

## Adolescents, Antidepressants, Suicide, and the FDA

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## Disclosures

Dr. Johnston has previously worked with many  
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He currently has no relevant conflicts of interest.

## Suicide Warnings And Antidepressant Medications

- A complicated story
  - Bad science
  - Bad politics
  - Bad terminology
  - Influence of money
  - Bureaucratic ineptitude

## The Critical Events

1. In 2004 the FDA mandated warnings (so-called black box warnings) about the relationship between antidepressant medications and suicidality in youth
2. Since that time, rates of prescribing antidepressants have *declined*
3. Since that time, rates of death by suicide have *increased*

A typical warning

**Suicidality and Antidepressant Drugs**  
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Celexa or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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. Celexa is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

## Conclusions

The FDA-mandated warning was a mistake

It's yet another case of bureaucratic ineptitude

*This could be the end of the story.*

## BUT WAIT! There Are Questions...

- Could suicide rates have gone up for some other reason?
  - Economics, politics, culture?
- What about the antidepressants?
  - Do they really increase suicidality?
  - Shouldn't antidepressants decrease suicidality?
  - How can reducing depression increase suicidality?
  - Are these drugs doing something else?
- What exactly is "suicidality?"
  - How do we decide who is and is not suicidal?
  - What are the implications of being suicidal?

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## Key Concepts

- I. Suicidality
- II. Developmental differences in drug response
- III. The nature of drug study data
- IV. Population data

If you grasp these concepts,  
you will understand this strange story.

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## I. Primer on Suicidality

- The terminology
- Subgroups within the universe of suicidality
- A few cautions

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## A Terminology Problem

- Suicide
- Suicidal
- Suicidality
- Suicide attempt
- Para-suicide
- Self-harm
- Etc.

*Surprisingly Murky Terms!*

<sup>2</sup>Rebuilding the tower of Babel: a revised nomenclature for the study of suicide and suicidal behaviors. Part 2: Suicide-related ideations, communications, and behaviors. *Suicide Life Threat Behav.* 2007 Jun;37(3):264-77.

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## All "Suicidal"

But, Two Distinct Groups

### Small Group: the "Enactors"

- Often secretive
- High-lethality attempts
- Low likelihood of discovery
- Intends to die

### Large Group: the "Communicators"

- Statements, letters, innuendoes
- Low-lethality attempts
- High likelihood of discovery
- Interpersonal goals
- Intends to live

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## Again, They Are All "Suicidal"

### Enactors

- We know very little
  - Lethal attempts
  - Psychological autopsies
  - An occasional "salvage"
  - Decreases with SSRI treatment

### Accidental Deaths

- Tragic misjudgments
  - Acetaminophen
  - Asphyxiation

### Communicators

- Making a powerful statement
  - Help me
  - Notice me
  - Take me seriously
  - Vengeance
- The "black box group"
  - Increases with SSRI treatment
  - No suicides in the FDA meta-analysis

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## A Few Words Of Caution

- Communicators must be taken seriously
  - Similar data across several studies, countries, and age groups
- Communicators must be treated with respect
  - There were no deaths from suicide in these data
- Current suicide screening methods do not reliably discriminate between communicators and enactors
- Communicators may turn into enactors
- Communicators are at risk for accidental death

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## II. Developmental Differences In Drug Response

- Young people respond differently to SSRIs<sup>1</sup>
  - The younger the child, the more likely a different response
  - The higher the dose, the more likely a different response
- What is this different response?
  - Disinhibition and activation
  - Some terminology
    - Behavioral side effects (BSE)<sup>1</sup>
    - Psychiatric adverse events (PSE)
- Why this difference?
  - Speculation about maturational rates of the 5-HT system
  - We really don't know

<sup>1</sup>King, R. A., Riddle, M. A., Chappell, P. B., Hardin, M. T., Anderson, G. M., Lombroso, P., et al. (1991). Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. *J Am Acad Child Adolesc Psychiatry*, 30(2), 179-186.

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## Why BSEs Are Important

- BSEs are often overlooked
  - They are not expected (like rashes, or constipation)
  - They can be inappropriately attributed to comorbid disorders, such as ADHD
- We speculate that BSEs are related to suicidality (communicators, enactors)
  - This may account for why the suicidality phenomenon is far more common in juveniles

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## III. The Nature Of Drug-Study Data

- Registration trials enroll a very unique population
  - They are designed to maximize the chances of approval
  - The subjects tend to be mildly ill and uncomplicated
- Naturalistic studies yield somewhat different results
  - Issues of suicidality were noted early<sup>1</sup>
- There are no drug studies explicitly focused on the treatment of suicidality
  - Ethical issues make such studies challenging
  - The rarity of the event (suicide) would make such studies difficult and expensive

<sup>1</sup>Teicher, M.H., Glod, C., & Cole, J. O. (1990). Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry*, 147(2), 207-210.

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## Suicide And Clinical Trials Of Medications<sup>1</sup>

- Suicidal subjects are excluded
  - It is not ethical to give them placebo
  - It is also inconvenient
- Also excluded
  - Substance users, those with personality disorders, those with a history of suicidality
  - Anyone severely or “atypically” depressed!
- When someone “looks” suicidal, they are ejected from the study
  - Ethics –what if they are on placebo?
  - Convenience

<sup>1</sup>Baldessarini RJ, Tondo L, Strombom IM, et al. Ecological studies of antidepressant treatment and suicidal risks. *Harv Rev Psychiatry*. 2007;15:133-145.

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## The Data On Suicidality In Registration Trials Of Medications

- There is no difference in suicide deaths between active drug and placebo<sup>1</sup>
  - This should not be surprising –there are almost no deaths!
- There is a statistically significant increase in suicidality in the active drug group<sup>1</sup>
  - Self-reports
  - Non-lethal overdoses
  - Para-suicidal activity (gestures, cutting, etc.)

### Antidepressants make suicidality worse

<sup>1</sup>For example: Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005; 330:396. and Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004; 292:338-346.

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## IV. Population Studies<sup>1</sup>

- Provide critical public health information
  - A window into what is actually happening
  - Often the methods are inexact
- Typically show associations, but not causality
  - Sometimes, causality can be inferred

Baldessarini RJ, Tondo L, Strombom IM, et al. Ecological studies of antidepressant treatment and suicidal risks. *Harv Rev Psychiatry*. 2007;15:133-145.

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## Colliding Data

- Rates of SSRI prescriptions are inversely associated with rates of teen suicide<sup>1</sup> (maybe)
  - Similar data across several studies, countries, and age groups
- The black box warning placed on antidepressants in October 2004, was based on “suicidality” data<sup>2</sup>
  - There were no deaths from suicide in these data

<sup>1</sup>Gibbons, et al. *Am J Psychiatry* 2007; 164:1356–1363)

<sup>2</sup>Hammad TA: Review and evaluation of clinical data. Washington, DC, Food and Drug Administration, Aug 16, 2004 (<http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammad-Review.pdf>)

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## Putting It All Together

- The FDA became concerned about “suicidality” and decided a warning was required
  - But they overlooked the absence of deaths by suicide
  - Perhaps were unaware of “enactors vs. communicators”
- The warning frightened practitioners and their clients resulting in a decrease in prescription rates
  - Depression/anxiety was under-treated and suffering increased
  - The number of “communicators” may well have gone down
  - The number of “enactors” went up
- The unfortunate result has been many unnecessary deaths
  - The estimates vary from hundreds to thousands<sup>1</sup>
  - More data will be appearing over time

<sup>1</sup>Bridge JA, Axelson DA. The contribution of pharmacoepidemiology to the antidepressant-suicidality debate in children and adolescents. *Int Rev Psychiatry*. 2008;20:209-214.

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## A Moment Of Reflection And Speculation

- Improvement in mood gives one the energy to try to “cope”
  - If one has few options, one way to “cope” is to send a strong message (such as para-suicidal act)
- Regulatory agencies need to change policy
  - The consequences of labeling need to be considered
  - There must be a capacity to reverse decisions

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## Clinical Recommendations

1. Families should be thoroughly informed
2. All juveniles taking an SSRI should be in a psychotherapeutic relationship
3. Treatment effect monitoring should be conducted systematically

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## 1. Informing Families

- Families should proactively “warned about the warning”
- Families should be told that SSRIs probably decrease the risk of death by suicide
- Families should understand BSE and be encouraged to monitor for behavioral changes

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## 2. The Role Of Psychotherapy

- Psychotherapy may improve the detection of suicidality (of any “variety”)
- Well-focused psychotherapy offers an evidence-based therapeutic advantage
- A psychotherapist is uniquely positioned to orchestrate systematic treatment effect monitoring

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## 3. Treatment Effect Monitoring

- Use established monitoring instruments
  - e.g. CDRS-R, CDI, Y-BOCS, etc.
- Collaborative information from school & home
- Medication specific side effects
  - Rash, weight gain, headache, sexual problems
  - Behavioral side effects

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## Summary Points

- The FDA’s action was well-intentioned but poorly informed
- The front-line clinician can play a significant role in minimizing the “damage”
- This is still an unfolding story
  - Will the FDA change its labeling requirements?
  - What will we see with the next generation of drugs?

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# Questions?

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