

Antidepressants, Outcomes, and Suicidality: The Good, The Bad, and the Ugly



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The Black Box Warning – October, 2004

Suicidality in Children and Adolescents

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) 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 except for patients with [Any approved pediatric claims here].

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Additional text of 2004 FDA Warning

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Ideally, such observation would include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

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The argument against the warning:

1. Historically, increases in SSRI prescription rates have resulted in reduced adolescent suicide rates
2. The FDA conclusion that SSRIs trigger suicidal behavior was faulty
3. After the FDA warning, doctors reduced rates of SSRI prescriptions
4. This has resulted in increased adolescent suicide rates

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Outline for this Talk

	Question	
1	Have increased SSRI prescriptions resulted in decreased suicide rates?	
2	Was the FDA conclusion that SSRIs trigger suicidality faulty?	
3	Did doctors reduce rates of SSRI prescriptions after FDA warning?	
4	Has reduced SSRI prescribing resulted in increased suicide rates?	

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1. Have increased SSRI prescriptions resulted in decreased suicide rates?

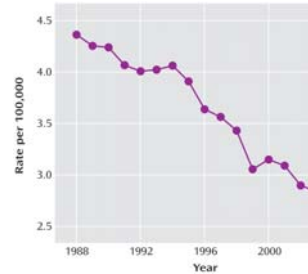
Multiple pharmaco-epidemiology studies in multiple countries...

- Europe (Issacson et al., 1996; Markowitz, 2001; Ohberg et al., 1998; Rich, 1999)
- Sweden and Finland (Henriksson et al., 2001; Issacson, 2000; Carlsten et al., 2001)
- USA (Olsson et al., 2003)
- Australia (Hall et al., 2003)

...find that decreases in suicide rates correlate with increases in ADM prescription rates.

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1. Have increased SSRI prescriptions resulted in decreased suicide rates?

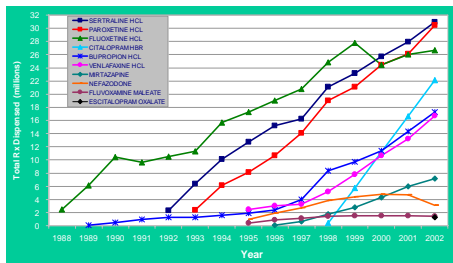


Suicide Rate in Children and Adolescents (Ages 5–19) in the US, 1988–2003

Gibbons et al. (2007). Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *American Journal of Psychiatry*, 164, 1356–1363.

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1. Have increased SSRI prescriptions resulted in decreased suicide rates?



Total U.S. Prescriptions Dispensed Annually for Selected Antidepressants, All Ages, 1988–2002

IMS Health, National Prescription Audit Plus™, Year 1988 to 2002, Data Extracted January 2004.

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1. Have increased SSRI prescriptions resulted in decreased suicide rates?

Depression is a risk factor for suicide

ADMs decrease depression

Therefore ADMs decrease suicide risk

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1. Have increased SSRI prescriptions resulted in decreased suicide rates?

However:

- England – Declines in suicide preceded increases in prescribing (Biddle et al., 2008)
- Ireland – SSRI use positively associated with rising suicide rates (Donovan et al., 1999)
- Iceland – no meaningful change in suicide rates despite 4-fold increase in ADM prescriptions (Helgason et al., 2004)
- Japan – suicide rates and SSRI prescription rates both on the rise (Takahashi, 2003)
- Italy – increased prescriptions correlate with increases in suicide rates in males but decreases in females (Barbui et al., 1999)

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1. Have increased SSRI prescriptions resulted in decreased suicide rates?

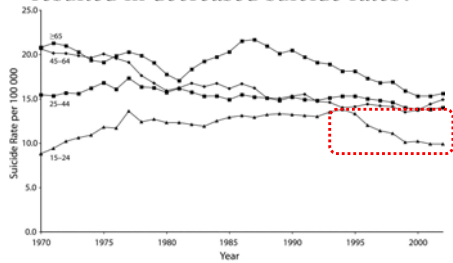
International review:

1. Suicide rates vary by age group within and between countries
2. Marked national differences in temporal association between suicide rates and SSRI prescription rates
3. In nearly half of the countries studied, decline in suicide rates *preceded* onset of use of SSRIs
4. Suicide rates have fluctuated dramatically in last century
5. Association in US, found from 1990–1999, not present between 2000–2004.

Safer, D.J., & Zito, J. M. (2007). Do antidepressants reduce suicide rates? *Public Health*, 121, 274–277.

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1. Have increased SSRI prescriptions resulted in decreased suicide rates?



Robert E. McKeown, Steven P. Cuffe, and Richard M. Schulz **US Suicide Rates by Age Group, 1970-2002: An Examination of Recent Trends** Am J Public Health 2006 96: 1744-1751

Why are the associations between SSRI use and suicide rates unclear?

SSRIs for children and adolescents are not as effective as the pharmaceutical industry would like us to think

Why are the associations between SSRI use and suicide rates unclear?

- No significant findings:
 - 8 of 12 published RCTs on ADMs vs. placebo for children/adolescents
 - Patient or parent reported measures
- Size of effect found:
 - 75% of SSRI effect is duplicated by placebo

Food and Drug Administration Testimony of Dr. Irving Kirsch and Dr. David Antonuccio on the Efficacy of Antidepressants with Children. (February 2, 2004). Retrieved from the World Wide Web: <http://www.ahrp.org/risks/SSRI0204/KirschAntonuccio.php>

Why are the associations between SSRI use and suicide rates unclear?

- When published and unpublished pharm studies are combined, risk-benefit ratios plummet and are no longer favorable.
- Only fluoxetine retains a favorable ratio.

Whittington, C.J., Kendall, T., Fonagy, P., Cottrell, D., Cotgrove, A., & Boddington, E. (2004). Selective serotonin reuptake inhibitors in childhood depression: Systematic review of published versus unpublished data. *Lancet*, 363, 1341-1345.

Jureidini, J.N., Dreeke, C.J., Mansfield, P.R., Haby, M.M., Menkes, D.B., & Tonkin, A.L. (2004). Efficacy and safety of antidepressants for children and adolescents. *British Medical Journal*, 328, 879-883.

Outline for this talk:

	Question	Conclusion
1	Have increased SSRI prescriptions resulted in decreased suicide rates?	Data is inconclusive
2	Was the FDA conclusion that SSRIs trigger suicidality faulty?	
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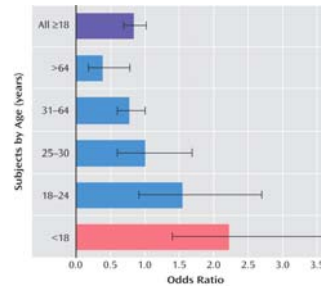
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2. Was the FDA conclusion that SSRIs trigger suicidality faulty?

- FDA conclusion based on analysis of 24 trials, over 4,400 patients:
- Risk of suicidal event on drug = 4%
- Risk of suicidal event on placebo = 2%

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2. Was the FDA conclusion that SSRIs trigger suicidality faulty?



Leon, A. C. (2007). The revised warning for antidepressants and suicidality: Unveiling the black box of statistical analyses. *American Journal of Psychiatry*, 164, 1786-1789.

Age-Specific Odds Ratios for Suicidal Ideation and Behavior

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2. Was the FDA conclusion that SSRIs trigger suicidality faulty?

Other studies (odds on SSRI vs. odds on placebo):

- 3.7% vs. 2.5% (9 UK studies; 1,700 patients)
 - Brent, D. (2004). Antidepressants and pediatric depression—the risk of doing nothing. *New England Journal of Medicine*, 351, 1598–1601.
- 3.8% vs. 2.1% (24 US studies; 4,100 patients)
 - Vitiello, B., & Swedo, S. (2004). Antidepressant medications in children. *New England Journal of Medicine*, 350, 1489–1491.
- Odds ratio = 2.28 (345 studies; 36,445 patients)
 - 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.

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2. Was the FDA conclusion that SSRIs trigger suicidality faulty?

Primary concern about all these datasets:

- No deaths, just attempts and ideation
- Most reported events are not serious suicide attempts or deaths
- Could be that SSRI use increases **reporting** of suicidal behavior, not the actual behavior
- Could be that SSRI use only increases **non-fatal suicidal behavior** but not fatal suicidal behavior

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2. Was the FDA conclusion that SSRIs trigger suicidality faulty?

- 8 naturalistic observational studies
- > 200,000 patients
- All patients with diagnosis of major depression

Odds of completed suicide on SSRI vs. not:

Elderly: 0.46

Adults: 0.57

Adolescents: 1.92

Barbui, C., Esposito, E., Cipriani, A. (2009). Selective serotonin reuptake inhibitors and risk of suicide: A systematic review of observational studies. *CMAJ*, 180 (3), 291-7.

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2. Was the FDA conclusion that SSRIs trigger suicidality faulty?

There are more adverse events related to SSRIs than the pharm industry wants us to think

- + results have been selectively reported and results withheld and reported with bias

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2. Was the FDA conclusion that SSRIs trigger suicidality faulty?

- Serious adverse events in Keller et al. (2001)
 - 11/93 Paroxetine (7 hospital admissions) vs. 2/87 with placebo
 - “paroxetine was generally well tolerated in this adolescent population, and most adverse effects were not serious”
- Serious adverse events in Wagner et al. (2003)
 - 17/189 sertraline withdrew from study because of adverse events vs. 5/184 on placebo
 - “sertraline is an effective, safe and well tolerated short-term treatment...”

Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. *BMJ* 2004; **328**: 879–83.

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What is it about SSRIs that leads to suicidality?

- Highest suicide risk is in first 9 days after ADM is prescribed.
 - Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004; **292**: 338–43.
- The longer you stay on meds, the lower your suicide risk.
 - Valuck, R.J., Libby, A.M., Sills, M.R., Giese, A.A., & Allen, R.R. (2004). Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: A propensity adjusted retrospective cohort study. *CNS Drugs*, **18**, 1119–1132.

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What is it about starting SSRIs?

1. Activation, behavioral disinhibition
2. Psychomotor agitation, akathisia
 - » Teicher, M.H., Glod, C., & Cole, J.O. (1990). Emergence of intense suicidal preoccupation during fluoxetine treatment. *American Journal of Psychiatry*, **147**, 207–210.
 - Long standing warnings in literature to assess carefully after starting meds and don't just reflexively increase dose
3. ADMs trigger bipolar or mixed agitated states
4. My research: Stigma

Bostwick, J. (2006). Do SSRIs cause suicide in children? The evidence is underwhelming. *Journal of Clinical Psychology: In session*, **62** (2), 235-241.

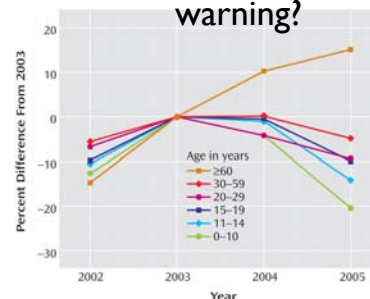
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3. Did doctors reduce rates of SSRI prescriptions after FDA warning?

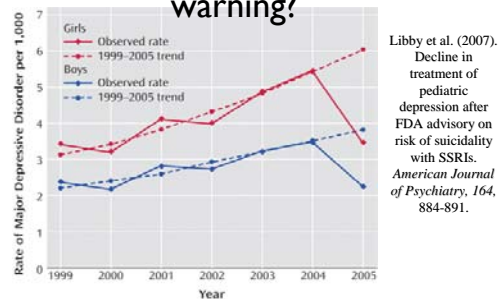


Gibbons et al. (2007). Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *American Journal of Psychiatry*, **164**, 1356-1363.

SSRI Prescription Rates in the United States, 2002–2005, Stratified by Age Group and Expressed as a Percentage of the 2003 Rate

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3. Did doctors reduce rates of SSRI prescriptions after FDA warning?



Libby et al. (2007). Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. *American Journal of Psychiatry*, 164, 884-891.

Annual Rates of Depression in the Pediatric General Medical and Specialty Managed Care Enrollee Population, 1999–2005, by Gender (N=65,349)

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3. Did doctors reduce rates of SSRI prescriptions after FDA warning?

- 1,521 Nebraska clinicians surveyed:
 - 16% reduced prescriptions to children
 - 37% reduced prescriptions to adolescents
 - 44% more referrals to specialists
 - 7.5% saw patients weekly first month (FDA rec)
 - 22% parent refused due to concerns about warning

Bhatia SK, Rezac AJ, Vitiello B, Sitorius MA, Buehler BA, Kratochvil CJ. *Antidepressant prescribing practices for the treatment of children and adolescents*. *Journal of Child and Adolescent Psychopharmacology*. 2008; 18(1): 70-80.

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3. Did doctors reduce rates of SSRI prescriptions after FDA warning?

- 670 Canadian pediatrician surveyed:
- 30% increased frequency of follow-up
 - 80% change prescribing practice
 - 25% increased referrals to psychiatry
 - 7% stopped SSRI tx in at least one patient
 - 8% patient stopped tx due to concerns about warning

Cheung et al. (2008). Pediatric prescribing practices and the FDA black-box warning of antidepressants. *Journal of Developmental and Behavioral Pediatrics*, 29, 213-215.

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3. Did doctors reduce rates of SSRI prescriptions after FDA warning?

- Analyzed administrative claims database representing 85 national managed care plans, > 500,000 patients
 - < 5% complied before FDA advisory
 - No significant change after advisory

Morrato et al. (2008). Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs. *American Journal of Psychiatry*, 165, 42-50.

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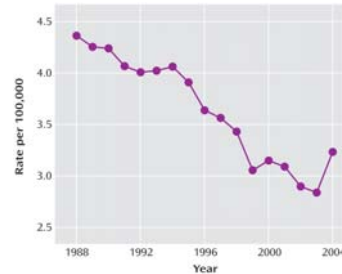
4. Has reduced prescribing resulted in increased suicide rates?

2003-2004:
Largest single year increase in 10-24 year old suicide rates since 1990

CDC, MMWR Weekly, September 7, 2007 / 56(35):905-908

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4. Has reduced prescribing resulted in increased suicide rates?

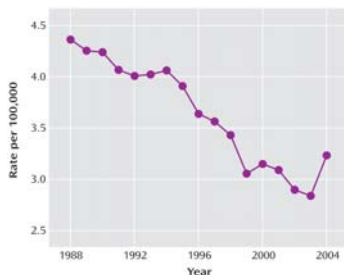


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Suicide Rate in Children and Adolescents (Ages 5-19 Years) in the United States, 1988-2004

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4. Has reduced prescribing resulted in increased suicide rates?



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Suicide Rate in Children and Adolescents (Ages 5-19 Years) in the United States, 1988-2004

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4. Has reduced prescribing resulted in increased suicide rates?

However:

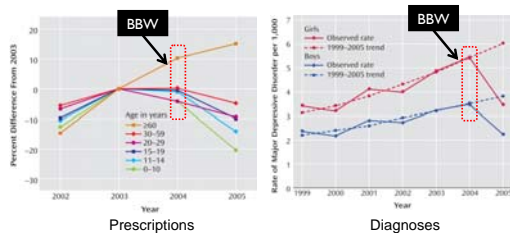
- Not in Great Britain:
 - ADM prescriptions dropped after warning
 - Deaths from suicides continued to decline annually from 1993
 - Hospital admission rates showed no change
- Biddle, L., Broch, A., Brookes, S. T., & Gunnell, D. (2008). Suicide rates in young men in England and Wales in the 21st century: time trend study. *British Medical Journal*, 336, 539-542.

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4. Has reduced prescribing resulted in increased suicide rates?

However:

- In U.S., prescription rates and diagnoses did not decrease until 2004-2005, *after suicide rates increased*.



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4. Has reduced prescribing resulted in increased suicide rates?

	5 - 14		15 - 24	
	N	Rate	N	Rate
2004	285	.7	4,316	10.3
2005	270	.7	4,139	9.8

For 2004-2005, suicides declined

Olfson, M. & Shaffer, D. (2007). SSRI prescriptions and the rate of suicide. *American Journal of Psychiatry*, 164, 1907-1908.

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4	Has reduced prescribing resulted in increased suicide rates?	No conclusive evidence yet

Conclusion: The Good

- The FDA's warning was valid
- With proper monitoring in place, ADMs (at least fluoxetine) decrease depression and suicide risk in children/adolescents
 - Combined ADM and psychotherapy is most effective

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Conclusion: The Bad

- ADMs do trigger suicidality in some patients
- The FDA seemingly did not predict the impact the warning would have on prescriber practices
 - The FDA wanted increased monitoring
 - The FDA got decreased prescribing
- How can AMA and related associations change practice guidelines and actual behavior to increase monitoring?

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Conclusion: The Ugly

This controversy needs to be interpreted in the context of this data being very threatening to the pharmaceutical industry which has mobilized all its vast resources in an effort to discredit the FDA's conclusions

Bostwick, J. M. (2006). Do SSRIs cause suicide in children? The evidence is underwhelming. *Journal of Clinical Psychology: In Session*, 62, 235-241.

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Questions?

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