# Idea Exchange: Time for a Change? The Antidepressant Black Box Warning in Youth

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# Disclosures

- Drs. Ferren and Stutzman do not have financial or other relationship with the manufacturer(s) of any commercial product(s) or provider(s) of any commercial service(s) discussed in this CE activity.
- This presentation will include discussion of off-label, experimental, and /or investigational use of drugs or devices: antidepressants

***Note to attendees**: while presenters are encouraged to disclose any conflicts and to use the best evidence available, the presentations are not peer reviewed and attendees should accordingly verify details prior to making significant practice changes.*

# Learning Objectives

1. Discuss the background surrounding the FDA's black box warning for antidepressants
2. Review a pertinent meta-analysis examining the association between suicidality and antidepressants
3. Summarize unintended outcomes of the FDA warning including monitoring for suicidality, depression diagnoses, antidepressant prescribing, and others
4. Participate in group discussion related to consequences of the FDA warning in clinical practice

# Background

# Antidepressant (AD) Black Box Warning (BBW)

**Dec 1997**
- Fluoxetine is the first SSRI FDA approved for MDD in children and adolescents (8-18 yrs).

**June 2003**
- First report sent to FDA by manufacturer of paroxetine suggests increased risk of SREs in youth with MDD.

**2003 – 2004**
- FDA issues health advisories warning that youth taking ADs are at increased risk of suicidality.

**Oct 2004**
- FDA mandates BBW on all ADs, indicating an increased risk of suicidal thoughts and behaviors in youth.

**May 2007**
- BBW is expanded to include young adults up to 24 years of age.

FDA warnings were intended to increase monitoring of suicidal thoughts and behaviors at antidepressant initiation.



SREs = suicide-related adverse events

Lu CY, et al. Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. BMJ. 2014.

# Black Box Warning Implications

## 2004 FDA Warning

- Retrospective evaluation, 24 placebo-controlled trials (N=4582 youth)
- Frequency of new-onset suicidal behavior: 4% (ADs) vs. 2% (Placebo)
- Increase in “harm-related behaviors”; none died by suicide

## 2004 Post-FDA Warning

- Antidepressant prescribing decreased by 10-26%
- Suicide rates increased by 14% in the US from 2003-2004

## 2004 and beyond

- Summary of literature suggests antidepressants offer a protective effect against suicide and may be associated with a 33% lower suicide rate

# Impact of FDA Regulatory Actions

- 2013 systematic review, including 11 studies
  - 50% of studies found no impact or weak/modest impacts of FDA actions
  - 33% of studies detected unintended consequences

- Unintended consequences:
  1. Spillover to patients not targeted by the warnings (i.e., adults after pediatric warning)
  2. Prescribing of substitute medications
  3. Fewer diagnoses
  4. Less appropriate treatment
  5. Reductions in care seeking individuals
  6. Adverse health outcomes



Briesacher BA. A critical review of methods to evaluate the impact of FDA regulatory actions. *Pharmacoepidemiol Drug Saf.* 2013.

# Literature

# Meta-Analysis Behind Initial BBW

| Study | Design | Data Extraction | Conclusion |
|---|---|---|---|
| Hammad TA. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006. | • FDA-solicited meta-analysis<br>• 24 randomized, placebo-controlled trials in pediatrics (1 multicenter study [TADS])<br>• Trial durations: 4 to 16 weeks<br><br>Outcomes:<br>• Primary: suicidal behavior or ideation<br>• Secondary: possible suicidal behavior or ideation<br><br>Suicidality Risk Estimates:<br>• All ADs across all indications<br>• Each individual AD<br>• All SSRIs in depression trials | 1) Electronic search of adverse event databases<br>2) Suicide item scores from depression scales<br><br>Exposure window: acute treatment period or within 1 day of treatment<br><br>Baseline Data:<br>• 4 trials excluded (no SREs)<br>• N=4582 patients<br>• 9 antidepressants<br>• 109 SREs in single-center studies and 11 events recorded in the TADS | • No completed suicides<br>• Overall RR for all ADs across all indications: 1.95 (95% CI, 1.28-2.98)<br>• TADS showed a statistically significant RR (4.62; 95% CI, 1.02-20.92)<br>• Overall RR for SSRIs in depression trials: 1.66 (95% CI, 1.02-2.68)<br>• Based on suicide item scores, no observed worsening or emergence of suicidality<br>• **Modestly increased risk of suicidality.** |



TADS = Treatment for Adolescents With Depression Study
SREs = suicide-related adverse events

# Venlafaxine & Paroxetine: Higher Risk?

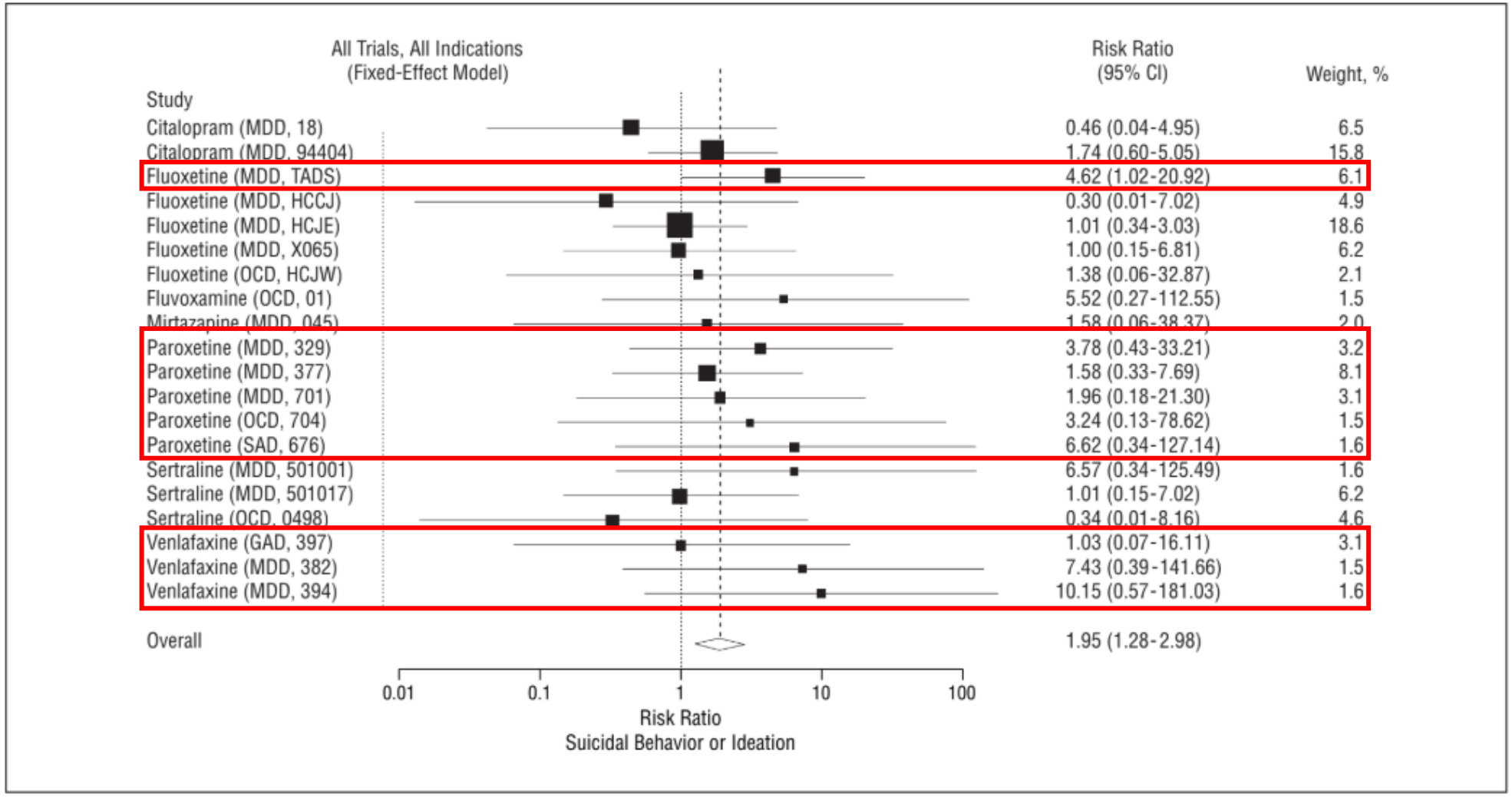



**Figure.** Risk ratios for the 20 evaluable trials of all drugs across all indications. CI indicates confidence interval; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SAD, social anxiety disorder. Percentage weight takes into consideration the sample size and the number of events in each trial. Vertical solid line represents the value 1; vertical dashed line, overall risk ratio.

# Study Designs Limit Generalizability

## Limitations

- Post hoc analysis design with multiple outcomes and subanalyses
- Short-term data (4-16 weeks)
- Sample size of <5000 patients
- Heterogenicity of studies (e.g., some had smaller databases than others)

## Take Aways

- Caution is warranted in the interpretation of these findings
- Implications for clinical practice are unclear
- FDA recommends to monitor patients as a way of managing risk



Hammad TA. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry.* 2006.

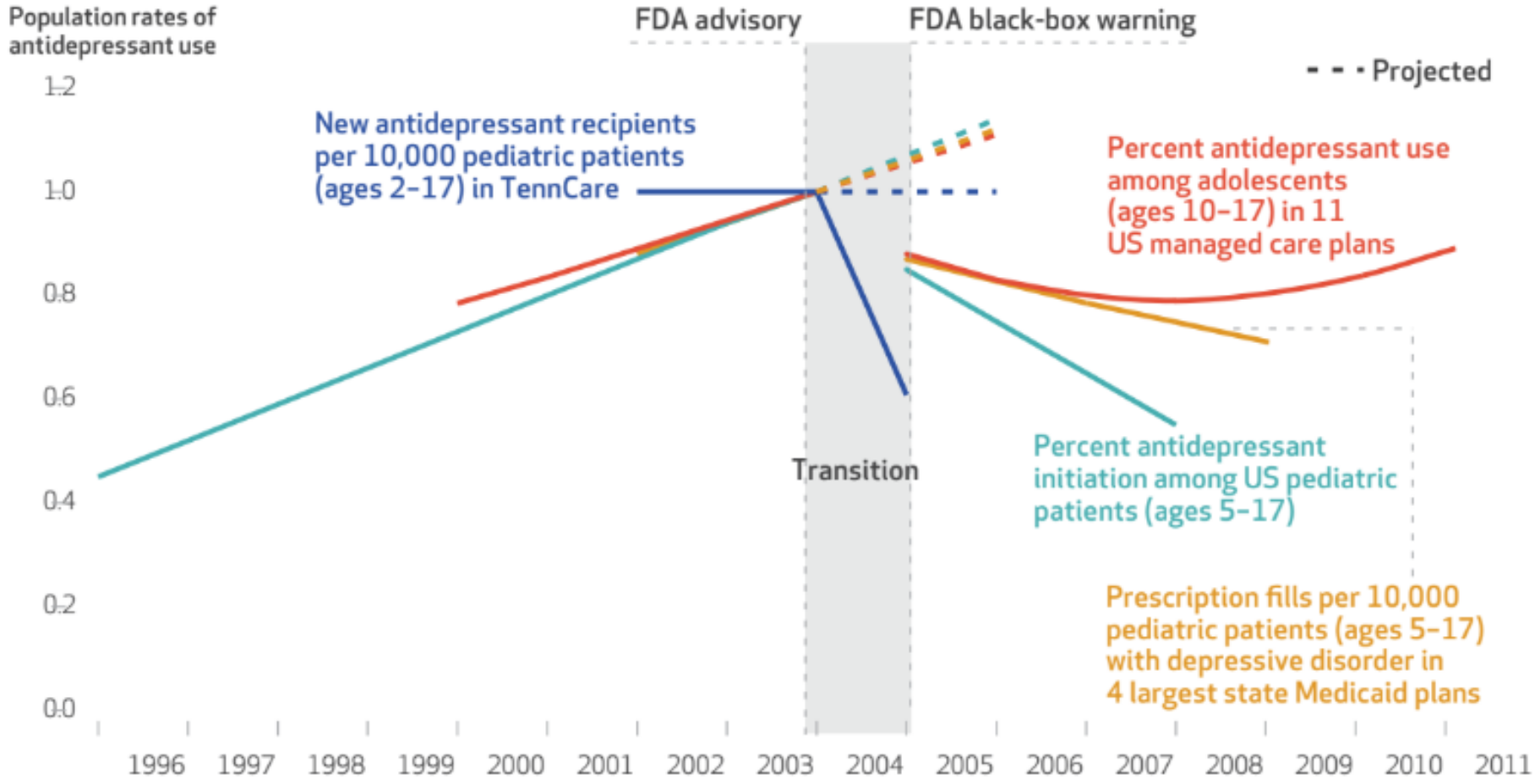
# Long-term Outcomes after FDA BBW

| Study | Design | Results | Conclusion |
|---|---|---|---|
| Soumerai SB. Intended And Unintended Outcomes After FDA Pediatric Antidepressant Warnings: A Systematic Review. *Health Aff (Millwood)*. 2024. | • Systematic review from 2003-2022<br>• 34 quasi-experimental studies measuring changes in outcomes after FDA warning (pre and post)<br><br>Primary Outcome: monitoring for suicidal thoughts and behaviors<br><br>Secondary Outcomes:<br>• AD treatment and use<br>• Physician visits for depression<br>• Depression diagnoses<br>• Psychotherapy visits<br>• Psychotropic drug poisonings<br>• Suicide deaths | Baseline Data:<br>• 11/34 studies included<br><br>Outcomes:<br>• Intended physician monitoring failed to increase (1 study)<br>• Significant unintended reductions in mental health care (multiple studies)<br>• Marked increases in psychotropic drug poisonings and suicide deaths | • Findings support reevaluation of risks and benefits of the FDA's BBW |

# AD Treatment and Use Decline

**EXHIBIT 2**

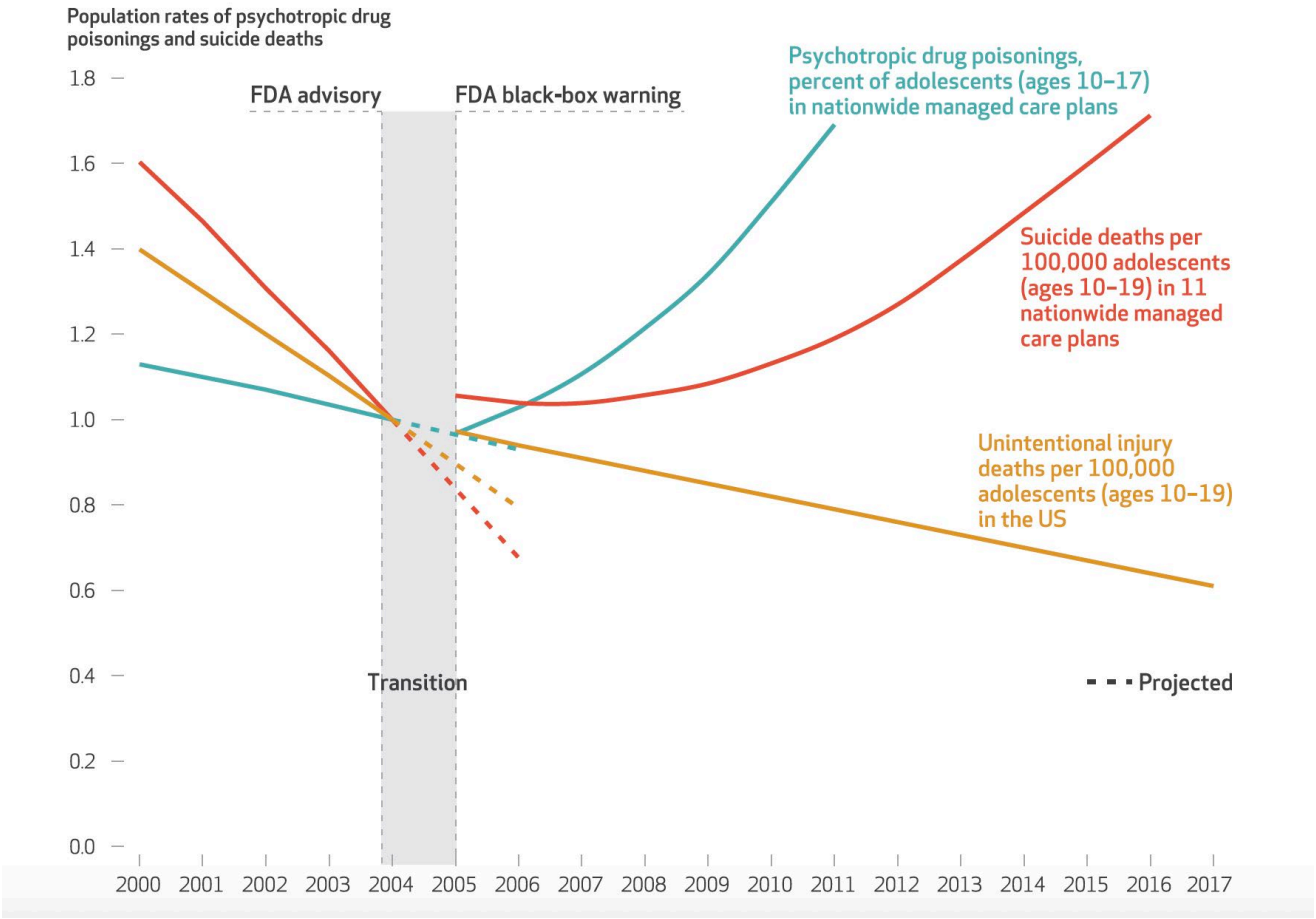
**Declines in population rates of antidepressant treatment and use among pediatric patients after Food and Drug Administration (FDA) pediatric antidepressant warnings, 1996–2011**



# Suicidal Behavior and Deaths

**EXHIBIT 3**

**Changes in population rates of psychotropic drug poisonings and suicide deaths among pediatric patients after Food and Drug Administration (FDA) pediatric antidepressant warnings, 2000–17**






Soumerai SB. Intended And Unintended Outcomes After FDA Pediatric Antidepressant Warnings: A Systematic Review. *Health Aff (Millwood)*. 2024.

# Unintended Consequences

**EXHIBIT 4**

**Summary of outcomes reported in a systematic review of studies on Food and Drug Administration (FDA) black-box warnings on youth antidepressant medications, 2007–17**

| Outcomes | No. of studies examining outcome | Distinct outcomes examined within included studies | | |
|---|---|---|---|---|
| | | No. of intended/ desirable outcomes[a] | No. of unintended/ adverse outcomes[b] | No. of neutral outcomes[c] |
| Monitoring for suicidal thoughts and behaviors | 1 | 0 | 2 | 0 |
| Physician visits for depression | 1 | 0 | 2 | 0 |
| Depression diagnoses | 3 | 0 | 6 | 0 |
| Psychotherapy visits | 1 | 0 | 1 | 0 |
| Antidepressant treatment and use | 6 | 0 | 16 | 5 |
| Psychotropic drug poisonings and suicide deaths | 3 | 0 | 8 | 3 |

**SOURCE** Authors' systematic review of studies ($N = 11$) published in the peer-reviewed literature between 2007 and 2020 (notes 7, 8, 11, and 28–35 in text). **NOTES** Some studies examined more than one outcome; therefore, the total number of studies listed in column 1 is greater than 11. Psychotropic drug poisonings were used as a proxy measure for suicide attempts, based on Lu CY, et al. (see note 7

# Monitoring for Suicidality, Doctor Visits for Depression, and Depression Diagnoses

| Study | Effect | Unintended Adverse Effect |
|---|---|---|
| Morrato et al., 2008. | • **No increase in monitoring** among pediatric patients (N=27,370) based on FDA and HEDIS guidelines. | X |
| Carson et al., 2017. | • **33% reduction in doctor visits** for depression among pediatric Medicaid patients (N=10,919,491). | X |
| Libby et al., 2009. | • **Decrease in rates of MDD diagnoses** in US health plans among pediatric and young adult patients (~45% and 20%; N=643,313).<br>• Most of the decline occurred with PCPs and pediatricians. | X |
| Clarke et al., 2012. | • **16% reduction in rates of adolescent depression** diagnoses (N=57,782). | X |
| Valuck et al., 2007. | • **28% reduction in annual rate of depression** diagnoses among comparison group of US adult plan enrollees (spillover effects; N=400,111). | X |



STB = suicidal thoughts and behaviors; HEDIS = Healthcare Effectiveness and Information Set; PCP = primary care provider

Soumerai SB. Intended And Unintended Outcomes After FDA Pediatric Antidepressant Warnings: A Systematic Review. *Health Aff (Millwood)*. 2024.

# Antidepressant Use

| Study | Effect | Unintended Adverse Effect |
|---|---|---|
| Kurian et al., 2007. | • **~35% reductions in incident use of all ADs** among TN Medicaid youth (N=405,000).<br>• Greater reduction in new vs continuing AD use. | X |
| Clarke et al., 2012. | • ~30% reduction in the percentage of adolescents receiving an AD within 30 days of a new depression diagnosis (N=57,782).<br>• **>50% reduction in total and refill prescriptions per 1000 adolescents.**<br>• >50% decrease in new AD prescriptions with 1 or more refills and increased use of refill limit policy (PA required). | X |
| Lu et al., 2014. | • Reduction in AD use from expected trend among adolescents in US health plan network (N=1.1 million); **31% reduction at 2 years**. | X |
| Carson et al., 2017. | • **~33% reduction in rate of AD prescription fills per 10,000** pediatric Medicaid patients (N=10,919,491) | X |



AD = antidepressant; PA = prior authorization

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# Antidepressant Use Continued

| Study | Effect | Unintended Adverse Effect |
|---|---|---|
| Libby et al., 2007. | • 33% decrease in percentage of adolescents obtaining an AD within 30 days of diagnosis (N=65,349).<br>• **Most of the reduction in AD treatment occurred among patients treated by pediatricians and PCPs**; a comparison group of specialists were less affected. | X |
| Parkinson et al., 2012. | • **~40% decline in AD initiation among youth in the US Medical Expenditure Panel Survey (N=28,782).**<br>• ~19% decline in AD initiation among comparison adult group. | X |



PCP = primary care provider

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# Suicidal Behavior and Deaths

| Study | Effect | Unintended Adverse Effect |
|---|---|---|
| Lu et al., 2014. | • Increase from expected trend in rate of psychotropic drug poisonings among adolescents in US health plan network (N=1.1 million); **21.7% increase at 2 years**.<br>• Increase from expected trend in rate of all drug poisonings.<br>• Similar increase from expected trend in rate of psychotropic drug poisonings among young adults (spillover effects). | X |
| Bridge et al., 2008. | • **Short-term (2004-2005) increase in national (CDC) suicide rates** among adolescents (N=represents total US population). | X |
| Lu et al., 2020. | • **Abrupt reversal in trend of US adolescent suicide rates** after the warnings, from a declining pre-warning trend (N=43 million per year).<br>• Similar abrupt reversal trend of US young adult suicide rates after the warnings (spillover effects).<br>• Trends pre- vs post-warning rates of suicide deaths did not change among a comparison group of middle-ages US adults. | X |



Soumerai SB. Intended And Unintended Outcomes After FDA Pediatric Antidepressant Warnings: A Systematic Review. *Health Aff (Millwood)*. 2024.

# Summary

## Take Aways

- FDA pediatric antidepressant warnings have not had the intended outcome of increased monitoring for suicidal thoughts and behaviors
- FDA warnings were associated with unintended outcomes
- Primary care physicians, including pediatricians, were more likely than specialists to reduce antidepressant treatment and depression diagnoses after the FDA warnings

## Next Steps

- FDA officials should review the totality of evidence and revaluate the FDA warnings



Soumerai SB. Intended And Unintended Outcomes After FDA Pediatric Antidepressant Warnings: A Systematic Review. *Health Aff (Millwood)*. 2024.

# Myths Heard in Clinical Practice

- *After starting an antidepressant in a pediatric patient, their energy level normalizes but their mood remains depressed; therefore, they are at increased risk for suicide.*
- *A pediatric patient is admitted to an inpatient psychiatric unit status post suicide attempt via intentional ingestion (patient is medically cleared), the team should not start an SSRI given patients acute SI.*
- *The timeline for suicidality risk and ADs is clearly defined and occurs only in the first 4 months.*

# Discussion

# Questions

1. What are unintended effects of the antidepressant black box warning that you frequently see in clinical practice?
2. What are common myths pertaining to the antidepressant black box warning that families/patients believe?
3. In your clinical practice, what are common barriers to antidepressant prescribing that you see as it pertains to the antidepressant black box warning?
4. What do you envision as important next steps the FDA should pursue regarding the black box warning, if any?

# Questions?

Thank you for attending!

# References


1. Briesacher BA, Soumerai SB, Zhang F, et al. A critical review of methods to evaluate the impact of FDA regulatory actions. *Pharmacoepidemiol Drug Saf*. 2013 Sep;22(9):986-94.
2. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006 Mar;63(3):332-9.
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6. Soumerai SB, Koppel R, Naci H, et al. Intended And Unintended Outcomes After FDA Pediatric Antidepressant Warnings: A Systematic Review. *Health Aff (Millwood*). 2024 Oct;43(10):1360-1369.