Illuminating the Black Box: Antidepressants, Youth and Suicide

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Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis

Interpretation: When considering the risk–benefit profile of antidepressants in the acute treatment of major depressive disorder, these drugs do not seem to offer a clear advantage for children and adolescents. Fluoxetine is probably the best option to consider when a pharmacological treatment is indicated.
Black Box
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Drug Name] is not approved for use in pediatric patients....

The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.
FDA Black Box

• Prompted by warning of increased suicide risk in adolescents treated with *paroxetine*, by British MHRA in June 2003

• FDA pooled data from 24 studies examining antidepressant use in children for depression and anxiety disorders
• September 2004, FDA reported increase in suicidality
  – Defined as
    • new onset SI
    • worsening of SI
    • new or increased suicidal behaviors
  – 3.8% on SSRIs v 2.1% on placebo
Black Box Analyses

• Examined Suicidality in 4,582 cases in 24 controlled clinical trials on all antidepressants in pediatric patients.
  – Text search with blind recoding
  – Risk ratio for depression trials 1.66
  – Risk difference 0.02 (excess of 1-3 patients/100)
• No increase in suicidality on clinician rating scales
• Very Few Suicide Attempts and
• No patients committed suicide or seriously harmed self

Hammad et al. AGP, 2006
Bridge, J. A. et al. JAMA 2007;297:1683-1696
Black Box

• Limitations
  – Post-hoc analyses, multiple sub-analyses
    • none of original 24 studies were designed to evaluate this
  – Few events of “suicidality” (78/4400)
  – Substantial differences between studies in classification
  – Noncompliance not considered
  – Patients with severe pathology excluded
Black Box

• Limitations, continued
  – increasing number of sites rapidly to accelerate trial
  – aggressive advertising to recruit patients
Placebo Response in Pediatric MDD Trials

Bridge JA et al., Am J Psychiatry 2009; 166:42-49
Black Box Revision

• February 2005
  – FDA altered warning
    • No “causal” relationship had been detected
    • Conclusion based on short-term studies
    • No suicides occurred in any of studies
SSRIs

• 1998 to 2002
  – 9% increase in juvenile SSRI prescriptions

• Began to drop since first quarter of 2004 after FDA and MHRA warnings
Unintended Effect of Black Box Warning?

Early Evidence of FDA Mandate on Youth Suicide

- Evaluation of large pharmacy claims database
- Determined SSRI use by age
- Compiled suicide data from the CDC

Antidepressants
Treatment: Antidepressants

- SSRIs
- Atypical Antidepressants
- SNRIs
- TCAs
- MOAIs
Treatment: Antidepressants

- **TCAs** generally avoided due to potential lethality and side effect burden
- **MAOIs** 80% of adolescents do not comply with dietary restrictions
- **SSRIs, SNRIs, Atypical Antidepressants** favored in practice due to relative safety in overdose and lower side effect burden
SSRIs

• **Fluoxetine** and **citalopram**
  – controlled trials demonstrating benefit over placebo

• **Escitalopram**
  – trial showed statistically significant benefit when subgroup analysis of adolescents was performed
Evidence: Antidepressants

• **Fluoxetine** and **Escitalopram** are the only FDA approved agents.

• Controlled data, published and unpublished now readily available.
SSRIs

• Recent meta-analysis incorporation of unpublished data gives further support to fluoxetine, while narrowing benefit-to-risk profiles of other agents
SSRIs

- The decrease in juvenile suicide has correlated with availability of SSRIs

- Systematic examinations of large databases have supported inverse relationship between SSRI prescriptions and suicide, particularly for ages 15-19
Efficacy of SSRIs

NNT=10  NNT=6  NNT=3

Meta-Analysis of Overall Rate of Emergent Suicidality All Types of Antidepressants

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number Needed to ‘Harm’ (NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>112</td>
</tr>
<tr>
<td>OCD</td>
<td>200</td>
</tr>
<tr>
<td>Anxiety</td>
<td>143</td>
</tr>
</tbody>
</table>

Atypical Antidepressants/ SNRIs

• No controlled trial data has shown statistically significant benefit of any of these agents (with exception of nefazadone) over placebo

• Venlafaxine
  – positive effect for adolescent subgroup
TCAs

• *Clomipramine* v. *paroxetine*
  – single multicenter trial
  – showed benefit for both agents

• No other study or meta-analysis has supported TCAs for juvenile depression
Treatment of Adolescents with Depression Study (TADS)

- NIMH sponsored multi-center controlled clinical trial
  - 13 sites
- 12-17 year olds with MDD
  - N=439
- Aim to compare efficacy of fluoxetine, CBT, combination, & placebo over 36 weeks with 1 year follow-up.
  - Fluoxetine 10-40 mg/day

TADS

• TADS Response Rates
  – Fluoxetine+CBT 71%
  – Fluoxetine 61%
  – CBT 43%
  – Placebo 35%
Adjusted mean Children's Depression Rating Scale-Revised (CDRS-R) total scores

The TADS Team, Arch Gen Psychiatry October 2007;64:1132-1143.
Using Medications for Pediatric Depressive Disorders

- May increase every one or two weeks by:
  - Fluoxetine* @ (Prozac) @ 5-10 mg QD
  - Sertraline*(Zoloft) 12.5-25 mg QD
  - Citalopram (Celexa) 5-10 mg QD
  - Paroxetine** (Paxil) 5-10 mg QD or 12.5 mg CR
  - Fluvoxamine* (Luvox) 12.5-25 mg QD
  - Venlafaxine (Effexor) 12.5-25 mg IR or 18.75-37.5 XR
  - Bupropion (Wellbutrin) 37.5 mg IR or 100 mg SR
  - Mirtazapine (Remeron) 3.75-7.5 mg QHS
  - Escitalopram@ (Lexapro) 2.5-5 mg QD
  - Duloxetine (Cymbalta) 20 mg QD

*=FDA approved to treat Pediatric OCD
@=FDA approved to treat Pediatric Depression
**=currently FDA recommends NOT using to treat Pediatric Depression
Using Medications for Pediatric Depressive Disorders

- Start low, go slow?
- After initiation of pharmacotherapy make plan for regular follow-up & emergency access
- Educate family
  - delay in onset of action
  - worsening depression/anxiety/sleep
  - negative behavior change
  - Discontinuation Syndrome
  - Potential for increase in ‘Suicidality’
  - Symptoms of mania, hypomania & mixed episodes
  - [www.parentsmedguide.org](http://www.parentsmedguide.org)
Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

- Adolescents (12-18) who failed 8 weeks of SSRI
  - N=334 patients; 6 centers
- Randomized to 12 weeks of switch to
  - Another SSRI
    - Paroxetine, citalopram or fluoxetine (20-40 mg)
    - Another SSRI + CBT
    - Venlafaxine (150-225 mg)
    - Venlafaxine + CBT
- CBT 9 times in 12 weeks

Brent et al. JAMA 2008
Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)  

Brent et al. JAMA 2008

- Higher response rate to switch to
  - New Medication + CBT (54.8%) vs.
  - New Medication alone (40.5%)

- No difference in response rate to switch to
  - Venlafaxine (48.2%) vs.
  - Second SSRI (47%)
    - No difference between the SSRIs

- No difference between treatments in
  - Adverse events
  - Self harm or suicidal adverse events
  - 17 subjects attempted suicide; no completers
Youth
Complications of Depressive Disorders

- Academic, interpersonal, and family difficulties
- Increased risk for suicide and other psychiatric problems (e.g., conduct problems, use/abuse of nicotine, alcohol and drugs)
- Increased risk for suicidal behaviors 10- to 50-fold
- 80% or attempters and 60% of completers are depressed
Diagnostic Considerations: Bipolar

• Rates of manic switching peak ages 10-14.

• No antidepressant uniquely “safe.”

• BPAD risk factors
Risk of Converting to Bipolar Disorder

• 20-40% of youth with MDD convert to Bipolar Disorder if they have:
  – Psychosis
  – Family History of Bipolar Disorder
  – Pharmacologically induced hypomania/mania

• BUT,
  – Not all youth who are activated by antidepressants have bipolar disorder
Suicide
Assessment of Suicidal Youth

- Characteristics of Suicidality
- Current and Lifetime Psychopathology
- Psychological Characteristics
- Family and Environmental Factors
- Availability of Lethal Means
- Use of Self-Report Instruments (e.g., Suicidal Ideation Questionnaire, Suicide Probability Scale) (Huth-Bocks et al., 2007)

Youth Suicide

• Male adolescents die by suicide at a rate $4 \times$ higher than females
  – Of all suicide completions, 80% are male
  – 75% are white males

• Female adolescents attempt suicide at a rate $3 \times$ higher than males
  – Asian-American females aged 14-24 years have the highest suicide rate (not attempts) of all females of ethnicity

• Gay, lesbian, bisexual, transgender, questioning have a $4 \times$ greater risk of suicide attempts than heterosexuals

Available at: http://www.cdc.gov/ViolencePrevention/pdf/Suicide-DataSheet-a.pdf.
Diagnostic Considerations: Suicide

• Juvenile suicide
  – increased markedly from the 1950s through the 1980s
  – decreased since early 1990s

• 8% of high school students make suicide attempts every year.

• 7% of youth with untreated depression complete.
# Leading Causes of Death 10-14 yo in United States

<table>
<thead>
<tr>
<th>Causes</th>
<th>2009 n</th>
<th>2008 n</th>
<th>%</th>
<th>Rate</th>
<th>%</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accidents</td>
<td>891</td>
<td>1024</td>
<td>28.5</td>
<td>4.5</td>
<td>32.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Cancer</td>
<td>426</td>
<td>433</td>
<td>13.6</td>
<td>2.1</td>
<td>13.8</td>
<td>2.2</td>
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<tr>
<td>Suicide</td>
<td>259</td>
<td>215</td>
<td>8.3</td>
<td>1.3</td>
<td>6.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Assault</td>
<td>201</td>
<td>207</td>
<td>6.4</td>
<td>1.0</td>
<td>6.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Congenital</td>
<td>161</td>
<td>161</td>
<td>5.3</td>
<td>0.8</td>
<td>5.1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

# Leading Causes of Death 15-19 yo in United States

<table>
<thead>
<tr>
<th>Causes</th>
<th>2009 n</th>
<th>2009 %</th>
<th>2009 Rate</th>
<th>2008 n</th>
<th>2008 %</th>
<th>2008 Rate</th>
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</thead>
<tbody>
<tr>
<td>Accidents</td>
<td>4758</td>
<td>41.5</td>
<td>22</td>
<td>5541</td>
<td>44.7</td>
<td>25.8</td>
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<tr>
<td>Assault</td>
<td>1893</td>
<td>16.5</td>
<td>8.8</td>
<td>2095</td>
<td>16.9</td>
<td>9.7</td>
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<tr>
<td>Suicide</td>
<td>1656</td>
<td>14.4</td>
<td>7.7</td>
<td>1604</td>
<td>12.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>654</td>
<td>5.7</td>
<td>3.0</td>
<td>685</td>
<td>5.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Heart</td>
<td>325</td>
<td>2.8</td>
<td>1.5</td>
<td>363</td>
<td>2.9</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Risk of Suicide Attempt Before and After Starting Treatment <25 yrs

CHANGES IN YOUTH SUICIDE RATES
— UNITED STATES, AGES 15–24 —

### MOST COMMON PSYCHIATRIC DIAGNOSES IN TEENS WHO SUICIDE

<table>
<thead>
<tr>
<th></th>
<th>MALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=213)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>50%</td>
</tr>
<tr>
<td>Antisocial</td>
<td>43%</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>38%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=46)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>69%</td>
</tr>
<tr>
<td>Antisocial</td>
<td>24%</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>17%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>48%</td>
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</tbody>
</table>

66% of 16- to 19-Year-Old Male Suicides Have Substance/Alcohol Abuse

Brent et al. 1999, Shaffer et al. 1996
Suicidality and SSRIs

• “Activation”
  – correlates with 7-fold increase in suicidality
• “Manic Switching”
• “Joy Returns Last”

• Specific “suicidal” effects on serotinergic pathways, “withdrawal syndrome” not supported.
Autopsy Studies of Suicide Victims

• 151 youth suicides studied in Utah
  – Of 137 with toxicology, only 4 with detectable levels of AD, AP, or MS

• 41 youth suicides studied in NYC, 1999-2002
  – Of 36 with toxicology, only 1 AD detected

• 1419 adult suicides studied in NYC, 2002-2004
  – 13.9% of young adults (18-24 years) had AD present on toxicology

Conclusions
Managing Depression in Children and Adolescents

- Depression in children & adolescents is common, identifiable and treatable
- Psychotherapy acceptable/emphasized as a first line in mild/moderate MDD
- Based on FDA meta-analysis, share with families
  - there is a 2-4% of SI vs. 1-2% on placebo.
  - TADS study shows 60-70% chance of improvement of MDD with medication treatment
- Fluoxetine and Escitalopram are FDA approved to treat Depression in Children and Adolescents (although may have good reason to use others)
- Educate families to watch for and report
  - increase in agitation or uncharacteristic behavior change or Suicidal/Self-Injurious Thoughts/Behaviors and how to get help if concerned;
- Weekly visits- not always practical- judge on case by case basis, qualified staff contacts acceptable
Impact on Treatment Guidelines

• Informed Consent
• Frequency of visits
• Reserve for moderate to severe cases
• SSRIs remain first line
• Diligent attention to deteriorations in mood/manic switching