MARK W. WILSON, MD
330 WEST 58TH STREET, SUITE 313
NEW YORK, NEW YORK 10019

Depression, Suicidality and SSRI's

- Critically important is survey of adolescents, zeroing in on adolescents in the survey who suffer from depression:

Prevalence of Suicidal Behavior in Adolescents
(Nock, M. et al; JAMA Psychiatry; 2013; 70; 300-310; K. Wagner, MGH, 2014)

National Comorbidity Survey of Adolescents (N=6483)

	MDD/Persistent Depression (%)
Ideation (N=717)	56.8
Plan (N=203)	69.7
Attempt (N=196)	75.7

- **More below, but meta-analysis of 27 trials of pediatric major depression in terms of risk of suicidal ideation and/or suicide attempts:**
  - **Antidepressants 3%**
  - **Placebo 2%**
- **Fuller summary of Benefit/Risk of suicidality (see separate handout as well)**
  - **% difference between response rates of SSRI's and placebo**
    - **11% in depression**
    - **20% in OCD**
    - **37% in non-OCD anxiety**
  - **Numbers needed to treat (NNT) to show benefit of med (above placebo); the smaller the number the better**
    - **10 in depression (overall; the number drops to 3 if you include only NIH studies)**
    - **5 in OCD**
    - **3 in non-OCD anxiety**
  - **% difference between suicidality in those on SSRI's vs. placebo**
    - **1-2% overall (0.7 - >2%, depending on the med)**
    - **0.9% for depression**
    - **0.5% for OCD**
    - **0.7% for non-OCD anxiety**
  - **Numbers needed to harm (NNH) to show risk of suicidality from med (above placebo risk); the higher the number the better**
    - **50-143 overall**
    - **~100 in depression**
    - **~200 in OCD**
    - **~140 in non-OCD anxiety**

Evidence ***SUPPORTING A REDUCTION OF SUICIDE RISK*** with the use of antidepressants:

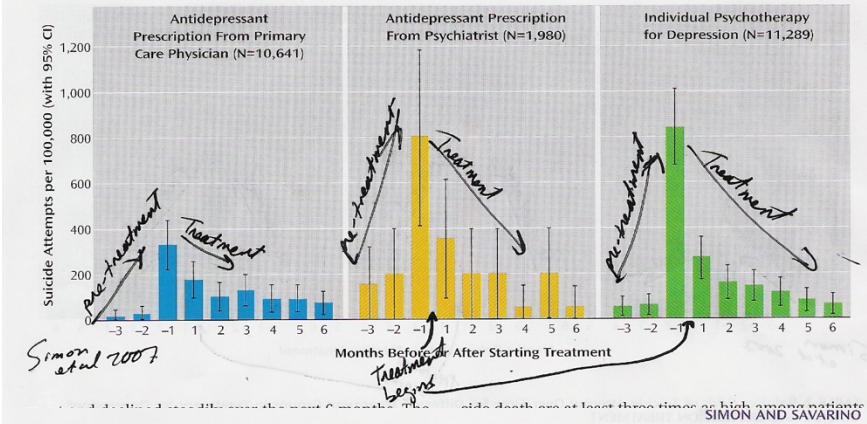
- Network Meta-Analysis of antidepressants in depression and suicidal behavior in youth, Lancet, 2016
  - 34 studies, 5260 kids
  - Reduced risk of suicidal behavior relative to placebo (numbers > 1 indicate increased risk)
    - **Cymbalta 0.14 (0-0.64)**

        - **Fluoxetine** **0.15** **(0-0.72)**
        - **Imipramine** **0.16** **(0-0.96)**
        - **Lexapro** **0.16** **(0-0.79)**
        - **Paxil** **0.19** **(0-0.9)**
        - Clomipramine ` 0.19 (0-1.04)
        - Zoloft 0.51 (0-3.11)
        - Effexor
    - Prozac significantly effective vs. placebo
- Miller et al, 2014; probability of self-harm in youth with depression
    - Modal dose: some risk over time thru 6 months
    - High dose: higher risk over time thru 6 months (but is this due to treatment resistance?)
- Cooper, et al 2013
    - Retrospective review of 36,842 youth who were new users of antidepressants (for ANY diagnosis)
    - Looking at risk of suicide attempts
    - Meds and corresponding risk ration (> 1 means increased risk, <1 means decreased risk)
        - Lexapro 0.8
        - Effexor XR 0.8
        - Paxil 0.8
        - Celexa 0.92
        - Zoloft 0.97
        - Prozac 1.0
        - MULTIPLE SSRI's ONLY 1.7 (but keep in mind that multiple antidepressants are usually reserved for folks with more severe and/or treatment resistant conditions, so unclear if illness vs treatment drove the increased risk)
- Decreases in suicide rate over time have been shown to correlate with increased antidepressant use in many studies around the world
    - including those in the US, Europe, Scandinavia, and Australia
    - in Sweden, the doubling of prescriptions for SSRI's correlated with a 25% decrease in the suicide incidence
    - in an analysis of 27 countries, Ludwig and Marcotte showed that an increase of 1 pill per capita (a 13% increase over 1999 levels) was associated with a 2.5% reduction in suicide rates, a relationship that was more pronounced in adults than in children
    - however, in Japan, there was a positive association between suicide rates and antidepressant prescriptions, BUT
        - in Japan both suicide rates and use of antidepressants increase with age
        - for any given age-group, suicide rates have decreased with increasing SSRI prescriptions over time
    - in Iceland, antidepressant prescription rates seemed unrelated to lower suicide rates, BUT
        - there is traditionally an extremely low suicide rates in Iceland, and there is so little room for a further decline in suicide rates that the relationship to prescription rates is extremely hard to detect
    - in Italy, there has been a decline in suicide rates linked to prescriptions in women but not in men, BUT
        - in Italy, most antidepressants are prescribed for women, and so the ability to detect such a relationship is greater in women
- Zisook et al, 2011: Combining Medications to Enhance Depression Outcomes study for chronic and/or recurrent major depression; compared Lexapro vs. Lexapro plus Wellbutrin SR vs. Effexor XR plus Remeron
    - depressive symptoms improvement was the same through 28 weeks of the various treatments
    - all treatments reduced suicidal ideation
    - Lexapro plus Wellbutrin SR reduced suicidal ideation the most
    - in patients with no baseline suicidal ideation, the treatments were no different (2.5% had suicidal ideation at 4 weeks, 1.3% at 12 weeks, 1.7% at 28 weeks)
    - four patients taking Effexor XR plus Remeron attempted suicide
- Leon et al, 2011: 757 folks over 27 years; risk of suicide attempts or suicides reduced by 20%
- Bramness et al, 2007: sales of non-tricyclic antidepressants (non-TCAs), including but not limited to SSRIs, during the period of 1980-2004 in Norway, and suicide completion were clearly negatively related; in other words, the fall in suicide rates in Norway were related to increased sales of non-TCAs.
- Simon et al, 2007

SUICIDE AND DEPRESSION TREATMENT

109,256 Patients

FIGURE 2. Risk of Suicide Attempt or Possible Suicide Attempt Before and After Starting Treatment Among Adolescents and Young Adults (age less than 25 years) Receiving New Antidepressant Prescriptions From Primary Care Physicians, Receiving New Antidepressant Prescriptions From Psychiatrists, or Starting Individual Psychotherapy for Depression



SIMON AND SAVARINO

109,856 patients

FIGURE 1. Risk of Suicide Attempt or Possible Suicide Attempt Before and After Starting Treatment Among Adolescents and Adults Receiving New Antidepressant Prescriptions From Primary Care Physicians, Receiving New Antidepressant Prescriptions From Psychiatrists, or Starting Individual Psychotherapy for Depression

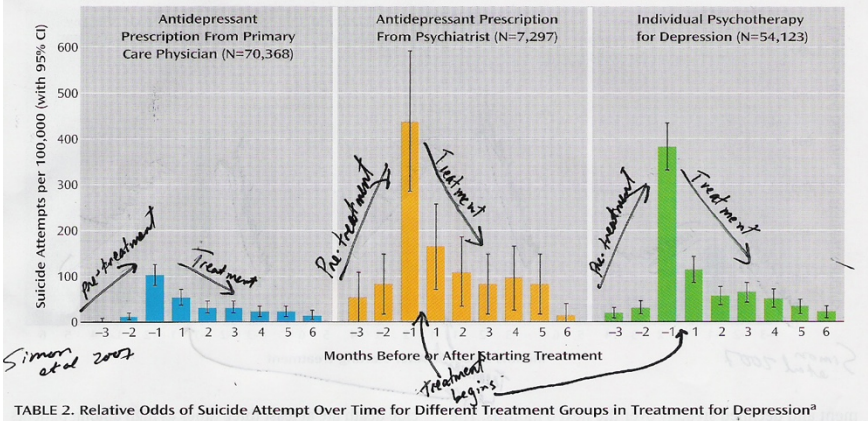


TABLE 2. Relative Odds of Suicide Attempt Over Time for Different Treatment Groups in Treatment for Depression[a]

- Nakagawa et al, 2007, Antidepressant prescriptions in Japan from 1999-2003:
  - Antidepressant prescriptions increased 57% among males and 50% among females
  - 80% of the increase in prescriptions involved SSRI's
  - An increase of 1 defined daily dose of SSRI use/1000 population/day was associated with a 6% decrease in suicide rate
- Gibbons et al, 2007:
  - 226,866, Veterans diagnosed with depression in 2003 or 2004 but with no history of depression 2000-2002
  - suicide attempt rates were lower among patients who were treated with antidepressants than among those who were not
    - 0.37-fold reduction in those treated with SSRIs
    - 0.29-fold reduction in those treated with tricyclic antidepressants (TCAs)
    - 0.83-fold reduction in those treated with non-SSRI/non-TCA antidepressants
  - Before and after treatment
    - 0.56-fold reduction in those treated with SSRIs
    - 0.57-fold reduction in those treated with tricyclic antidepressants (TCAs)
    - 0.51-fold reduction in those treated with non-SSRI/non-TCA antidepressants
  - for SSRI's this was significant in all age groups but the 18-25 yo age group
- Meta-analysis of studies examined by the UK Medicines and Healthcare Products Regulatory Agency involving more than 40,000 patients in 477 randomized placebo-controlled trials of SSRI's, mostly for the indication of depression
  - SSRI's associated with a 0.85-fold reduction in suicide
  - SSRI's not associated with suicide attempts or non-fatal self-harm
- Sondergard et al, 2007: data on over 31,000 hospitalized patients with depression (who were followed after discharge) from databases in Denmark from 1995-2000
  - 310 of the >31,000 patients died by suicide over the 6-year study period
  - Patients who filled one antidepressant prescription had a 1.13-fold increased risk of suicide compared to those who filled none
  - Patients who filled 2 or more prescriptions had a 0.35-fold risk of suicide compared to those who filled none
  - Patients who filled 2 or more prescriptions had a 0.31-fold risk of suicide compared to those who filled one prescription only
  - The rate continued to decline with each additional prescription
- Korkeila et al, 2007: decline in suicides correlated with increased use of antidepressants, especially in those aged 15-44 yo.
- Pediatrics, 12/03, 3/05, 2/07: deaths from youth suicide decreased from 2000-2001, 2001-2002, 2002-2003, but then increased by 18.2% from 2003-2004 following (NOT preceding) the FDA warning for antidepressants amidst the controversy over suicide; clinicians (including myself) fear that this disturbing rise in youth suicides represents a precipitous decline in prescribing of antidepressants to depressed youth

- National Vital Statistics from the Centers for Disease Control and Prevention: lower suicide rates in association with increased use of SSRIs
- Levenson et al, 2006; antidepressants and suicide in adults; FDA-obtained clinical trial data from the manufacturers of 11 modern antidepressants (6 SSRIs, 3 SNRIs, Wellbutrin, Remeron); 372 RCT's in almost 100,000 patients
  - In the 295 clinical trials for psychiatric indication, the overall odds ratio for suicidal behavior and ideation was 0.84, indicating a lower rate suicidality in patients taking active medications, which nearly reached statistical significance
  - There was no differences between classes or individual agents
  - Of the 509 suicidal adverse events
    - Number of adverse events
      - 0.62% of patients taking test drug
      - 0.72% of patients who received placebo
    - 358 of which were the onset of suicidal ideation
    - 133 of which were non-fatal suicide attempts
    - 8 of which committed suicide
      - 5 taking the study drug
      - 2 taking placebo
      - 1 taking an active comparator
- Bastiaens et al, 2006, retrospective chart review of 92 youths attending one psychiatric clinic who were started on an antidepressant
  - 50% had preexisting suicidality, of which:
    - 79% did not exhibit suicidality after antidepressant treatment
    - 21% still had suicidality after antidepressant treatment
  - 50% did not have preexisting suicidality (but did have more co-morbidity as well as less recent exposure to antidepressant treatment for analysis below), of which
    - 92% did not exhibit suicidality after antidepressant treatment
    - 8% exhibited new onset suicidality
- McKeon, 2006:
  - Suicide rates among teens have been dropping since the 1990's
  - Suicide rates among young adults have been dropping since the 1990's
  - Suicide rates among elderly folks have been dropping since peaks in the 1980's
  - Among 15-24 yo's, suicide rates peaked in 1994, at 13.8 suicide deaths per 100,000 people, followed by a steady decline through 2002 where the number was 9.9 suicide deaths per 100,000.
- Gibbons et al, 2006: higher SSRI prescription rates were associated with a reduction in suicide rates in youth (CDC vital statistics data on suicide, 1996-1998; the data included 933 suicide deaths aged 5-14 yo :
  - National average annual suicide rate
    - 0.8 per 100,000 persons aged 5-14 years overall
    - 1.7 per 100,000 in counties with the lowest SSRI prescription rates
    - 0.7 per 100,000 in those with the highest prescription rates
  - Controlling for access to mental health care, the correlation between lower rates of suicide and higher prescription rates
  - It is estimated that if there were no SSRI use, 253 more suicides would occur each year, an 81% increase
- Deutschman, 2006: analyzed 2,500 "real-world" trials of antidepressant medications in 1,742 youth patients; overall, apparent increases in suicidality after beginning treatment were more likely due to obvious stressors or interruptions in treatment:
  - 2.6% had an increase in suicidal thoughts
    - Obvious intervening stressors in 38%
    - Interruption in treatment in 27%
    - Documentation errors in 26%
  - 11% had a decrease in suicidal thoughts
  - 12.4% had a decrease in suicidal threats and gestures
- **Simon, 2006: the risk of suicide in adolescent depression decreased by 60% in the first month AFTER ANTIDEPRESSANT TREATMENT BEGAN and continued to decline in the following 5 months of the study; the risk of suicide was HIGHEST IN THE MONTH PRIOR TO THE STUDY.**
- Simon, 2005: of 65,103 patients with 82,285 prescriptions for antidepressants (5,107 of which were for kids under 17), the risk of suicide and serious suicide attempt was highest in the 30 days PRIOR to starting an atidepressant medication. With continued antidepressant treatment, the risk of completed suicide remains fairly constant through six months of antidepressant treatment, while the risk of serious suicide attempt serious enough to result in hospitalization steadily decreases. SSRI use was associated with much greater DECREASES in suicide attempts than with older antidepressant classes.
- Hellerstein, 2005: antidepressants in the treatment of dysthymia; 1405 weeks of patient medication exposure in 108 patients; no suicidal acts occurred and there was a reduction on suicidal ideation.
- **Olfson: A recent study has demonstrated that a 1% increase in prescription of antidepressant medication was associated with a 0.23 per 100,000 decrease in adolescent suicides**
- A study of 200 elderly patients admitted to a psychiatric hospital in Israel found that antidepressants, including SSRI's, reduced the risk of suicide attempts by about 50% (Barak, 2005).

- A recent study by Szanto and colleagues demonstrated that Paxil or nortriptyline in depressed elderly patients led to the elimination of suicidal ideation with no exacerbation in suicidality.
- In a long term follow-up study (done over 22 years), antidepressant use appeared to reduce the risk of suicide
- In the U.S., there appears to be a correlation between antidepressant usage and a decrease in youth suicides (Gould and colleagues)
- Isaacson and colleagues examined Swedish data and noted a decrease in the suicide rate from 1990-1997 (during which there was a fourfold increase in antidepressant usage). Data regarding 15,400 suicides between 1992-2000 demonstrated that only 20.1% of those that suicided had positive toxicology screens for antidepressants despite a fivefold increase in the antidepressant usage during this same period; of note, Paxil was the least likely to be found on toxicology screens.
- Suicide rates have dropped by almost half between the pre-antidepressant era and the period after introduction of antidepressant medications.
- Beasley and colleagues analyzed 17 randomized, controlled trials of antidepressants; the analysis not only showed no increase in suicidality, but it showed a decrease.
- Reboxetine had been associated with decreased suicidal thoughts.
- Montgomery and colleagues found a decrease in suicide rates and attempts in patients taking Paxil versus placebo.
- Martinez and colleagues (2005) examined data from over 146,000 patients with a new diagnosis of depression (unipolar, bipolar, and dysthmia) who were prescribed an antidepressant from 1995-2001. Overall, the risk of non-fatal self harm did not differ between patients taking SSRI's or tricyclic antidepressants, and the risk was not elevated in relation to any specific SSRI. Suicide was not associated with the category of antidepressant used. Patients under 18 taking an SSRI may be more likely than those taking tricyclic antidepressants (a 1.59-fold increase risk (range 1.01-2.5-fold risk)). No patient under 18 committed suicide while taking an antidepressant.
- US county-level data on suicide rates and antidepressant prescription rates were analyzed for 1996-1998
  - After adjusting for sex, race, age, income, and unobservable county-level effects, the analyses revealed that increases in SSRI and SNRI prescriptions were associated with decreases in suicide rates both between and within counties over time
  - Counties with higher rates of tricyclic antidepressant (TCA) prescriptions were associated with higher suicide rates; this may be because of the higher toxicity of the TCAs and/or because of their greater use in areas with poorer access to quality mental health care
  - These findings have been replicated in youth 5-14 years of age

Evidence ***SUPPORTING EFFICACY*** of SSRI treatment (but data updated above in sections on each SSRI in the general SSRI handout)

- Walkup, 2016: "Significant controversy surrounds the efficacy of the newer antidepressants for children and adolescents with depression. The controversy largely hinges on meta-analyses of studies that suggest that antidepressants are minimally effective, not effective, or equivalent to placebo. In this review, the author discusses several scientific and clinical complexities that are important to understand in reviewing the antidepressant literature: the strengths and weaknesses of meta-analyses; the scientific and regulatory context for the large number of antidepressant trials in the late 1990s and early 2000s; and the distinction between a *negative* trial, where the treatment does not demonstrate efficacy, and a *failed* trial, where methodological problems make it impossible to draw any conclusion about efficacy. It is the premise of this review that meta-analyses that include the large number of industry-sponsored antidepressant trials distort the picture of antidepressant efficacy for teen depression. Industry-sponsored child and adolescent depression trials suffer from a number of implementation challenges and should be considered *failed* trials that are largely uninformative and not eligible to be included in efficacy meta-analyses. In contrast to the industry-sponsored trials, depression trials funded by the National Institute of Mental Health (NIMH) (N=2) are characterized by many methodological strengths, lower placebo response rates (30%−35%), and meaningful between-group differences (25%−30%) that support antidepressant efficacy. The NIMH-funded trials, taken together with the demonstrated efficacy of the serotonin reuptake inhibitors for childhood-onset obsessive-compulsive disorder and the anxiety disorders, suggest a broad and important role for antidepressant medications in pediatric internalizing conditions."

- Meta-analysis of 13 studies, 3004 youth with depression, looking at Prozac, Paxil, Lexapro, Celexa, Zoloft; Varigonda et al, 2015
  - No difference between the 5 SSRI's
    - But Prozac has stronger benefit in Bridge et al, 2007 and Cipriani et al, 2016
  - No difference of age, number of sites, or maximum dose
    - But, less effective in younger kids (except for Prozac) in Bridge et al, 2007
    - But, higher dose associated with more improvement in Heiligenstein et al, 2006 and Sakolsky et al, 2011
  - **Ultimate response evidence within 2 weeks**
    - **Also seen in Tao et al**
    - **Also seen in Emslie 2010**
  - Lower response rates than adults
  - Slow improvement through at least 10 weeks
- Meta-analysis of 9 studies of antidepressants in pediatric anxiety
  - All studies and overall effect size favors med over placebo
  - Risk of activation 1.86 fold increase overall (0.98-3.53 range; values >1 indicate risk)

- Risk of suicidality 1.30 fold increase overall (0.53-3.16 range; values > 1 indicate risk)
- Meds studied
  - Prozac
    - Beidel et al, 2007
    - Birmahar et al, 2003
  - Zoloft
    - Walkup et al, 2008
    - Rynn et al, 2001
  - Fluvoxamine
    - Rupp, 2003
  - Paxil
    - Wagner et al, 2004
  - Effexor
    - March et al, 2007
    - Rynn et al, 2007
  - Cymbalta
    - Strawn et al, 2013
- Brent et al, 2007: new analysis of 27 randomized, placebo-controlled clinical trials involving 5,310 youth studying the effects of second generation antidepressants in children and adolescents; the medications were efficacious, especially in anxiety disorders:
  - Anxiety disorders (total): 69% response rate vs. 39% in placebo
  - Obsessive compulsive disorder: 52% response rate vs. 32% in placebo
  - Major depressive disorder: 61% response rate vs. 50% in placebo (an extraordinarily high placebo rate)
- Bramness et al 2007: national and county-level data obtained from databases of drug prescriptions and suicide rates in Norway from 1980-2004, adjusted for unemployment rates and per-person alcohol consumption; sales of nontricyclic antidepressants were associated with a decrease in suicide rates
- ***Published*** U.S. studies (all double-blind, placebo, randomized, controlled) demonstrated positive safety and efficacy of SSRI's in the treatment of pediatric depression)
  - TADS, 2005 (see above)
  - (Emslie, 2004)
  - AJP, 2004: randomized, placebo-controlled eight-week study of Celexa for the treatment of major depression in children and adolescents supported the safety and efficacy of Celexa; the results, though, were controversial. Evidence of increased suicidality was not clear.
  - Published studies at the time of the FDA review
    - Wagner et al, 2003 (Zoloft); this was supported financially by Pfizer Pharmaceutical; this was the combination of two studies that on their own did not show evidence of efficacy.
    - Emslie et al, 2002 (Prozac); this was supported financially by Lilly Pharmaceutical
    - Keller et al, 2001 (Paxil); this was supported financially by SKB Pharmaceutical; FDA actually deemed it a negative study; evidence of risk of suicidality was present though labeled as "emotional lability"
    - Emslie et al, 1997 (Prozac); this was supported financially by National Institute of Mental Health
    - Total number of kids in these studies is 972.

Evidence ***SUGGESTING NO CHANGE IN SUICIDE RISK*** with antidepressants

- Gibson, 2012: fluoxetine not associated with increased suicidality in youth; fluoxetine and venlafaxine safe and effective in adults, along with reduced suicidality
- 2010 study in Norway: decrease in suicide rate not linked to newer antidepressants
- Meta-analysis of data compiled by the FDA from new drug applications and of data on paroxetine in adults found no evidence higher rates of suicide or suicide attempts
- FDA, 2006: second meta-analysis of 372 randomized control trials of newer antidepressants in an adult population of approximately 100,000 patients, based on spontaneous adverse-event reports from the randomized control studies
  - Overall, no evidence of more suicide-related adverse reports in the antidepressant group than in the placebo report
  - Stratification by age showed that for the primary endpoint of suicidal ideation or behavior in 18-24 year-olds, the risk was increased with medication compared with placebo, approaching statistical significance (the risk was 1.62 fold higher with medication
  - For adults aged 25-64, the risk was significantly DECREASED (risk was 0.79) with medications compared to placebo
  - For geriatric patients, the risk was markedly DECREASED (risk was 0.37) with medications compared to placebo
- Valuck et al: youth and adult data from large-scale insurance claims database, including 24,119 adolescents with a first diagnosis of major depression; at least 6 months of follow-up data were available
  - treatment with SSRI's, other antidepressants, or combinations of antidepressants did not increase the risk of suicide attempts
- Simon and colleagues found similar results to Valuck above
- Ferguson et al examined 702 randomized controlled studies in which SSRI's were compared with placebo or an active comparator, for any clinical condition; only 345 trials provided evidence on suicide/suicide attempts
  - No association with suicide/suicide attempts
- 1998-2004: data from FDA Adverse Event Report System (MedWatch) for all antidepressants; dataset involved 28,317,382 records, including all reported adverse events and drug combinations:
  - SSRI's and SNRI's showed a lower than national average suicide adverse-event report rate for antidepressants as a class

- Tricyclic antidepressants (TCAs) showered a higher than national average suicide adverse-event report rate for antidepressants as a class (AND, TCA's are much more dangerous in overdose than SSRI's and SNRI's)

- Matched case-control study of 159,810 patients in the UK using antidepressants from 1993-1999, the risk of first-time suicidal ideation or behavior did not differ between those receiving SSRI's and those receiving tricyclic antidepressants
- Acharya et al, 2006: in premarketing clinical trials, Cymbalta not found to be associated with increased risk of suicidal behaviors or ideation, according to a meta-analysis
  - 12 industry-sponsored trials including nearly 3,000 patients
  - In placebo-controlled trials 2 suicides occurred: 1 with Cymbalta and 1 with placebo
  - Rates of suicide, nonfatal suicide attempts, self-injury, suicidal ideation did not differ significantly from placebo
  - There was a small increase in suicide attempts and ideation, but this was attributed to one trial in severely depressed patients given doses now known to be subtherapeutic
  - In the 7 trials using active comparators, Cymbalta not associated with a higher rate of suicidal acts or ideation than other antidepressants (specific drugs not listed)
- Bauer, 2006, part of an ongoing NIMH pilot analysis of data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) clinical trial, first 1,000 patients (21 yo or older) who completed 1 year of treatment
  - Cross-sectional evaluation of 433 patients experiencing a major (bipolar) depressive episode
  - Prospective evaluation of 376 patients with new-onset major (bipolar) depressive episode
  - In both, Paxil was not associated with increased suicidality nor a trend towards increased suicidality
  - In a subgroup of 144 patients aged 10-20 yo, there was a trend towards reduced suicidality
  - Another prospective analysis of 2,000 patients participating in STEP-BD, also showed no association of suicidality with the initiation or change of any antidepressant
- Olfson et al, 2006: 607 hospitalized adults with depression; antidepressant drug therapy not associated with suicide attempts
- Leon et al, 2006: 41 youths committed suicide in NYC between 1999-2002, only one of which had antidepressant(s) (Zoloft and Wellbutrin in the single case) on serum toxicology analysis
- Guaiana, 2005: data was collected on dispensing of antidepressants (from 1983-2000) as well as data on suicide deaths from the Italian Ministry of Health from (from 1955-2000). There was not a correlation between antidepressant use and an increase or decrease in the risk of suicide.
- Recent analysis (2005): 11% of 123 youth suicides and 21% of 2,674 adults who died by suicide tested positive for the presence of an antidepressant in a comprehensive multistate study; of note SSRI's did not lead the list of antidepressants for which suicide completers tested positive.
- Khan and colleagues (2003) examined the FDA database of completed suicides and did not find a correlation between suicide rates and the use of antidepressants.

Evidence ***NOT SUPPORTING EFFICACY*** OF SSRI/SRI treatment of pediatric depression (also see general SSRI handout):

- In addition to the above study, there was another study of Celexa demonstrated lack of efficacy.
- One published negative study of SSRI's in pediatric depression (double-blind, placebo, randomized, controlled) from Simeon et al, 1990
- FDA analysis of unpublished data as below

Increased or Mixed Evidence of Suicide Risk, and Other Data

- Cipriani, Zhou, et al, 2016
  - 34 double-blind, randomized, controlled trials on pediatric depression, investigating at least one of 14 antidepressants, all published before May 31, 2015; ~5000 kids studied
    - TCA's (not used in children anymore for depression for years
      - Amitriptyline
      - Clomipramine
      - Desipramine
      - Imipramine
      - Nortriptyline
      -
    - SSRI's
      - Celexa
      - Lexapro
      - Prozac
      - Paxil
      - Zoloft
    - SNRI's
      - Effexor XR
      - Cymbalta
    - Other
      - Remeron
      - Serzone (rarely used in any patients due to risk of liver problems)
    - Not studied:
      - Fluvoxamine
      - Brintellix
      - Viibrid
      - Pristiq

        - Fetzima
        - MAOI's
    - Prozac found to have statistically significant benefit
    - Effexor XR found to increase risk of suicidality
- Researchers in Denmark analyzed clinical studies and summary trial reports, looking at data on Paxil, Effexor, Cymbalta, Zoloft, and Prozac; 68 reports of 70 trials involving 18,526 patients
    - In adults, no link to suicide and aggression
    - In youth, risk of suicide and aggression doubled (not clear which agents and the degree of risk per agent)
    - Some trials failed to report adverse effects and/or marred by design flaws
- Miller et al, 2013
    - Large claims-based study
    - No difference in the incidence of self-harm between SSRI and SNRI antidepressants
- More recent summary of meta-analytic findings for suicide-related events in pediatric clinical trials of antidepressants (combining analysis from Office of Drug Safety Analysis and Columbia University DNDP Analysis); note: numbers above 1 indicate increased risk and numbers below 1 indicate reduced risk
    - ALL major depression studies (1586 on drug, 1299 on placebo): 1.71-1.95 incident rate ratio (full range 1.05-3.21)
    - SSRI major depression studies (955 on SSRI, 843 on placebo): 1.41-1.87 incident rate ratio (full range 0.84-3.18)
    - NON-depression studies (712 on drug, 653 on placebo): 1.31-2.17 incident rate ratio (full range 0.26-6.72)
    - ALL trials (2298 on drug, 1925 on placebo): 1.78-1.89 incident rate ratio (full range 1.14-3.04)
- A nested case-control study of 146,095 individuals receiving a first antidepressant prescription for treatment of depression found a greater risk of nonfatal self-harm among youths receiving SSRI's compared with those receiving tricyclic antidepressants (1.9-fold increase) but not in adults
- FDA analysis, 2007: meta-analysis of 372 antidepressant trials involving over 100,000 subjects; suicidality adverse effect risk
    - SSRI's: 1.23 (increased)
    - Tricyclic antidepressants: 0.8 (decreased)
    - Other antidepressants: ~0.8-1.2
    - Patients aged 18-24 yo showed an increase of 55% in suicidal behaviors relative to those not on antidepressants
    - No increase was found in adults overall
    - Protective effect in patients aged 65 yo or more
    - ***CRITICAL: Suicidality found in 0.26% of subjects who responded to antidepressant treatment, 1.18% of those who didn't***
    - Completed suicides
        - 5 in ~40,000 (0.0125%) of those taking investigational antidepressant medication
        - 1 in ~15,000 (0.0067%) of those taking active comparator medication
        - 2 in ~27,000 (0.0074%) of those on placebo
        - ***There is a 2.2-15% lifetime risk of suicide in depression; this is a 176- to 1200-fold increased risk compared to the risk of completed suicide taking investigational antidepressant medication***
- Tiithonen et al, December, 2006, Archives of General Psychiatry; 15,390 patients with depression (but not psychosis) hospitalized after a suicide attempt, followed-up over 3.4 years; NOTE: data from this study demonstrates an increase in suicide attempts, but a reduction in completed suicide and mortality, as follows:

	Incidence per 1000 person-years	Relative risk; <1 is protective >1 increases risk
Completed suicides, overall		
No antidepressant:	11	1
Prozac:	**6.7**	**0.52-fold risk (less)**
Celexa:	**10.5**	**0.80 (less)**
Zoloft:	**10.6**	**0.82-fold risk (less)**
Paxil:	**10.7**	**0.90-fold risk (less)**
Luvox:	**12**	**0.95-fold risk (less)**
Remeron:	**16.6**	**0.98-fold risk (less)**
Effexor:	22.5	1.61-fold risk (**more**)
Suicide attempts, overall:		
No antidepressant:	106.2	
Zoloft:	148.2	1.41-fold risk (**more**)
Remeron:	171.3	1.50-fold risk (**more**)
Prozac:	189.3	1.54-fold risk (**more**)
Celexa:	173.7	1.55-fold risk (**more**)
Paxil:	164.5	1.63-fold risk (**more**)
Luvox	207.9	1.75-fold risk (**more**)
Effexor XR	189.8	1.79-fold risk (**more**)
Suicide attempts, ages 10-19 yo		
No antidepressant :	82.9	1
Zoloft:	**46.8**	**0.71-fold risk (less)**
Luvox:	**44.9**	**0.82-fold risk (less)**

- Remeron: 101.9 1.06-fold risk (**more**)
- Celexa: 155.5 2.27-fold risk (**more**)
- Paxil: 161.4 2.32-fold risk (**more**)
- Prozac: 159.2 2.44-fold risk (**more**)
- Effexor XR: 186.6 2.65-fold risk (**more**)

- Mortality, overall
  - No antidepressant: 32.3 1
  - **Prozac: 13.9 0.42-fold risk (less)**
  - **Zoloft : 18.8 0.55-fold risk (less)**
  - **Luvox: 19.1 0.57-fold risk (less)**
  - **Celexa: 25.4 0.62-fold risk (less)**
  - **Remeron: 31.2 0.63-fold risk (less)**
  - **Paxil: 26.0 0.85-fold risk (less)**
  - **Effexor XR: 34.2 0.91-fold risk (less)**

- Riggs et al, 2006: Prozac in the treatment of adolescent depression, 126 youth, all receiving CBT, randomized to Prozac (20 mg) or placebo, 16 weeks:
  - PRIOR to study, 39% reported mild to severe suicidal ideation
  - Overall significant DECREASE in suicidal ideation in BOTH Prozac and placebo-treated youth
  - 5 of the 126 youth were referred to the ER or a hospitalization for worsening suicidality
    - 4 of these 5 were on Prozac
- Guerrero et al 2006:review of systematic studies which employ SSRIs in child psychiatry patients (similar to the FDA review in 2005):
  - 23 double blind studies examined from 1991-2004, 3732 subjects from 5-18 yo
    - 21% of studies done on depressed youth
    - 26% done on youth with OCD
    - 17% done on youth with other anxiety disorders
  - Medications used
    - 47.8% Prozac
    - 26.1% Zoloft
    - 13% Paxil
    - 13% fluvoxamine
  - Results
    - NB: suicidal behavior not fully or formally assessed prior to the start of the studies
    - On SSRIs
      - 18 subjects recorded suicidal ideation
      - 7 suicidal gestures
      - No deaths
    - On placebo
      - 9 subjects recorded suicidal ideation
      - 5 suicidal gestures
      - No deaths
    - Psychiatric illness
      - 1 in 5 depression studies recorded suicidal ideation or gestures
      - 2 in 4 anxiety (other than OCD) studies recorded suicidal ideation or gestures
      - Only in studies involving anxiety was there a statistically significant correlation between suicidal ideation OR suicidal gestures and SSRI use
      - Only in studies involving depression was there a statistically significant correlation between parasuicidal events (self-harm without suicidal intent) and SSRI use
- FDA, 2005: "pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs in children and adolescents with major depressive disorder, obsessive compulsive disorder, or other psychiatric disorders (**MWW: <u>a total of 24 trials involving over ~4600 patients</u>**) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few motnhs of treatment in those receiving antidepressants. **<u>The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials."</u>**

Specifically, the average increased risk, in an analysis of the same data, is as follows:

		<u>DEPRESSION STUDIES</u>	<u>ALL USES</u>
○	**Effexor XR**	**8.84-fold (1.12- to 69.51-fold)**	**4.97-fold (1.09- to 22.72-fold)**
○	**Luvox**	**No depression studies**	**5.52-fold (range includes 0.27-fold REDUCTION)**
○	**Paxil**	**2.15-fold (range includes 0.71-fold REDUCTION)** Carpenter, 2006: 2.2-2.6% on Paxil; 0.9-1.3% on placebo	**2.65-fold (1- to 7.02-fold)**
○	**Zoloft**	**2.16-fold (range includes 0.48-fold REDUCTION)**	**1.48-fold (0.42- to 5.24-fold)**
○	**Prozac**	**1.53-fold (range includes 0.74-fold REDUCTION)**	**1.52-fold (0.75- to 3.09-fold)**
○	**Celexa**	**1.37-fold (range includes 0.53-fold REDUCTION)**	**1.37-fold (0.53- to 3.5-fold)**
○	**Serzone**	**No events**	**No events**
○	**Wellbutrin**	**No depression studies**	**No events**
○	**<u>ALL</u>**	***1.66-fold (range includes NO CHANGE)***	***1.95-fold (1.28- to 2.98-fold)***

Timeline of events related to controversy of SSRI use in pediatric depression

- 1/03: Prozac approved by the U.S. FDA for pediatric use for major depression and obsessive compulsive disorder.

- 6/03: British regulatory agency (MHRA) issues warning about Paxil and pediatric use; FDA issues precaution on use of Paxil and a variety of antidepressant medications in kids, especially around risk of increased suicidality, calling for further study.
- 8/03: Zoloft study (positive) published in the Journal of the American Medical Association; however, the study combined two studies which, each on their own, did not demonstrate efficacy of Zoloft though, when combined, a small degree of efficacy was demonstrated.
- 9/03: MHRA issues warning on Effexor and pediatric use; Wyeth-Ayerst issues warning to doctors about Effexor and increased risk of suicidality.
- 10/03: Revised FDA talk paper updating need for further review.
- 12/03: British warning regarding antidepressants extended to all SSRI's except Prozac saying that all SSRI's except Prozac are *contraindicated* in pediatric depression. Note that Serzone and Wellbutrin are not approved drug products in the UK.
- 2/04: FDA will meet to make recommendations based on its own review of the data.
- 3/22/04: FDA warns about worsening depression and development of suicidality in patients treated with second generation antidepressants (including SSRI's). Discussed changing medication warning labeling.
- 4/19/04: NY Times and LA Times published articles regarding "Mosholder" muzzling; Mosholder is an epidemiologist who worked for the FDA looking into the issue of SSRI and suicidality; he found, ~12/03, that there was some evidence of risk of suicidality in SSRI use in pediatric depression. He wrote a 15 page memo concluding that the evidence of efficacy was weak and the evidence of risk of suicidality was strong enough to warrant discouraging the off-label use of SSRI's in pediatric depression. The FDA held back this information. His memo was leaked to the press. Two congressional investigations re: this leak are now in progress.
- 6/04: The initial presentation of the acute efficacy data from the National Institute of Mental Health-sponsored TADS trial (comparing Prozac to cognitive behavior therapy to the combination in the treatment of adolescent depression).
- *8/04: Another memo was leaked to the public that stated the second analysis by the FDA confirms the original analysis of Mosholder showing a twofold increase in the risk of suicidality with SSRI's in pediatric depression (versus placebo). The FDA will publish this formally in the next few weeks. TADS study of 439 moderately to severely depressed adolescents released showing safety and efficacy of Prozac for the treatment of adolescent depression; the rate of suicidal thinking decreased by 1/3 when Prozac was used in combination with CBT.*
- ***May, 2007: since the warnings by the FDA, there has been a 20% decline in antidepressant prescribing in youth which parallels an overall 18% INCREASE in complete suicides in youth. This is tragic, tragic, tragic. And shameful.***
- ***Libby et al, 2007: from 1999-2004***
  - ***pediatric diagnoses of depression have increased from 3/1000 to 5/1000***
  - ***after the FDA advisory was issued, the rate dropped back down to 3/1000, a significant deviation from historical trend***
  - ***pediatricians and non-pediatrician primary care physicians accounted for the largest reductions in new diagnoses***
  - ***among patients with depression***
    - ***the proportion receiving no antidepressant increased to three times the rate predicted by the preadvisory trend***
    - ***SSRI prescription fills were 58% lower than predicted by the trend***
    - ***there was no evidence of a significant increase in the use of treatment alternatives (including psychotherapy)***

- Study in England and Wales, 1998-2000
  - SSRI's: 2 deaths per million prescriptions
  - TCA's: 14 deaths per million prescriptions
  - Venlafaxine: 13 deaths per million prescriptions
- Study in Sweden, comparing 14,857 deaths by suicide ith 26,422 deaths by accident or natural causes from 1992-2000
  - SSRI's detected less often than other antidepressants in suicide victims
    - In those younger than 15
      - In those who died in accidents or from natural causes, three of four of the antidepressants found were SSRI's
      - In the 52 children who had committed suicide, no SSRI's were found
    - In those aged 15-19
      - In those who died in accidents or from natural causes, three of five (60%) antidepressants found were SSRI's
      - In the 326 cases of suicide, 6 of 13 (46%) antidepressants found were SSRI's
- Completed suicides in NYC, younger than 18 y.o., 1990-1998
  - Antidepressants detected in 4 (7.3%) of 55 cases, two of which were imipramine, two of which were fluoxetine
  - Antidepressants detected in 3 (0.07%) of 407 accident victims, two amitryptiline, one fluoxetine

CONCLUSIONS

- The FDA and MHRA were examined data from 24 placebo-controlled studies conducted in 9 drug company-supported programs and 1 multicenter trial (the Treatment for Adolescents with Depression Study (TADS)).
  - 16 studies in depression
  - 4 in obsessive compulsive disorder
  - 2 in generalized anxiety disorder
  - 1 in social anxiety disorder, 1 in ADHD)
- Only 20 trials included in the risk ratio analysis of suicidalitybecause 4 trials had no events in the drug or placebo group
- ***4582 pediatric clients***
  - 2298 clients treated with active drug
  - 1952 treated with placebo
- All studies used "Adverse Event Reports" which are made only if a patient or their parent ***SPONTANEOUSLY*** shares thoughts of suicide or describes potentially dangerous behavior
- 17 of the 24 studies used a structured form to ask about suicidal thoughts or actions
- When looking at Adverse Event Report
  - ***3-4%*** on active drug with suicide-related events, 72.9%of which were considered serious
    - ***Overall risk ratio for SSRI in DEPRESSION trials was 1.66 (1.02-2.68)***
    - ***Overall risk ratio for all drugs across ALL indications was 1.95 (1.28-2.98)***
  - ***2%*** on placebo with suicide-related events, 70.6% of which were considered serious
  - When looking at structured forms asking about suicidal thoughts or actions
  - Active drug did NOT increase suicidality that had been present before treatment
  - Active drug did NOT induce new suicidality in those who were not thinking about suicide at the start of the study
  - ***ACTIVE DRUG WAS ASSOCIATED WITH A REDUCTION IN SUICIDALITY OVER THE COURSE OF TREATMENT***
  - ***NO DEATHS OCCURRED***
  - Bridge, 2005: rates and predictors of emergent suicidality in 88 medication-free depressed adolescent outpatients who reported NO current suicidality who were assessed over 12-16 weeks of psychotherapy: *12.5% reported emergent suicidality*
  - Family members should contact their child's physician if the youth:
    - Expresses new or more frequent thoughts of wanting to die
    - Engages in self-destructive behavior
    - Shows signs of increased anxiety/panic, agitation, aggressiveness, impulsivity
    - Experiences involuntary restlessness (akathisia)
    - Experiences extreme degree of unwarranted elation or energy accompanied by fast, driven speech and unreleastic plans or goals
  - The APA and AACA
    - "averaging all clinical trials conducted with eight different atidepressants…***active medication was associated with approximately a doubling (1.78-1.89) of the risk of suicidal events (but not completed suicide)*** in youth taking the medications (in comparison to placebo pill). Within this group of medications, ***fluoxetine had a risk ratio ranging from 0.88-0.92, implying reduced risk in comparison to placebo***, although the reduction is not statistically significant. Statistically significant elevations of risk for medication over placebo in individual clinical trials were found for only two medications—venlafaxine and paroxetine."
  - Important to note that the highest risk was during the first 9 days of the antidepressant being prescribed
  - Patients are more likely to commit suicide as they are coming out of depressive state
  - Problems with the research that was analyzed
    - Inconsistent inclusion criteria
    - Inconsistent exclusion criteria
    - Inconsistent outcome measures
    - Inconsistent ways to ascertain adverse events (only the fluoxetine trial (Emslie, 2002a) used a standardized side effects checklist
    - Inconsistent definitions of suicidality
    - No clear distinctions between ideation, gestures, attempts, intent, lethality
    - Unknown cause(s) of suicidality
    - Methodological differences
    - Ages of youth included
    - Unknown history of suicidality prior to the trials (with the exception of TADS)
    - Unknown whether or not suicidality came from depression (which was occurring before the trial began) or from treatment of depression
    - Outcome measures broken down by age
      - In some studies, benefits were seen in adolescents but not in children
      - In children, more responsive to placebo
    - The risks of not treating or undertreating depressio
      - 5-10% of depressed adolescents will die by suicide in the 10-15 years of diagnosis
      - 2-5% of depressed youth will die by suicide in the 10-20 years following an initial attempt
      - Depressed youth have increased risk for suicidality when they become adults—5-fold increase in suicide attempts in adulthood

- Pediatric depression leads to an increased risk for substance abuse, conduct disorder, impaired functioning, long-term psychiatric and medical conditions

ParentsMedGuide

The Use of Medication in Treating Childhood and Adolescent Depression: Information for Patients and Families

Prepared by the **APA and AACAP** in consultation with
A National Coalition of Concerned Parents, Providers, and Professional Associations

What prompted the FDA warning?

In 2004, the FDA reviewed 23 clinical trials involving more than 4,300 child and adolescent patients who received any of nine different antidepressant medications. **No suicides occurred in any of these studies.** Most of the studies that the FDA examined used two measures to assess suicidal thinking and behavior, which the FDA refers to collectively as "suicidality":

- All used "Adverse Event Reports" which are reports made by the research clinician if a patient (or their parent) spontaneously shares thoughts about suicide or describes potentially dangerous behavior. The FDA found that such "adverse events" were reported by approximately 4 percent of all children and adolescents taking medication compared with 2 percent of those taking a placebo, or sugar pill. One of the problems with using this approach is that most teenagers do not talk about their suicidal thoughts unless they are asked, in which case no report is filed.
- In 17 of the 23 studies a second measure was also available. These were standardized forms asking about suicidal thoughts and behaviors completed for each child or teen at each visit. In the views of many experts, these measures are more reliable than event reports. The FDA's analysis of the data from these 17 studies found that, medication neither increased suicidality that had been present before treatment, nor did it induce new suicidality in those who were not thinking about suicide at the start of the study. In fact, on these measures, all studies combined showed a slight reduction in suicidality over the course of treatment.

Although the FDA reported both sets of findings, the agency did not comment on the contradiction between them.

It is important to recognize that suicidal thoughts are common part of depressive illnesses. In fact, research demonstrates that over 40 percent of children and adolescents with depression think about hurting themselves. Treatment that increases communication about these symptoms can lead to more appropriate monitoring which decreases the actual risk of suicide.

Did the FDA prohibit the use of antidepressant medications by children and adolescents?

No, the FDA did not prohibit use of the medications for youth. Rather, the agency called on physicians and parents to closely monitor children and adolescents who are taking antidepressants for a worsening in symptoms of depression or unusual changes in behavior. The "black box warning" states that antidepressant medications are associated with an increased risk of suicidal thinking and/or behavior in a small proportion of children and adolescents, especially during the early phases of treatment.

Can antidepressant medications help children and adolescents with depression?

Yes. A large number of clinical research trials supported by pharmaceutical companies and by the federal government have clearly demonstrated the effectiveness of medications in relieving the symptoms of depression. An important recent study, funded by the National Institute of Mental Health (NIMH), examined the effectiveness of three different treatment approaches for adolescents with moderate to severe depression.

- One treatment approach used was the antidepressant medication fluoxetine, or Prozac®, which is approved by the FDA for use with pediatric patients.
- The second treatment was a form of psychotherapy called cognitive behavioral therapy, or CBT; the aim of CBT is to help a patient recognize and change negative patterns of thinking that may contribute to depression.
- The third approach combined medication and CBT.

These active treatments were compared to the results obtained from a placebo.

At the end of 12 weeks, the researchers found that 71 percent, or nearly three in four, of the young patients who received the combination treatment (i.e., medication + CBT) improved significantly. Of those receiving medication alone, slightly more than 60 percent improved. The combination treatment was nearly twice as effective in relieving depression as the placebo or psychotherapy alone.

Importantly, all three treatments were shown to significantly reduce the frequency of suicidal thinking and behavior. Participants in the study were systematically asked about such thoughts and behaviors. After three months of treatment, the number of young people experiencing such thoughts and behaviors dropped from one-in-three to one-in-ten. There were no completed suicides among the adolescents in the study.

A key lesson of this research is that medication can be an important and valuable treatment for depression in children and adolescents, but that combined treatments, customized to the needs of patients, may be even better. Optimal treatment often will include individual psychotherapy, both to enhance the effectiveness of medication and to help reduce the risk of suicidal thoughts or behaviors.

Do antidepressants increase the risk of suicide?

There is no evidence that antidepressants increase the risk of suicide. There is, however, much evidence that *depression* significantly increases a child's or adolescent's risk for suicide. Not all suicidal children have depression, and very rarely does a depressed child die as a result of suicide. Nonetheless, children with a mood disorder such as depression are five times more likely to attempt suicide than children who are not affected by these illnesses.

This question brings to the fore the important point noted above: that is, the FDA reported an increase in spontaneous reports of suicidal thoughts and/or behavior among children receiving medication, but there is no evidence that these suicidal thoughts or behaviors lead to an increased risk of suicide.

Research further demonstrates that the *treatment* of depression – including treatment with antidepressant medication -- is associated with an overall decrease in the risk of suicide. Data collected by the Centers for Disease Prevention and Control (CDC) show that between 1992 and 2001, the rate of suicide among American youth ages 10 – 19 declined by more than 25 percent. It is noteworthy that the same ten-year period was marked by a significant increase in the prescribing of antidepressant medications to young people. The dramatic decline in youth suicide rates correlates with the increased rates of prescribing one particular category of antidepressant medication, called selective serotonin reuptake inhibitors, or SSRI's, to young people in this age group.

What factors other than depression increase the risk of suicide?

Research has identified risk factors for suicide in addition to depression. One very important risk factor is a previous suicide attempt. A child who has attempted suicide once is much more likely to try to kill himself than a child who has never made an attempt. Other risk factors include the presence of serious mental disorders other than depression – for example, eating disorders, psychosis, or substance abuse. Events in a child's life, such as the loss of or separation from a parent, or – in adolescence – the end of a romantic relationship, physical or sexual abuse, or social isolation may increase the risk of suicide, especially if such events lead to depression in a vulnerable child.

Suicidal thoughts and behaviors are common among youth, especially during the turbulent years of adolescence. The CDC reports that nearly one-in-six adolescents think about suicide in a given year. Fortunately, very few of these young people die as a result of suicide

Every suicide is a tragedy. Because suicidality is a key symptom of depression, optimal treatment for children and adolescents with depression must include careful monitoring for suicidal thoughts or behavior. It is important to keep in mind that suicidal thoughts and actions decline with appropriate treatment.

Does talking about suicide signal increased likelihood that a child will hurt him/herself?

Any expression of suicidal thoughts or feelings by a child or adolescent is a clear signal of distress and should be taken very seriously by health care professionals, parents, family members, teachers, and others.

Psychiatrists and other mental health specialists have found that when a young person talks about suicidal thoughts, it often opens the door to discussion regarding the need to take special safety precautions or protective measures; thus a treatment approach that increases discussion of previously unspoken suicidal thoughts or impulses is helpful. Much more worrisome and potentially dangerous is a young person with depression who successfully hides the fact that he or she is having suicidal thoughts.

How can I be certain that my child has depression?

A parent, physician, teacher, or other observant adult may notice indications of depression in a child or adolescent. If you suspect the presence of depression, you should seek a comprehensive evaluation and an accurate diagnosis. These are essential to the development of an appropriate and effective treatment plan.

While research has identified the signs and symptoms of major depression, depression is not always an easy disorder to recognize. In children, the classic symptoms often may be obscured by other behavioral and physical complaints – features such as those listed in the right column of the table below. In addition, many young people who are depressed will also have a second psychiatric condition.

At least five of the following symptoms must be present to the extent that they interfere with daily functioning over a minimum period of two weeks.

Signs and Symptoms of Major Depressive Disorder	**Signs of Depression Frequently Seen in Youth**
Depressed mood most of the day	Irritable or cranky mood; Preoccupation with song lyrics that suggest life is meaningless
Decreased interest/enjoyment in once-favorite activities	Loss of interest in sports, video games, and activities with friends
Significant weight loss/gain	Failure to gain weight as normally expected; anorexia or bulimia; frequent complaints of physical illness, e.g., headache, stomach ache
Insomnia or hypersomnia	Excessive late-night TV; refusal to wake for school in the morning
Psychomotor agitation/retardation	Talk of running away from home, or efforts to do so

Fatigue or loss of energy	Persistent boredom
Low self-esteem; feelings of guilt	Oppositional and/or negative behavior
Decreased ability to concentrate; indecisive	Poor performance in school; frequent absences
Recurrent suicidal ideation or behavior	Recurrent suicidal ideation or behavior (writing about death; giving away favorite toys or belongings)

Major depression, or clinical depression, is one form of the larger group of mood disorders, also called "affective" disorders. These include *dysthymia*, a mood disorder in which symptoms generally are less severe than in major depression, but the illness is marked by a more chronic and persistent course; rather than shifting episodically into well-defined periods of depression, the child with dysthymia lives in world tinted a joyless gray. Another form of the illness is *bipolar disorder* in which periods of depression alternate with periods of mania, the hallmarks of which are unnaturally high levels of energy, grandiosity and/or irritability. Bipolar disorder may first appear as a depressed episode. Research has shown that treating unrecognized bipolar depression with antidepressant medications may trigger the manic phase of the illness. Children who have a family history of bipolar disorder will require special treatment considerations that should be discussed with your child's physician.

What should treatment consist of?

Your child's physician, in consultation with the parents/guardians, and, as appropriate, with your child, should develop a comprehensive treatment plan. This will typically include a combination of individual psychotherapy and medication. It may also include family therapy, or work with the counseling office at your child's school.

The physician should describe and discuss with you and your child or adolescent patient the risks and benefits of any treatment, which may or may not include treatment with medication.

One antidepressant medication – fluoxetine, or Prozac® – is formally approved by the FDA for treating depression in pediatric patients. You should know, however, that off-label prescribing of antidepressants – that is, prescribing an antidepressant that has not been formally approved by the FDA for use with child and adolescent patients – is common and consistent with general clinical practice. Of the approximately 30- to 40 percent of children and adolescents who do not respond to an initial medication, a substantial number will respond to an alternate medication.

If you and your child's physician do not see evidence of improvement in your child's health within 6-8 weeks, the doctor should reevaluate the treatment plan and consider changes.

How can I help monitor my child?

General strategies for suicide prevention should be employed if a child, or any member of a family, has depression.

- Lethal means, such as guns should be removed from the house, and large quantities of dangerous medications, including over-the-counter drugs, should not be left in an accessible location.
- Families should work in consultation with their child's physician or other mental health professional to develop an emergency action plan, including access to a 24-hour number available to deal with crises.
- If your child voices new or more frequent thoughts of wanting to die or to hurt him- or herself, or takes steps to do so, you should contact your child's doctor immediately.

The APA and AACAP believe that rather than requiring adherence to a prescribed monitoring schedule – that is, a fixed schedule that dictates how often and over what period of time children receiving antidepressant medications should be seen by a physician - the frequency and nature of monitoring should be individualized to the needs of the child and family.

Some children and teens may also show other physical and/or emotional reactions to antidepressants. These include increased anxiety or even panic, agitation, aggressiveness, or impulsivity. He or she may experience involuntary restlessness, or an unwarranted elation or energy accompanied by fast, driven speech and unrealistic plans or goals. These reactions are more common at the start of treatment, although they can occur at any point in the course of treatment. If you see these symptoms, consult your doctor. It may be appropriate to adjust the dosage, change to a different medication, or stop using medication.

In a small number of instances, a child or adolescent might have extreme reactions to antidepressants or other commonly used medications such as penicillin or aspirin as a result of genetic, allergic, drug interaction, or other unknown factors. Whenever you are concerned about any unexpected symptoms you observe in your child, immediately contact the child's doctor.

What treatments for childhood and adolescent depression other than medication are available?

Various forms of psychotherapy, including cognitive behavioral therapy (CBT), and interpersonal therapy (IPT) have been shown to be effective in treating milder forms of depression as well as anxiety and other mental and behavioral disorders. The aim of CBT is to help a patient recognize and change negative patterns of thinking that may contribute to depression. The focus of IPT is to help an individual address issues involving interpersonal relationships and conflicts that seem to be important in the onset and/or continuation of depression. Simply seeing a skilled health professional regularly for several weeks will

result in a reduction in the symptoms of depression in about a third of teenagers. As noted previously, however, it may require several months of treatment before depressed mood and accompanying suicidal thoughts and feelings begin to improve.

Research has also shown that when used in combination with a medication, interventions such as CBT may have a significant protective effect against suicidal ideation and/or behaviors.

Will my child's depression pass without treatment?

Depression tends to come and go in episodes, but once a child or adolescent has one period of depression, he or she is more likely to get depressed again at some point in the future. Without treatment, the consequences of depression can be extremely serious. Children are likely to have ongoing problems in school, at home, and with their friends. They are also at increased risk for substance abuse, eating disorders, adolescent pregnancy, and suicidal thoughts and behaviors.

Can my child keep taking an antidepressant medication now being prescribed?

If your child is being treated with a medication and is doing well, he or she should continue with the treatment. Research suggests that any increased risk of suicidal thoughts or behaviors is most likely to occur during the first three months of treatment. Teens especially should know about this possibility, and the patient, parents, and physician should discuss a safety plan – for example, who the child should immediately contact – if thoughts of suicide occur.

More critically, no patient should abruptly stop taking antidepressant medications because of the possibility of adverse withdrawal effects such as agitation or increased depression. Parents contemplating changing or terminating their child's antidepressant treatment should always consult with their physician before taking such action.

How can I advocate effectively for my child who has depression?

As your child's guardian and strongest advocate, you have the right to any and all information available about the nature of your child's illness, the treatment options, and the risks and benefits of treatment. Make sure your child receives a comprehensive evaluation. Ask lots of questions about the diagnosis and any proposed course of treatment. If you are not satisfied with the answers or the information you receive, seek a second opinion. Help your child or teen-ager learn, in an age-appropriate way, about the illness so he or she can be an active partner in treatment.

From the National Institutes of Mental Health:

Antidepressant Medications for Children and Adolescents: Information for Parents and Caregivers

Depression is a serious disorder that can cause significant problems in mood, thinking, and behavior at home, in school, and with peers. It is estimated that major depressive disorder (MDD) affects about 5 percent of adolescents.

Research has shown that, as in adults, depression in children and adolescents is treatable. Certain antidepressant medications, called selective serotonin reuptake inhibitors (SSRIs), can be beneficial to children and adolescents with MDD. Certain types of psychological therapies also have been shown to be effective. However, our knowledge of antidepressant treatments in youth, though growing substantially, is limited compared to what we know about treating depression in adults.

Recently, there has been some concern that the use of antidepressant medications themselves may induce suicidal behavior in youths. Following a thorough and comprehensive review of all the available published and unpublished controlled clinical trials of antidepressants in children and adolescents, the U.S. Food and Drug Administration (FDA) issued a public warning in October 2004 about an increased risk of suicidal thoughts or behavior (suicidality) in children and adolescents treated with SSRI antidepressant medications. In 2006, an advisory committee to the FDA recommended that the agency extend the warning to include young adults up to age 25.

More recently, results of a comprehensive review of pediatric trials conducted between 1988 and 2006 suggested that the benefits of antidepressant medications likely outweigh their risks to children and adolescents with major depression and anxiety disorders. The study, partially funded by NIMH, was published in the April 18, 2007, issue of the Journal of the American Medical Association.[1]

What Did the FDA Review Find?

In the FDA review, no completed suicides occurred among nearly 2,200 children treated with SSRI medications. However, about 4 percent of those taking SSRI medications experienced suicidal thinking or behavior, including actual suicide attempts—twice the rate of those taking placebo, or sugar pills.

In response, the FDA adopted a "black box" label warning indicating that antidepressants may increase the risk of suicidal thinking and behavior in some children and adolescents with MDD. A black-box warning is the most serious type of warning in prescription drug labeling.

The warning also notes that children and adolescents taking SSRI medications should be closely monitored for any worsening in depression, emergence of suicidal thinking or behavior, or unusual changes in behavior, such as sleeplessness, agitation, or withdrawal from normal social situations. Close monitoring is especially important during the first four weeks of treatment. SSRI medications usually have few side effects in children and adolescents, but for unknown reasons, they may trigger agitation and abnormal behavior in certain individuals.

What Do We Know About Antidepressant Medications?

The SSRIs include:

fluoxetine (Prozac)
sertraline (Zoloft)
paroxetine (Paxil)
citalopram (Celexa)
escitalopram (Lexapro)
fluvoxamine (Luvox)

Another antidepressant medication, venlafaxine (Effexor), is not an SSRI but is closely related.

SSRI medications are considered an improvement over older antidepressant medications because they have fewer side effects and are less likely to be harmful if taken in an overdose, which is an issue for patients with depression already at risk for suicide. They have been shown to be safe and effective for adults.

However, use of SSRI medications among children and adolescents ages 10 to 19 has risen dramatically in the past several years. Fluoxetine (Prozac) is the only medication approved by the FDA for use in treating depression in children ages 8 and older. The other SSRI medications and the SSRI-related antidepressant venlafaxine have not been approved for treatment of depression in children or adolescents, but doctors still sometimes prescribe them to children on an "off-label" basis. In June 2003, however, the FDA recommended that paroxetine not be used in children and adolescents for treating MDD.

Fluoxetine can be helpful in treating childhood depression, and can lead to significant improvement of depression overall. However, it may increase the risk for suicidal behaviors *in a small subset of adolescents*. As with all medical decisions, doctors and families should weigh the risks and benefits of treatment for each individual patient.

What Should You Do for a Child With Depression?

A child or adolescent with MDD should be carefully and thoroughly evaluated by a doctor to determine if medication is appropriate. Psychotherapy often is tried as an initial treatment for mild depression. Psychotherapy may help to determine the severity and persistence of the depression and whether antidepressant medications may be warranted. Types of psychotherapies include "cognitive behavioral therapy," which helps people learn new ways of thinking and behaving, and "interpersonal therapy," which helps people understand and work through troubled personal relationships.

Those who are prescribed an SSRI medication should receive ongoing medical monitoring. Children already taking an SSRI medication should remain on the medication if it has been helpful, but should be carefully monitored by a doctor for side effects. Parents should promptly seek medical advice and evaluation if their child or adolescent experiences suicidal thinking or behavior, nervousness, agitation, irritability, mood instability, or sleeplessness that either emerges or worsens during treatment with SSRI medications.

Once started, treatment with these medications should not be abruptly stopped. Although they are not habit-forming or addictive, abruptly ending an antidepressant can cause withdrawal symptoms or lead to a relapse. Families should not discontinue treatment without consulting their doctor.

All treatments can be associated with side effects. Families and doctors should carefully weigh the risks and benefits, and maintain appropriate follow-up and monitoring to help control for the risks.

What Does Research Tell Us?

An individual's response to a medication cannot be predicted with certainty. It is extremely difficult to determine whether SSRI medications increase the risk for completed suicide, especially because depression itself increases the risk for suicide and because completed suicides, especially among children and adolescents, are rare. Most controlled trials are too small to detect for rare events such as suicide (thousands of participants are needed). In addition, controlled trials typically exclude patients considered at high risk for suicide.

One major clinical trial, the NIMH-funded Treatment for Adolescents with Depression Study (TADS)[2], has indicated that a combination of medication and psychotherapy is the most effective treatment for adolescents with depression. The clinical trial of 439 adolescents ages 12 to 17 with MDD compared four treatment groups—one that received a combination of fluoxetine and CBT, one that received fluoxetine only, one that received CBT only, and one that received a placebo only. After the first 12 weeks, 71 percent responded to the combination treatment of fluoxetine and CBT, 61 percent responded to the fluoxetine only treatment, 43 percent responded to the CBT only treatment, and 35 percent responded to the placebo treatment.

At the beginning of the study, 29 percent of the TADS participants were having clinically significant suicidal thoughts. Although the rate of suicidal thinking decreased among all the treatment groups, those in the fluoxetine/CBT combination treatment group showed the greatest reduction in suicidal thinking.

Researchers are working to better understand the relationship between antidepressant medications and suicide. So far, results are mixed. One study, using national Medicaid files, found that among adults, the use of antidepressants does not seem to be related to suicide attempts or deaths. However, the analysis found that the use of antidepressant medications may be related to suicide attempts and deaths among children and adolescents.[3]

Another study analyzed health plan records for 65,103 patients treated for depression.[4] It found no significant increase among adults and young people in the risk for suicide after starting treatment with newer antidepressant medications.

A third study analyzed suicide data from the National Vital Statistics and commercial prescription data. It found that among children ages five to 14, suicide rates from 1996 to 1998 were actually lower in areas of the country with higher rates of SSRI antidepressant prescriptions. The relationship between the suicide rates and the SSRI use rates, however, is unclear.[5]

New NIMH-funded research will help clarify the complex interplay between suicide and antidepressant medications. In addition, the NIMH-funded Treatment of Resistant Depression in Adolescents (TORDIA) study, will investigate how best to treat adolescents whose depression is resistant to the first SSRI medication they have tried. Finally, NIMH also is supporting the Treatment of Adolescent Suicide Attempters (TASA) study, which is investigating the treatment of adolescents who have attempted suicide. Treatments include antidepressant medications, CBT or both.

Complete list of all NIMH Clinical Trials.

Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA, MD. 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.

Treatment for Adolescents with Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial . *Journal of the American Medical Association*, 2004 Aug 18; 292(7):807-20.

Olfson M, Marcus SC, Shaffer D. Antidepressant Drug Therapy and Suicide in Severely Depressed Children and Adults . *Archives of General Psychiatry*. 2006 Aug. 63:865-72

Simon GE, Savarino J, Operskalski B, Wang P. Suicide Risk During Antidepressant Treatment .*American Journal of Psychiatry*. 2006. 163 (1): 41-47.

Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationships between antidepressant prescription rates and rate of early adolescent suicide . *American Journal of Psychiatry* 2006. 163 (11): 1898-1904

Time Course and Predictors of Suicidal Ideation During Citalopram Treatment in the STAR*D Trial

Catherine G Coughlin, Ewgeni Jakubovski, Michael H Bloch

Journal of Clinical Psychiatry 2016 September 13

OBJECTIVE: Selective serotonin reuptake inhibitors are first-line treatment for major depressive disorder (MDD), but their impact on suicidal ideation is equivocal. Our goal is to examine the time course and clinical predictors of citalopram-induced suicidal ideation during phase 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.

METHODS: Of the 4,041 subjects with DSM-IV nonpsychotic MDD in the STAR*D trial phase 1 (2001-2006), we included in our analysis 3,577 subjects who reported side-effect data and had received citalopram (20-60 mg/d) for 8-14 weeks. Suicidal ideation was reported on item 12 of the Quick Inventory of Depressive Symptomatology, Self-Report. Survival analysis and receiver operating characteristic analysis were used to assess baseline characteristics associated with emergence and worsening of suicidal ideation.

RESULTS: Suicidal ideation was more likely to occur early in citalopram treatment, with few subjects showing emergence or worsening occurring after 6 weeks of treatment. Clinical variables explained very little of the variance in worsening or emergence of suicidal ideation with citalopram treatment (generalized $R^2 \leq 2\%$ in survival analysis). Being Hispanic, taking sedative medications, increased depression severity, absence of hypersomnia, and cardiac comorbidity were significantly ($P \leq .04$) associated with greater likelihood of emergence of suicidal ideation in patients without suicidal ideation at baseline. Being widowed, better work performance, weight loss at baseline, and the presence of vascular or neurologic comorbidities were associated with a greater likelihood of worsening of suicidal ideation.

CONCLUSIONS: Baseline clinical variables were poor predictors of emergence or worsening of suicidal ideation. As such, increased research focusing on clinical correlates rather than clinical predictors of suicidal ideation may be useful, as intervening events may be crucial in bringing about increased suicidality.

In a 2018 article in the journal *The Lancet*, researchers led by Andrea Cipriani compared the efficacy of 21 different antidepressants and established that antidepressants are more effective than placebo at reducing unipolar depression. **To date, this is the largest meta-analysis of double-blind, randomized controlled studies of antidepressant efficacy, including 522 trials and a total of 116,477 participants. All 21 of the antidepressants were found to be more effective than placebo.**

Looking at head to head studies, Cipriani and colleagues found that the most effective antidepressants were agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine. The least effective antidepressants were fluoxetine, fluvoxamine, reboxetine, and trazodone.

In terms of tolerability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were most tolerable to patients, while amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine caused the most study dropouts due to side effects. Only agomelatine and fluoxetine had better dropout rates than placebo.

Interestingly, agomelatine, the medication found to be most effective and most tolerable, is unavailable in the US. Pharmaceutical company Novartis, which owns the rights to the drug, was disappointed by some lackluster studies of the drug and never applied for Food and Drug Administration approval to sell it in the US. The studies found potential problems regarding drug interactions related to the metabolic enzyme CYP1A2 and a risk of liver damage with longer-term use.

Update on Randomized Placebo-Controlled Trials in the Past Decade for Treatment of Major Depressive Disorder in Child and Adolescent Patients: A Systematic Review

Martha J Ignaszewski, Bruce Waslick

Journal of Child and Adolescent Psychopharmacology 2018 July 31

OBJECTIVES: Antidepressant treatment for major depressive disorder (MDD) has been a topic of continued interest with a number of placebo randomized-controlled trials (RCTs) being published in the past decade. We review the updated literature since the 2007 Bridge meta-analysis, and reassess safety data looking at signals of treatment-emergent suicidality with the Columbia Suicide Severity Rating Scale (CSSR-S).

METHODS: PubMed literature review was performed searching for RCTs published since the 2007 article and supplemented with manual search.

RESULTS: Findings from seven trials (five industry sponsored, one NIMH funded, and one other) were included in this systematic review, which showed high medication and placebo response rates, with only fluoxetine and escitalopram treatment reaching statistical significance. Fluoxetine was also shown to prevent relapse of MDD with continued treatment with an odds ratio of 3.2 for prevention of relapse compared with placebo. There were no increases in treatment-emergent suicidality associated with antidepressant medication in any trial measuring suicidality systematically using the CSSR-S.

CONCLUSIONS: Depressed pediatric patients respond similarly in these trials to antidepressant intervention and placebo, with recent studies showing that newer agents did not clearly demonstrate benefit above placebo. The evidence continues to support fluoxetine and escitalopram as first-line treatment and demonstrated effect to prevent relapse. Use of newer rating scales reveals similar rates of treatment-emergent suicidality in patients on antidepressants as placebo, in contrast to increased suicide signal suggested by past research using adverse events data. Antidepressant treatment is generally safe and well tolerated in this age group.