Treating Young Minds

Widespread use, Minimal data, Need for Caution and Close Monitoring

James F. Leckman
What are we treating?

- Psychiatric disorders (PTSD, other/comorbid conditions)
- Psychological “issues” (guilt, shame, impaired trust, family problems, behavior problems)
Current Standard of Care

• Clear evidence that CBT interventions are effective in treating:
  – PTSD
  – Depression
  – Behavioral problems
  – Anxiety
  in multiply traumatized child populations
Why consider pharmacologic treatments?

• Limited access to specialized treatments
• Adult studies indicate efficacy of pharmacologic treatments for PTSD
• Many children are already receiving pharmacologic treatments
• Some children do not respond to CBT/psychotherapy alone
Why consider pharmacologic treatments?

• To treat co-morbid conditions that are common in children and adolescents with PTSD
Comorbidity in PTSD is Common

- ADHD
- Depression
- Anxiety Disorders (Panic, Separation Anxiety, Phobias)
- Substance Abuse
- ODD and Conduct Disorder
Why Psychopharmacology?

- Ideally the therapeutic goals of psychopharmacologic therapy are to decrease intrusive thoughts and images, phobic avoidance, pathological hyperarousal, vigilance, impulsivity, and depression.
Why Psychopharmacology?

In adults drug therapies have been most effective in:

• Decreasing arousal and the re-experiencing of symptoms such as nightmares and flashbacks
• Less effective for the symptoms of avoidance, numbing, and withdrawal.
• However, it may be difficult to differentiate negative symptoms from depression, which is a frequent psychiatric comorbidity.
Selective Serotonin Reuptake Inhibitors (SSRIs) - Adults

- SSRIs were found to be effective as first-line drug therapy in a systematic review of 35 randomized trials in adults (Stein et al., 2006).
- They are recommended in treatment guidelines for PTSD from the American Psychiatric Association.
SSRIs - Adults

• Fluoxetine (30 mg/d). The efficacy of the SSRIs was demonstrated in a RCT of 53 patients with PTSD who received (30 mg daily) or placebo (Conner et al., 1999).

• Sertraline (50 - 200mg/d). Effective at daily dosages of 50 to 200 mg in a RCT of patients with PTSD (Brady et al., 2000). Another RCT of sertraline has found that continuing the drug for six months in initial responders reduced the rate of relapse (Davidson et al., 2001).

• Paroxetine (20 to 40 mg/day) was also associated with improved outcomes compared with placebo in a RCT of 551 patients with PTSD (Marshall et al., 2001).
Common Side Effects

Jitteriness, restlessness, agitation, headache, gastrointestinal symptoms (diarrhea and nausea), and insomnia are common side effects with SSRIs.
Other Agents

• **Anxiolytics** — Anxiolytics are generally ineffective in PTSD, which is surprising considering the constellation of anxiety, jitteriness, hyperarousal, and autonomic instability seen in these patients.

• **Mood stabilizers** — Mood stabilizers such as carbamazepine and valproic have been found to improve impulsive behavior, arousal and flashbacks in patients with PTSD.

• **Alpha blockers** — The alpha blocker prazosin improved nightmares, sleep disturbance, and other PTSD symptoms in a small crossover study of 10 patients.

• **Antipsychotics** — Patients with symptoms refractory to the above therapies may require treatment with second generation antipsychotic medications.
Rationale for Pharmacologic Strategies for Children

• Has the child completed and failed a trial of Trauma focused CBT? Availability of CBT?
• Specific symptoms and Co-morbid diagnosis
• Distress of child and family (functionality)
• Phase of disorder (ASD, Acute or Chronic PTSD)
• Developmental and neuromaturational level
Adult Studies Are Insufficient

• Lack of randomized, double-blind clinical trials in children and adolescents
• Some medications effective in adult conditions are not in children with the same diagnosis
• Medications may cause unexpected responses in some children
• Metabolic, developmental factors may influence dose, frequency
Studies in Children

- Open label studies are available in the medical literature and at least two double-blind studies have been published on the treatment of PTSD in children.
- Drawbacks to these studies include modest sample sizes. A total of 128 children included in these studies, with wide age range.
- Recent studies on the use of the Selective-Serotonin-Reuptake-Inhibitor agents (SSRI’S) have shown promise in the treatment of this anxiety disorder, despite serious recent warning about their use in children by FDA.
Why placebo-controlled trials are essential

• The story of TCAs in childhood MDD
• The emerging story of SSRIs in childhood MDD
• Placebo response is high (30-50%) and rising
• Need to determine efficacy of medication per se
  – to prevent overuse of ineffective meds
  – to minimize unnecessary or dangerous SEs
  – so that effective but more expensive or inconvenient treatments are offered
Why randomized trials are essential

• Self- or researcher-selection may bias results for or against the index treatment
• Non-randomized assignment (by school, clinic, etc.) may contain significant biases
Why double-blind trials are essential

- Child expectation/bias
- Parent expectation/bias
- Researcher/clinician bias
What we know from randomized, placebo-controlled double blind medication trials in traumatized children

• TCA (Imipramine) for acutely burned children reduced PTSD symptoms more than chloral hydrate (Robert et al., 1999)
A Pilot Randomized Controlled Trial of Combined Trauma-Focused CBT and Sertraline for Childhood PTSD Symptoms

JUDITH A. COHEN, M.D., ANTHONY P. MANNARINO, Ph.D., JAMES M. PEREL, Ph.D., AND VIRGINIA STARON, M.S.

Cohen et al., 2007
Cohen et al., 2007

10-17 yr olds confirmed sexual abuse

175

151 Ineligible

Randomized

24

TF-CBT + P

12

TF-CBT + S

12

Dropout

1

1

Final Cohort

11

11

Dropout
Ineligibles (N = 151)

- Refused screening - concerns about medication, N = 59
- Already on psychotropic medications, N = 29
- MR, PDD, N = 8
- Age, N = 9
- Failed PTSD criteria, N = 31

Cohen et al., 2007
Results

• Both groups experienced significant improvement in PTSD

• No significant group x time differences between groups except in Child Global Assessment Scale ratings: TF-CBT + sertraline > TF-CBT + placebo

• Only minimal evidence suggests a benefit to adding sertraline to TF-CBT. Current evidence therefore supports an initial trial of CBT before adding medication.

Cohen et al., 2007
Conclusions from Pilot RCT

• Non-response rate for TF-CBT is consistent across studies (in range of about 20% across studies)
• Addition of sertraline may be helpful in decreasing that non-response rate.
• No evidence of serious SEs in this VERY SMALL SAMPLE
• More studies are needed
Adult Studies Are Insufficient

• Lack of randomized, double-blind clinical trials in children and adolescents
• Despite their wide spread use in children, some medications effective in adults are not as effective in children with the same diagnosis
• Medications may cause unexpected responses in some children
• Metabolic, developmental factors may influence dose, frequency
Widespread Use

• Since the early 1990s there has been a 3- to 5-fold increase in the prevalence of antidepressant treatment of youth, aged 2 to 17, in the US

• This dramatic increase continued until 2003 when the FDA as well as British and European regulators issued public health advisories concerning the risk of suicide and self-harm associated with the use of these medications in the pediatric population
Facts:

• In the wake of these advisories there has been a marked reduction in the number of SSRI prescriptions written both in the US and Europe.
Questions:

Is this a positive development?
Or will it lead to increased morbidity and mortality because of a failure to treat anxious and depressed children and adolescents?
Answer:
Children and adolescents with PTSD and other mental disorders are deserving of timely, safe, efficacious and closely monitored treatment.
In some cases this may involve the use of SSRIs or other pharmacological agents; however, the comparison of risk to benefit varies by age and indication.
Editorial

A Developmental Perspective on the Controversy Surrounding the Use of SSRIs to Treat Pediatric Depression

Leckman & King, 2007
Outline:

• Time trends in rates of SSRI prescriptions
• Evidence for efficacy of SSRIs
• Evidence for risk of increased suicidal or self-harming behavior following SSRI use
• Other risks – mood instability conversion to bipolar disorder
Outline:

• Long-term effects of SSRIs administered early in brain development
• Child and Adolescent Psychiatry Trials Network (CAPTN) Initiative
• Recommendations and Discussion
Time trends in the rate of SSRI prescriptions

- Population-based analysis of nearly 900,000 youths enrolled in 2 US health care systems and from a group-model HMO.
- Ten 1-year cross-sectional data sets from 1987-1996

Zito et al., 2003
Time trends in the rate of SSRI prescriptions

- The increase in prescriptions for antidepressants was second only to the increase in stimulant use.
- Prescriptions for antidepressants increased 2- to 3-fold for children and adolescents.

Zito et al., 2003
Time trends in the rate of SSRI prescriptions

- The increase in the use of psychotropic medications is not limited to adolescents
- Zito et al. (2000) documented a clear increase in pre-school children, aged 2 to 4 years of age
Time trends in the rate of SSRI prescriptions

- For example, by 1995 the overall prescription rate for antidepressants in the pre-school children covered by Medicaid in a Midwestern state was 3.2 per 1000 compared to 1.4 per 1000 in 1991

Zito et al., 2000
Time trends in the rate of SSRI prescriptions

• “In press” reports indicate that both in the US and in European countries the rates of SSRI prescriptions have fallen by more than 20% since the “Black box” warnings were issued by the FDA and European regulatory agencies.
Question:

Is there a relationship between the number of SSRI prescriptions written and the rate of suicide?
The Relationship Between Antidepressant Prescription Rates and Rate of Early Adolescent Suicide

Gibbons et al., 2006
Ecological study of suicidal behavior in youth 5-14 years

• National county-level suicide rate data among children ages 5–14 were broken down by sex, income, and race during the period 1996–1998. National county-level antidepressant prescription rate data were expressed as number of pills prescribed per person

Gibbons et al., 2006
Ecological study of suicidal behavior in youth 5-14 years

Gibbons et al., 2006
FIGURE 2. Relationship Between SSRI Prescriptions and Observed Suicide Rate (per 100,000) in the United States, 1996–1998

Gibbons et al., 2006
Ecological study of suicidal behavior in youth 5-14 years

- After adjustment for sex, race, income, access to mental health care, and county-to-county variability in suicide rates, higher SSRI prescription rates were associated with lower suicide rates in children and adolescents.

Gibbons et al., 2006
Ecological study of suicidal behavior in youth 5-14 years

- The aggregate nature of these data precludes a direct causal interpretation.
- However, more SSRI prescriptions are associated with lower suicide rates.
- This may reflect antidepressant efficacy, treatment compliance, or better quality mental health care.

Gibbons et al., 2006
Rates of suicide following the “Black Box” warnings

• “In press” reports indicate a possible increase in rate of suicide in children and adolescents in the years immediately following the “Black Box” warnings.
Outline:

• Time trends in rates of SSRI prescriptions
• Time trends in suicidal behavior
• Evidence for efficacy of SSRIs
• Evidence for risk of increased suicidal or self-harming behavior following SSRI use
• Other risks – mood instability conversion to bipolar disorder
Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment
A Meta-analysis of Randomized Controlled Trials

Bridge et al., JAMA, 2007
Evidence for efficacy of SSRIs

• 27 SSRI randomized trials for the treatment of pediatric mood and anxiety disorders were selected (MDD 15, OCD 6, Anxiety 6; >5,000 participants)

• Data with regard to treatment response and for suicidal ideation/suicide attempt were estimated by random-effects methods

• Subjects were stratified by age, 2-11 vs. 12-19 years.

Bridge et al., 2007
Efficacy of SSRIs

Although the response rate favored antidepressants for MDD (11.0%; [CI: 7.1 - 14.9%], corresponding to a number needed to treat (NNT) of 10 (CI: 7-15), this effect was limited to adolescents
Number Needed to Treat (NNT)

Number of patients who must be treated for one to benefit:

\[
\text{NNT} = \frac{1}{\text{AI}}
\]

Absolute improvement (AI) = Percent improved (new treatment) – percent improved (placebo or standard treatment)

Example: Emslie et al. Fluoxetine, 8 wk trial, 219 children and adolescents

\[
\text{AI} = 0.65 - 0.53 = 0.12; \quad \text{NNT} = \frac{1}{0.12} = 8.33
\]
Evidence for efficacy of SSRIs

<table>
<thead>
<tr>
<th>Age Grouping</th>
<th>No. of Trials</th>
<th>No. Responses/No. of Participants (%)</th>
<th>Risk Difference, % (95% CI)(^b)</th>
<th>(P) Value</th>
<th>Variance Explained, %</th>
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<td></td>
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<tr>
<td>All participants</td>
<td>13</td>
<td>944/1552 (61) 678/1358 (50)</td>
<td>11 (7 to 15) &lt;.001</td>
<td>14.3(_{12}) .28</td>
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<tr>
<td>Children</td>
<td>5</td>
<td>175/269 (65) 156/270 (58)</td>
<td>7 (−1 to 15) .08</td>
<td>3.8(_{4})  .43</td>
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<tr>
<td>Adolescents</td>
<td>10</td>
<td>563/901 (62) 391/790 (49)</td>
<td>13 (8 to 17) &lt;.001</td>
<td>13.4(_{9}) .14</td>
<td>33</td>
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</tbody>
</table>

Bridge et al., 2007
Efficacy of SSRIs

In contrast, children and adolescents treated with SSRIs for OCD or other anxiety disorders showed a significant benefit corresponding to a NNT of 6 (CI: 4-8), and 3 (CI: 2-5), respectively.

Bridge et al., 2007
Evidence for efficacy of SSRIs

<table>
<thead>
<tr>
<th>Age Grouping</th>
<th>No. of Trials</th>
<th>No. Responses/No. of Participants (%)</th>
<th>Risk Difference, % (95% CI)</th>
<th>P Value</th>
<th>Qdf</th>
<th>P Value</th>
<th>Variance Explained, %</th>
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<td>Treatment</td>
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<td>All participants</td>
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<td>387/562 (69)</td>
<td>223/574 (39)</td>
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<td>62/88 (70)</td>
<td>37/88 (42)</td>
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<td>.45</td>
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<td>Adolescents</td>
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<td>134/173 (77)</td>
<td>54/168 (32)</td>
<td>46 (36 to 55)</td>
<td>&lt;.001</td>
<td>1.12</td>
<td>.58</td>
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</table>

Bridge et al., 2007
Efficacy of SSRIs

The rate of placebo response for OCD and non-OCD anxiety disorders was in the range 40% for children and 30% for adolescents in contrast to MDD studies where the placebo response rates were 58% and 49% for the children and adolescent groups, respectively.

Bridge et al., 2007
Outline:

- Time trends in rates of SSRI prescriptions
- Time trends in suicidal behavior
- Evidence for efficacy of SSRIs
- Evidence for risk of increased suicidal or self-harming behavior following SSRI use
- Other risks – mood instability conversion to bipolar disorder
Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment
A Meta-analysis of Randomized Controlled Trials

Bridge et al., JAMA, 2007
Evidence for risk of increased suicidal or self-harming behavior following SSRIs

- There was increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug vs. placebo (0.7%; CI: 0.1% to 1.3%) (NNH = 143 [CI: 77 to 1000])

Bridge et al., 2007
Number Needed to Harm (NNH)

Number of patients who must be treated for one to be harmed:

NNH = 1/AH

Absolute harm (AH) = Percent harmed (AD exposure) – percent harmed (unexposed to ADs, placebo or other treatment)
Take Home Message

• There is a small increased risk of suicidal ideation and self-harming behavior associated with the use of SSRIs.
• The risk-benefit ratio from the randomized trials favors their use in non-OCD anxiety (PTSD?) disorders and OCD.
• The relative benefit is more modest for MDD, no significant benefit for children.
Antidepressant Drug Therapy and Suicide in Severely Depressed Children and Adults

A Case-Control Study

Mark Olfson, MD, MPH; Steven C. Marcus, PhD; David Shaffer, MD
Evidence for risk of increased suicidal or self-harming behavior following SSRIs

- Medicaid beneficiaries from all 50 states who received inpatient treatment for depression, excluding patients with other severe co-morbid disorders.
- Controls were matched for age, sex, race, substance use disorder, recent suicide attempts, days since discharge, and use of other psychotropic medications.

Olfson et al., 2006
Evidence for risk of increased suicidal or self-harming behavior following SSRIs

Main Outcome Measures: Suicide attempts and suicide deaths.

Olfson et al., 2006
Evidence for risk of increased suicidal or self-harming behavior following SSRIs

• In adults (aged 19-64 years), antidepressant use was not significantly associated with suicide attempts (OR, 1.10; CI: 0.86-1.39 [521 cases and 2394 controls]) or suicide deaths (OR, 0.90; CI: 0.52-1.55 [86 cases and 396 controls]).

Olfson et al., 2006
Evidence for risk of increased suicidal or self-harming behavior following SSRIs

- However, in children and adolescents (aged 6-18 years), antidepressant use was significantly associated with suicide attempts (OR, 1.52; CI, 1.12-2.07 [263 cases and 1241 controls]) and suicide deaths (OR, 15.62; CI, 1.65-infinity [8 cases and 39 controls]).

Olfson et al., 2006
Take Home Message

- Large N case-control studies support the view that antidepressant use is associated with an increased risk of suicide and suicide attempts.
- This may be more likely the case for severely depressed children and adolescents.
Take Home Message

• These findings support careful clinical monitoring during antidepressant drug treatment of severely depressed young people.
Outline:

- Time trends in rates of SSRI prescriptions
- Time trends in suicidal behavior
- Evidence for efficacy of SSRIs
- Evidence for risk of increased suicidal or self-harming behavior following SSRI use
- Other risks – mood instability conversion to bipolar disorder
Is Antidepressant Use Associated with Manic Conversion in Pediatric Patients?
Age Effects on Antidepressant-Induced Manic Conversion

Andrés Martin, MD, MPH; Christopher Young, MD; James F. Leckman, MD; Chengeto Mukonoweshuro, DMD, MPH; Robert Rosenheck, MD; Douglas Leslie, PhD
• Antidepressants may precipitate mania in vulnerable individuals
  - Antidepressants have been associated with “switching” (Bunney, 1972; Lewis, 1982; Peet, 1994) and cycle acceleration (Altshuler et al., 1995)
  - Tricyclic antidepressants in particular have been linked to switching and onset of bipolarity in depressed youths ages 6 to 12 (Geller et al., 1993)
Background

• Little is known about the possible association between age and this phenomenon
• Understanding this possible relationship is important because of the increasing use of antidepressants in children (Zito, et al., 2002, 2003)
Purpose

These analyses examine the relationships among antidepressants, age, and diagnostic conversion from anxiety and non-bipolar mood disorders to bipolar disorder.
Methods

STUDY POPULATION

• Secondary analyses of MEDSTAT’s MarketScan Research Database, consisting of over 7 million privately insured individuals living in the U.S.

• Study population consisted of individuals 5 to 29 years of age with ICD-9 codes for anxiety disorders and non-bipolar mood disorders who were insured between 1997 and 2001 (N=87,920)
## Demographics

**Gender**
- Male: 34,667 (39%)
- Female: 53,253 (61%)

**Age**
- 5-9: 9,810 (11%)
- 10-14: 14,995 (17%)
- 15-19: 24,576 (28%)
- 20-24: 16,757 (19%)
- 25-29: 21,782 (25%)
Diagnoses

- Anxiety (28%)
- Mild DEP (53%)
- Severe DEP (19%)
- HOSP DEP (<1%)
Methods

Analyses and Outcomes

- Demographic, diagnostic and medication variables were linked in order to estimate the proportion and cumulative hazard of the outcome of interest: diagnostic change from anxiety and non-bipolar mood disorders to bipolar disorder
Methods

Outcome:

• Diagnosis change was defined as change from depression or anxiety disorder to new diagnosis of bipolar illness
  - New diagnosis of bipolar illness was assigned only if it was indicated by two or more consecutive claims
  - If outcomes occurred within the first two months of initiation of antidepressant, subjects were dropped from the study population to limit possible diagnostic errors due to “activation”
Outcome

• If diagnostic change was preceded by a change to a mood stabilizer, the earlier event was used to mark the conversion date
Results

- There were 4,786 “converters” (5.4%) among the 87,920 patients.
- Subjects were followed for a median of 41 weeks – yielding a total of cumulative total 79,408 person years of observation and a conversion rate of 6.0% per year.
### Cox Proportional Hazards

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<tr>
<td>Number of medications</td>
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## Cox Proportional Hazards

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<td>Age</td>
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Conversion Rate by Exposure to ADs

Percent per year

None  Any  TCA  Other  SSRI

CR
Cox Proportional Hazards

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<td>SSRI</td>
<td>1.2 (1.1, 1.2)</td>
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Conversion Rate by Age

- 5 to 9
- 10 to 14
- 15 to 19
- 20 to 24
- 25 to 29
Conversion Rate by Age and Exposure to ADs

Percent per year

CR-UE
CR-E
### Cox Proportional Hazards

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Number Needed to Harm (NNH)

Number of patients who must be treated for one to be harmed:

\[ \text{NNH} = \frac{1}{\text{AH}} \]

\text{Absolute harm (AH)} = \text{Percent harmed (AD exposure)} - \text{percent harmed (unexposed to ADs, placebo or other treatment)}
Number Needed to Harm - All Diagnoses & All ADs

NNH
Number Needed to Harm - Mild Depression and Anxiety by ADs

Number Needed to Harm (NNH) for different ranges of medication usage:
- NNH-TCA
- NNH-Other
- NNH-SSRI

Ranges:
- 5 to 9
- 10 to 14
- 15 to 19
- 20 to 24
- 25 to 29
Limitations

- Reliance on administrative data with no independent confirmation of diagnosis
- Diagnosis of bipolar disorder at baseline may be low, and consequently, findings may be spurious
- Lack of information regarding pubertal status
- No information on medication adherence
Limitations

Another threat to the study’s validity has to do with disentangling what may be natural progression of the illness from the larger secular trends of increased prescribing of antidepressants and mood stabilizers.
Conclusion

Despite the short and long term benefits for many children with mood and anxiety disorders, there may be a subset of children who are vulnerable to induction of bipolar disorder secondary to the long term use of antidepressants.
Outline:

• Time trends in rates of SSRI prescriptions
• Time trends in suicidal behavior
• Evidence for efficacy of SSRIs
• Evidence for risk of increased suicidal or self-harming behavior following SSRI use
• Other risks – mood instability conversion to bipolar disorder
Outline:

- Long-term effects of SSRIs administered early in brain development
- CAPTN Initiative
- Recommendations
Data available concerning long-term behavioral effects of early SSRI exposure in developing animals

• Ansorge et al., 2004
• Maciag et al., 2006a; 2006b
• LaRoche et al., 2007
Early-Life Blockade of the 5-HT Transporter Alters Emotional Behavior in Adult Mice

Mark S. Ansorge,¹,²,³ Mingming Zhou,²,³ Alena Lira,²,³ René Hen,²,⁴ Jay A. Gingrich²,³∗
Early exposure to SSRIs leads to an increase in depression- and anxiety-related behaviors

• Serotonin (5-HT) acts as a trophic factor modulating developmental processes such as neuronal division, differentiation, migration, and synaptogenesis

• Mice lacking the 5-HTT gene (5-HTT-/-) exhibit increased depression- and anxiety related behaviors.
Early exposure to SSRIs leads to an increase in depression- and anxiety-related behaviors

• What about early exposure to SSRIs?
• Mixed litters were randomly assigned to either saline or FLX (10 mg/kg, intraperitoneally) treatments (P4 to P21).
• Will the effect be similar to what is seen in the 5-HTT-/- knockouts when tested in adulthood?
Early exposure to SSRIs leads to an increase in depression- and anxiety-related behaviors

• Starting at 12 weeks of age (9 weeks after the last injection of FLX), the FLX treated wild type animals were similar to the 5-HTT-/- knockouts with regard to a reduction in exploratory behavior in the open field and in the elevated plus-maze.

Ansorge et al., 2004
Elevated Plus Maze

Ansorge et al., 2004
Early exposure to SSRIs leads to an increase in depression- and anxiety-related behaviors

• The FLX treated wild type animals were also similar to the 5-HTT-/- knockouts with regard to in the novelty suppressed feeding paradigm and a shock avoidance test (paradigm that assesses behavioral responses to stress).

Ansorge et al., 2004
Shock Avoidance

Ansorge et al., 2004
Take Home Message

• Transient inhibition of 5-HTT during early development with fluoxetine, a commonly used serotonin selective reuptake inhibitor, produced abnormal exploratory and “stress response” behaviors in adult mice.
Long-term behavioral effects of early SSRI exposure in developing animals

• In another series of studies SSRIs caused profound reductions in the levels of tryptophan hydroxylase in dorsal raphe and in serotonin transporter expression in the cerebral cortex that persisted into adulthood

• Impaired sexual behavior in male rats

Maciag et al., 2006a; 2006b
Long-term behavioral effects of early SSRI exposure in developing animals

• Sex-specific alterations in visual discrimination and attention (LaRouche et al., 2007)
Take Home Message

• Despite the explosion of knowledge in the developmental sciences there is a paucity of data concerning the impact of SSRIs on the developing mammalian brain.
• We ignore the potential long-term adverse effects to the peril of the children and families we seek to serve.
Outline:

• Long-term effects of SSRIs administered early in brain development
• CAPTN Initiative
• Recommendations
Need for RCTs

- Need RCTs of medications for traumatized children with
  - PTSD alone
  - PTSD + comorbid conditions
  - No PTSD; other psychiatric conditions present
The current generation of clinical trials in pediatric psychiatry often fails to maximize clinical utility for practicing clinicians.

The Child and Adolescent Psychiatry Trials Network (CAPTN) will conduct large, simple "practical" trials that provide generalizable answers to important clinical questions without bias.
CAPTN

- "Large" means the random allocation of thousands of patients in hundreds of clinical centers to different treatments as they are delivered in community settings.
- "Simple" means that the number and type of data elements is small and straightforward in order to encourage provider or patient participation.
CAPTN

• CAPTN has just begun a prospective longitudinal cohort “safety registry” study of SSRIs and other newer antidepressants in children with MDD, OCD, other anxiety disorders and eating disorders

• This study is long overdue
Recommendations

• Clear need to evaluate risk factors such as familial history of suicide, bipolar disorder; patterns of impulsive aggressive behavior; and substance use

• History of use of SSRIs (safety and efficacy) in parents or in other adults may be misleading
Recommendations

• There is a need to undertake a collaborative discussion with patient and family in which data concerning age and indication specific risk and benefit data are presented.

• This discussion should include the lack of evidence concerning long term safety as well as evidence of differential benefits based on age and indication.
Recommendations

• Avoid the use of SSRIs in young patients especially those with MDD, if possible
• Treat only if close monitoring is possible
• Monitor long term outcomes (as is being done in CAPTN)
• Develop new interventions, with fewer risks
Recommendations

• Use medications cautiously, only after:
  – Psychotherapy (CBT) has been found to be ineffective (how long; with whom)
  – Any co-morbid condition causing significant impairment has been treated with agents known effective

• Safety concerns outweigh potential risks of using medication
Recommendations

• Careful assessment to assure comorbidities are not variations of PTSD symptoms (consider developmental level)
• May need to treat comorbid conditions prior to concurrent with CBT for PTSD
  • stimulants or buproprion for ADHD
  • SSRI for suicidal/severe depression and anxiety disorders (adolescents only)
  • Appropriate treatment for drug/alcohol abuse concurrent with PTSD treatments