorder* seem to put that number around 10-15% (though the methodology in all such studies has been questioned and the issue as to whether SSRI's do indeed "switch" people into mania is far from settled). The possibility that 1 out of 1000 adolescents may convert to mania should not deter a clinician from treating depression.

The DSM-5 diagnosis of Disruptive Mood Dysregulation Disorder (DMDD) has changed the way we consider mood problems in children. Its classification as a "depressive disorder" may prompt new research as to whether antidepressants ought to be reconsidered in young people with extreme moodiness and irritability – largely overlooked in the past when these individuals were being wrongfully diagnosed with bipolar disorder.

IN YOUNG CHILDREN?

Are Depression Medications Safe and Indicated in Young Children?

Important Points

- Safety data exist for children as young as 6, though younger children do seem to have more tolerability issues
- Only fluoxetine has demonstrated efficacy for depression in children as young as 8
- Psychoeducation with family and school interventions should be considered first-line treatment in young children

FDA Approved

Approved for Depression
- Fluoxetine ≥ 8 years
- Escitalpram ≥ 12 years

Approval for OCD
- Clomipramine ≥ 10 years
- Fluvoxamine ≥ 8 years
- Sertraline ≥ 6 years
- Fluoxetine ≥ 7 years

Approval for non-OCD Anxiety
- None

Evidence from more than one RCT supports the use of **fluoxetine** in the treatment of childhood and adolescent depression as well as escitalopram in the treatment of adolescent depression. Based on these RCTs, fluoxetine has been given an FDA indication for the treatment of MDD in youth aged 8 years and older whereas **escitalopram** has been given an FDA indication for the treatment of MDD in adolescents aged 12 years and older.

To date, only one RCT has demonstrated the effectiveness of **sertraline** or **citalopram**, thus neither of these medications has received FDA approval for the treatment of MDD in youth.

Keep in mind that the high placebo response rate in studies of youth with MDD decreases the power of RCTs to detect differences between medication and placebo, though "response" to both is usually >50%.

Major Depression in prepubertal children is quite rare, estimated at 1 to 2.5% (Arch Gen Psychiatry. 2003; 60: 837–844) and comorbidity is the rule. Assess for medical illness, anxiety, developmental delay, learning disorders or ODD.

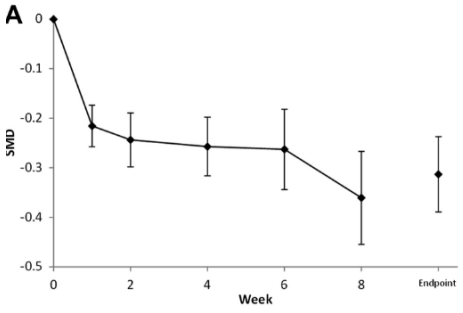
Although symptoms vary according to the child's developmental level, the "core" symptoms of anhedonia (with its lowered positive affectivity) and dysphoria remain the most reliable cornerstones (J Am Acad Child Adolesc Psychiatry. 2004; 43: 708–717)

HOW TO DOSE?

What Dose Do I Start and How Quickly Should I Titrate?

Important Points

- Fluoxetine is the best studied for depression, and one of two with an FDA indication for depression in adolescents
- If initial SSRI trial is ineffective, switch to alternate SSRI and add psychotherapy (3). As third line, try venlafaxine, or bupropion
- Consider twice daily dosing in medications other than fluoxetine
- Start low but don't go too slow. Increase dose weekly until at "effective range" then every 2-4 weeks until response. See graph for response time (4)



Medication	Starting Dose (mg/d)	Titration Increments (mg)	Effective Range (mg)	Maximum Dose (mg)
Fluoxetine	**10**	**10**	**20-40**	**80**
Escitalopram	**5**	**5**	**10-20**	**20**
Citalopram	10	10	20-40	40
Sertraline	25	25	50-150	200
Venlafaxine ER	37.5	37.5	75-150	225
Duloxetine	30	30	30-90	120
Bupropion XL	150	150	150-300	450

*Starting doses may be lower in sensitive, young, or neuroatypical kids

Pharmacokinetic considerations

- Fluoxetine - High intersubject variability, but steady state concentrations in children can be twice as high as adolescents. Body weight more significant than age. Consider starting 5 or 10 mg in younger children. (1)
- Escitalopram, Citalopram and Sertraline seem to have lower half-lives at lower doses. Consider twice daily dosing in the low-dose range if withdrawal side effects are reported during parts of the day (GI upset, dizziness, irritability, sleep difficulty, flulike symptoms). (2)

References:

1. Wilens, T.E., Cohen, L., Biederman et al. Fluoxetine pharmacokinetics in pediatric patients. J Clin Psychopharmacol. 2002; 22: 568–575
2. Sakolsky and Birmaher. Developmentally Informed Pharmacotherapy. Child Adolesc Psychiatric Clin N Am 21 (2012) 313-325
3. Brent et al. TORDIA Study. JAMA. 2008 Feb 27;299(8):901-13.
4. Varigonda et al. Early Treatment Responses of SSRIs in Pediatric MDD. JAACAP. 2015; 54: 557-564

WHEN TO STOP?

How Long Should Patients Expect to Stay on the Medication?

Important Points

- In general, the acute and continuation phases of treatment should last 3-12 months. Some patients may warrant prolonged maintenance treatment
- Trials off the medication may be most appropriately timed for the Spring or Summer.
- Slow taper to avoid discontinuation syndrome

Discontinuation Syndrome

More than 20% of patients will experience adverse medication side effects if stopped too suddenly. These include dizziness, nausea, lethargy, headaches, irritability, crying spells, sensory disturbances or flu-like symptoms. Plan to taper medications over 2-6 weeks when possible for all antidepressants other than fluoxetine.

Antidepressant use usually involves three phases:

1. The **acute phase** which is when ap person first begins antidepressants until he or she feels full benefit
2. The **continuation phase** is next, with the primary goal of preventing relapse, usually lasting 3 months to a year. Usually the acute phase dose is continued. Many people may consider going off the medication after a symptom free period.
3. For some people, a **maintenance phase** is indicated, lasting a year or longer. Maintenance treatment may be indicated for individuals with any of the following:
   - A history of three or more episodes of Major Depression
   - A history of severe depressive symptoms, especially if need for hospitalization or other intensive treatment program
   - A strong family history of depression
   - A substance use disorder
   - A pattern of seasonal depressive symptoms.

The decision as to when to stop antidepressants is highly individualized. Consider that children and adolescents are undergoing developmental brain changes (proliferation, pruning, myelination, etc.). On one hand, aggressive treatment of depression is important for enabling healthy development and decreasing the likelihood of relapse in adulthood. On the other hand, each year of life presents a different child in many ways — socially, emotionally, cognitively, physically — and intermittent trials off of the medication to reaffirm the ongoing need for treatment are reasonable. Work to promote the adolescent's autonomy in the decision process.