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REVIEW ARTICLE

# Intended And Unintended Outcomes After FDA Pediatric Antidepressant Warnings: A Systematic Review

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**ABSTRACT** **Since 2003, the Food and Drug Administration (FDA) has warned that antidepressants may be associated with suicidal thoughts and behaviors among youth. An FDA advisory in 2003 and a black-box warning in 2005 focused on children and adolescents younger than age eighteen. The FDA expanded the black-box warning in 2007 to include young adults. Both warnings were intended to increase physician monitoring of suicidal thoughts and behaviors. Our systematic review identified thirty-four studies of depression and suicide-related outcomes after these warnings; eleven of these studies met research design criteria established to reduce biases. The eleven studies examined monitoring for suicidal thoughts and behaviors, physician visits for depression, depression diagnoses, psychotherapy visits, antidepressant treatment and use, and psychotropic drug poisonings (a proxy for suicide attempts) and suicide deaths. We assessed possible spillover to adults not targeted by the warnings. The one study that measured intended physician monitoring of suicidal thoughts and behaviors did not find evidence of an increase. Multiple studies found significant unintended reductions in mental health care after the warnings. After these reductions, there were marked increases in psychotropic drug poisonings and suicide deaths. These findings support reevaluation of risks and benefits of the FDA's black-box antidepressant warnings.**

Depression is the leading cause of suicide,[1] and suicide is the second-leading cause of death among youth and young adults ages 10–24.[2] Evidence consistently demonstrates that access to mental health care, including psychotherapy and antidepressant medications, can improve outcomes among youth with depression.[3,4]

The Food and Drug Administration (FDA) is responsible for identifying and communicating possible drug risks to prescribers, patients, and the public. Risk communications are challenging because they can have both intended and unintended consequences. For example, FDA warnings contributed to intended reductions in aspirin use in children, which is a cause of Reye's syndrome.[5] In contrast, an FDA-commissioned 2013 systematic review found that a third of FDA warnings on medications had unintended consequences, including spillover to patients not targeted by the warnings, prescrib-

ing of substitute drugs, reductions in detection and treatment of disease, and adverse health outcomes.[6]

In October 2003, an FDA advisory warned that antidepressants may be associated with suicidality (a term that refers to suicidal thoughts and behaviors) among those younger than age eighteen soon after the initiation of treatment.[7] In January 2005, the FDA required a permanent black-box warning of this risk on product labels and in television and print advertising for all antidepressant drugs. In May 2007, the FDA expanded the 2005 black-box warning to include young adults through age twenty-four;[8] this broader warning remains in effect today. We refer to these three actions collectively as "the FDA warnings."

Although the FDA warnings were intended to increase monitoring of suicidal thoughts and behaviors at the start of antidepressant drug treatment, the warnings may have the unintended effect of frightening both physicians and youth.[9] A study published in 2016 found that two-thirds of youth with major depressive episodes did not seek any depression care, and the FDA warnings have the potential to reduce care seeking among this group.[10] In addition, such warnings may result in fewer diagnoses and less-appropriate treatment of youth depression by clinicians, especially pediatricians and other primary care providers,[11,12] who, at the time of the warnings, were the most frequent prescribers of antidepressants.[13] The FDA recognized that the warnings could have the unintended effect of reducing the prescribing and use of antidepressants, thus possibly increasing depression and suicidality. According to a member of the FDA committee approving the black-box warning: "The black box warning is not meant to discourage the prescription of antidepressants. In fact, the warning refers to the hazard of untreated depression."[14]

Nevertheless, the terminology used in the warnings, such as "suicidality," could lead to the misperception that these drugs cause suicides.[9,15] The black-box warning, which suggests a link between youth antidepressant use and suicidal thoughts and behaviors, is the same today as it was in 2005, and it appears widely on product labels and in television and print ads, patient drug information, and internet resources. Because these warning messages are ongoing, they may continue to affect patient and physician behaviors.

To evaluate the totality of credible evidence on the relationship between FDA antidepressant warnings and changes in specified care and outcomes among youth, we conducted the only comprehensive systematic review of the most rigorous quasi-experimental studies ever published on the topic, to our knowledge.[16,17] Our study went beyond previous research to focus not only on studies investigating changes in antidepressant treatment and use among youth (the most studied outcome) but also on evidence regarding other outcomes after the warnings. These included the outcome targeted by the FDA—monitoring for youth suicidality—as well as several other potential outcomes: changes in physician visits for depression, depression diagnoses, psychotherapy visits, antidepressant treatment and use, and psychotropic drug poisonings (a proxy for suicide attempts) and suicide deaths.

## Study Data And Methods

Our systematic review is reported in accordance with the 2020 PRISMA statement[18] (see PRISMA table in online appendix 7),[19] and our protocol was registered with PROSPERO on December 17, 2021 (Registration No. CRD42021261192).

**INFORMATION SOURCES AND SEARCH STRATEGY** We searched the Medline Ovid, Embase Ovid, and PsycINFO Ovid databases using keywords, subject headings, and search operators for the concepts of FDA, boxed warnings, and antidepressants. The search covered the period between January 1, 2003, and October 31, 2022. We excluded animal studies, commentaries, editorials, and letters. Search results were exported to EndNote and deduplicated.

**ELIGIBILITY CRITERIA** We identified thirty-four original investigations published in the peer-reviewed literature on changes in specified youth outcomes associated with the FDA's antidepressant warnings, as well as potential spillover among two subpopulations not targeted by the warnings before the black-box warning was expanded in 2007: young adults (ages 18–24) and adults older than age 24.

Because it was not possible to randomize exposure to antidepressant warnings, the most rigorous studies available for inclusion in the review were those with quasi-experimental study designs. We judged the strength of study designs according to Cochrane systematic review and quasi-experimental design criteria.[16,17,20] To focus on studies with the strongest possible quasi-experimental research designs, we limited the review to interrupted time series with more than five data points both before and after the antidepressant warnings and a minimum of fifty patient observations per time point, with or without control groups. We included only interrupted time series studies that controlled for baseline trends and numerous threats to internal validity, such as other changes in trends of study outcomes before the warnings (for example,

physician visits for depression); changes in the study populations around the time of the warnings, such as age or illness progression that could confound study outcomes; and selection bias. All included studies estimated pre-post changes in the levels or trends of study outcomes immediately after the warnings. Intermediate-quality studies met our criteria for inclusion if they had more than five pre-warning measurement points and two to five post-warning points, and they controlled for baseline trends.[21] We excluded studies that provided weak evidence, such as those with uncontrolled pre-post designs, studies including fewer than six pre-warning data points, and studies with post-only designs that could not measure pre-post change.[17,22] Eleven of the thirty-four studies met the above criteria for inclusion in this systematic review.

**SCREENING AND SELECTION PROCESS** One investigator screened article titles and abstracts. For quality control, two sets of 100 titles and abstracts were randomly selected and screened blindly by one other investigator each. During screening, any published studies investigating the warnings' effects on care processes, such as mental health care, or on outcomes, such as suicidal behavior, were obtained for full-text review. Conflicting determinations were resolved by discussion. Two investigators then reviewed potentially relevant full-text articles according to the eligibility criteria described above.

**DATA EXTRACTION** We extracted all figures from the included studies, as well as data on study populations, sample sizes, comparison groups (if reported), measures, validity of measures, results by outcome, immediate-level and slope changes in study outcomes after the warnings (95% confidence intervals or $p$ values), differences between predicted versus expected (counterfactual) values up to three years after the warnings, comparison outcomes (if reported), and conclusions. We used Cochrane's risk-of-bias tool for interrupted time series studies[20] to identify possible biases in the reviewed studies, such as a possible confounding cointervention. We investigated potential biases to determine their implications and how to address them in our analysis. Details on our assessment of possible biases are in appendix 8.[19] All data from eligible studies were extracted by one investigator and carefully reviewed by a second investigator. Any discrepancies were discussed and resolved.

**ANALYSIS** We collected data from the included studies on changes in reported trends after the FDA antidepressant warnings with respect to the single intended outcome of the policy: prescriber monitoring of suicidal thoughts and behaviors among youth after initiating antidepressant treatment.[14] We also examined potential unintended outcomes, including reductions in physician visits for depression, depression diagnoses, psychotherapy visits, and antidepressant treatment and use, as well as increases in psychotropic drug poisonings and suicide deaths. We analyzed trends in unintentional injury deaths per 100,000 adolescents before and after the FDA antidepressant warnings as a comparison outcome for suicide deaths because unintentional injury deaths are unrelated to the stated goal of the FDA warnings. We summarized each study's analyses of individual outcomes and categorized the reported outcomes as intended/desirable, unintended/adverse, and neutral. We considered adult subpopulations ages 18–24 and older than age 24 to be comparison groups because they were not targeted by the FDA warnings (2003, 2005). However, we collected outcome data on young adults (ages 18–24) and adults older than age 24, where available, to identify potential spillover to adult subpopulations.

**Our findings suggest a reduction in access to care among pediatric patients and fewer opportunities for suicide prevention.**

Our summaries included outcome data by age, race and ethnicity, and provider type if these data were reported in the studies. We excluded specific outcomes if they were likely to be biased because of failure to account for large baseline differences in subgroup effects or floor effects when outcomes were so close to zero on the $y$-axis that further reductions in a study outcome (such as use of antidepressants) were difficult to measure. In each case, we cited the excluded outcome measure and explained why it could have biased the results if it had been retained (see appendixes 4 and 5).[19]

Using extracted trend lines from the original studies, we modified some of the figures published with these studies to align the pre-post periods consistently across studies and reflect the implementation dates of the FDA advisory and black-box warning. Similarly, we modified axis minimum and maximum values, as needed,

**The overwhelming evidence suggests that the ongoing use of these warnings may result in more harms than benefits.**

to improve visualization of trends if study group trends were too close to the floor of a graph.

The included studies were based on data from state Medicaid programs; death certificates for all US counties, captured in the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (WONDER) database; nationwide managed care plan data sets; and nationally representative surveys.

**LIMITATIONS** This review had several limitations. Although interrupted time series analysis is one of the strongest quasi-experimental designs to control for co-occurring interventions,[16,17] the strength of the relationship between the FDA's actions and reported outcomes in the reviewed studies varied according to the size and abruptness of changes in outcomes and possible co-interventions. The most important potential threat to the validity of this review and the reviewed studies was the possibility that events or forces other than the warnings contributed to increases in psychotropic drug poisonings and suicide deaths. Possible co-occurring events that might have confounded the outcomes of the warnings include increased social media use, the opioid epidemic, and the 2008 recession. We carefully considered each of these events and concluded that they were not likely to have been confounders, for several reasons. First, although the use of social media among youth[7,8] may be associated with anxiety and depression,[23] longitudinal data on the use of early social media platforms, such as Facebook, WhatsApp, and WeChat, suggest that it was minimal at the time of the FDA warnings.[24] Use of social media increased substantially about five to twelve years after the start of the 2003 FDA advisory, thus making it implausible as a rival explanation. Second, although opioid use might be associated with some suicides, the longitudinal data on opioid-related deaths suggest that their trends were opposite to that of suicide death.[25] When nationwide opioid deaths were increasing before the warnings, suicides were decreasing substantially. When opioid deaths flattened and then decreased after the warnings, suicide deaths increased. Thus, the opioid epidemic was unlikely to have confounded the association between the FDA warnings and increases in suicide deaths. Moreover, accidental injury deaths among adolescents, including those caused by drugs of abuse, declined after the warnings. Third, although thf008 recession has been associated with a small increase in middle-age adult suicide rates, meta-analyses[26] have concluded that the recession was unlikely to have affected suicides in any other age group.

Our review identified only one study examining the FDA-intended effect on prescriber monitoring for suicidal thoughts and behaviors; the scarcity of published research on this outcome means that caution must accompany conclusions about such monitoring.

Finally, our review identified only one study examining changes in psychotropic drug poisonings after the FDA antidepressant warnings.[7] The dearth of studies on this topic reflects the fact that diagnostic coding for suicide attempts is unreliable.[27] Psychotropic drug poisonings account for a small subset of suicide attempts, and not all poisonings are with self-harm intent. Nevertheless, the sharp increases in psychotropic drug poisonings immediately after the warnings among adolescents and young adults, together with other studies included in this review that found increases in suicide deaths, suggest a possible association between the warnings and suicidal behavior.

## Study Results

Our database searches identified 1,841 studies that included any discussion of the FDA antidepressant warnings. Of thirty-four studies examining the warnings' outcomes, eleven met research design criteria and were included in the systematic review (see PRISMA table in appendix 7).[19]

**OVERVIEW OF INCLUDED STUDIES** All eleven included studies measured changes in outcomes after the October 2003 FDA advisory or January 2005 black-box warnings. Six of these eleven studies used comparison outcomes or groups when they analyzed changes in outcomes after the FDA warnings. These included changes in unintentional injury deaths versus suicide deaths and changes in outcomes among children or adolescents versus in adults not targeted by the warnings (spillover outcomes). Appendix 1 summarizes outcomes of the pediatric warnings in all eleven included studies and provides full

citations for each of the studies.[19] Exhibits 1–3, based on results from very large studies (with sample sizes greater than 100,000), focus on changes in outcomes among pediatric patients (the group targeted by the FDA warnings); these findings represent the strongest evidence of their impact. We also present results suggesting spillover among adults. No studies observed the direct effects of the 2007 expansion of the pediatric black-box warnings to young adults.

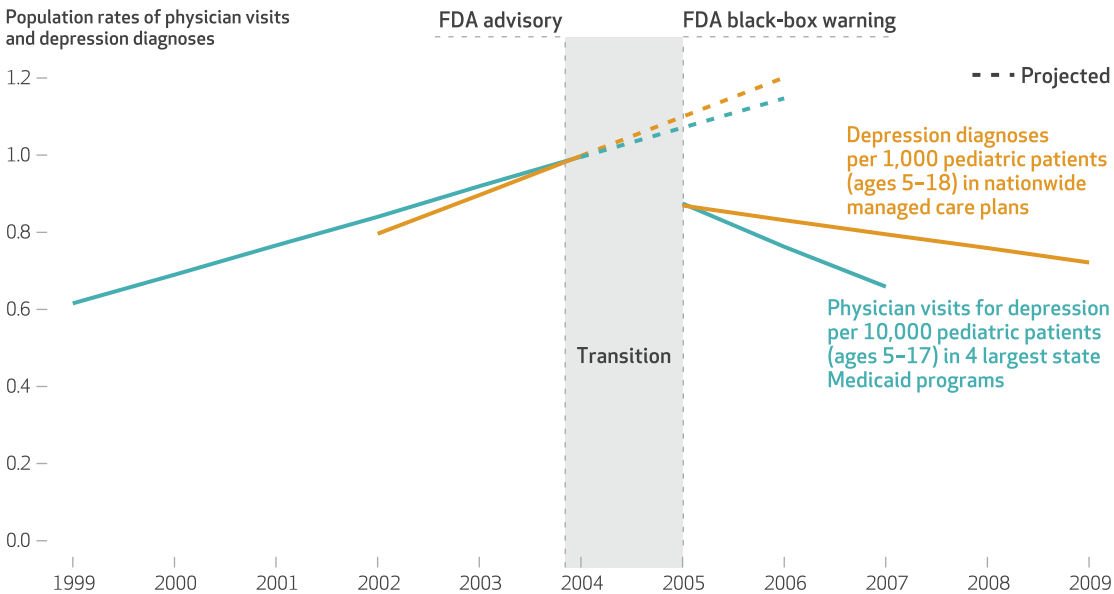
**MAJOR FINDINGS FOR PEDIATRIC PATIENTS TARGETED BY THE WARNINGS** After the FDA warnings, multiple studies reported substantial reductions in physician visits for depression and depression diagnoses (exhibit 1), reductions in antidepressant treatment and use (exhibit 2), and increases in psychotropic drug poisonings and suicide deaths (exhibit 3) among pediatric patients. These results provide evidence of substantial, immediate changes in unintended outcomes after the FDA warnings across different pediatric subpopulations and data sources. The findings show increasing rates of depression diagnosis and treatment and declines in rates of psychotropic drug poisonings and suicide deaths before the FDA warnings. The increased rates of adolescent suicide attempts and deaths after the warnings contrast with reductions in rates of unintentional injury deaths among adolescents during the study period, a comparison outcome (exhibit 3).[16]

**DETAILED RESULTS BY OUTCOME IN TARGETED AND NONTARGETED POPULATIONS** In the following section, we provide detailed descriptions of reported results by outcome category for pediatric populations (who were targeted by the FDA warnings) and adult populations (who were not targeted by the warnings). Overall, there were no reported findings indicating intended/desirable outcomes, thirty-five reported findings indicating unintended/adverse outcomes, and eight reported findings indicating neutral outcomes (exhibit 4).

▶ **MONITORING FOR SUICIDAL THOUGHTS AND BEHAVIORS:** One study, based on medical records for 27,370 pediatric patients, examined whether clinician monitoring for suicidal thoughts and behaviors when starting antidepressant treatment increased after the FDA warnings[28] (appendix 1).[19] The authors con-

**EXHIBIT 1**

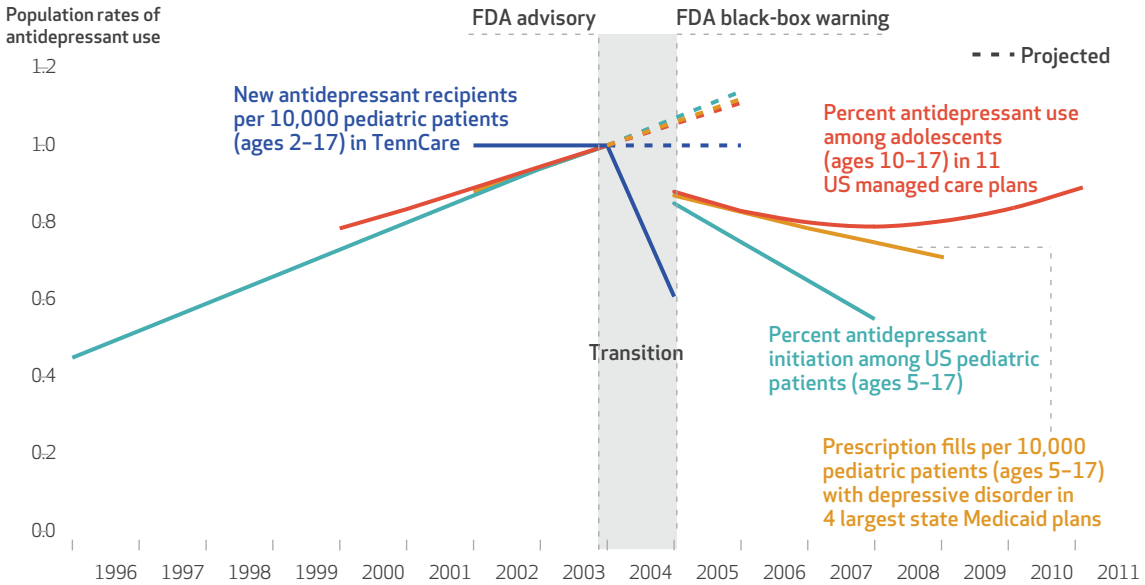
**Reductions in population rates of pediatric visits for depression and depression diagnoses after Food and Drug Administration (FDA) pediatric antidepressant warnings, 1999–2009**




**SOURCES** For physician visits for depression per 10,000 pediatric patients (ages 5–17) in the 4 largest state Medicaid programs ($N = 10.9$ million), Carson N, et al. (see note 29 in text). For depression diagnoses per 1,000 pediatric patients (ages 5–18) in nationwide managed care plans ($N = 792,807$), Libby AM, et al. (see note 11 in text). **NOTES** The projected lines after the warnings reflect the projection of baseline trends before the FDA advisory and black-box warning. The gray-shaded transition period is defined as the time between the 2003 FDA advisory and the 2005 FDA black-box warning (October 2003–January 2005). Managed care plan data are from more than 95 US managed care plans representing more than 55 million covered patients nationwide (January 1999–December 2007). Based on permissions received from publishers of the cited articles, the exhibit reflects modifications to figures published with the original sources to align pre-post periods consistently across studies and reflect the implementation dates of the FDA advisory and black-box warning. In addition, trend lines are standardized to the same unit (1.0) at the date of the 2003 advisory to depict multiple time series in a single exhibit.

**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**




**SOURCES** For new antidepressant recipients per 10,000 pediatric patients (ages 2–17) in TennCare (Tennessee's Medicaid; $N = 405{,}000$), Kurian BT, et al. (see note 32 in text). For percent antidepressant use among adolescents (ages 10–17) in 11 US managed care plans ($N = 1.1$ million), Lu CY, et al. (see note 7 in text). For percent antidepressant initiation among US pediatric patients (ages 5–17) ($N = 110{,}000$), Parkinson K, et al. (see note 33 in text). For prescription fills per 10,000 pediatric patients (ages 5–17) with depressive disorder in the 4 largest state Medicaid plans ($N = 10.9$ million), Carson N, et al. (see note 29 in text). **NOTES** The projected lines after the warnings reflect the projection of baseline trends before the FDA advisory and black-box warning. The gray-shaded transition period is defined in the exhibit 1 notes. Based on permissions received from publishers of the cited articles, the exhibit reflects modifications to figures published with the original sources to align pre-post periods consistently across studies and reflect implementation dates of the FDA advisory and black-box warning. In addition, trend lines are standardized to the same unit (1.0) at the date of the 2003 advisory to depict multiple time series in a single exhibit.

ducted an interrupted time series analysis with comparison series that included forty-seven monthly points before and twenty-five observations after the advisory. The two monitoring measures included the FDA's recommended contact schedule of seven visits in the three months after treatment initiation and the less-stringent Healthcare Effectiveness Data and Information Set (HEDIS) measure specifying three contacts in these three months.[28]

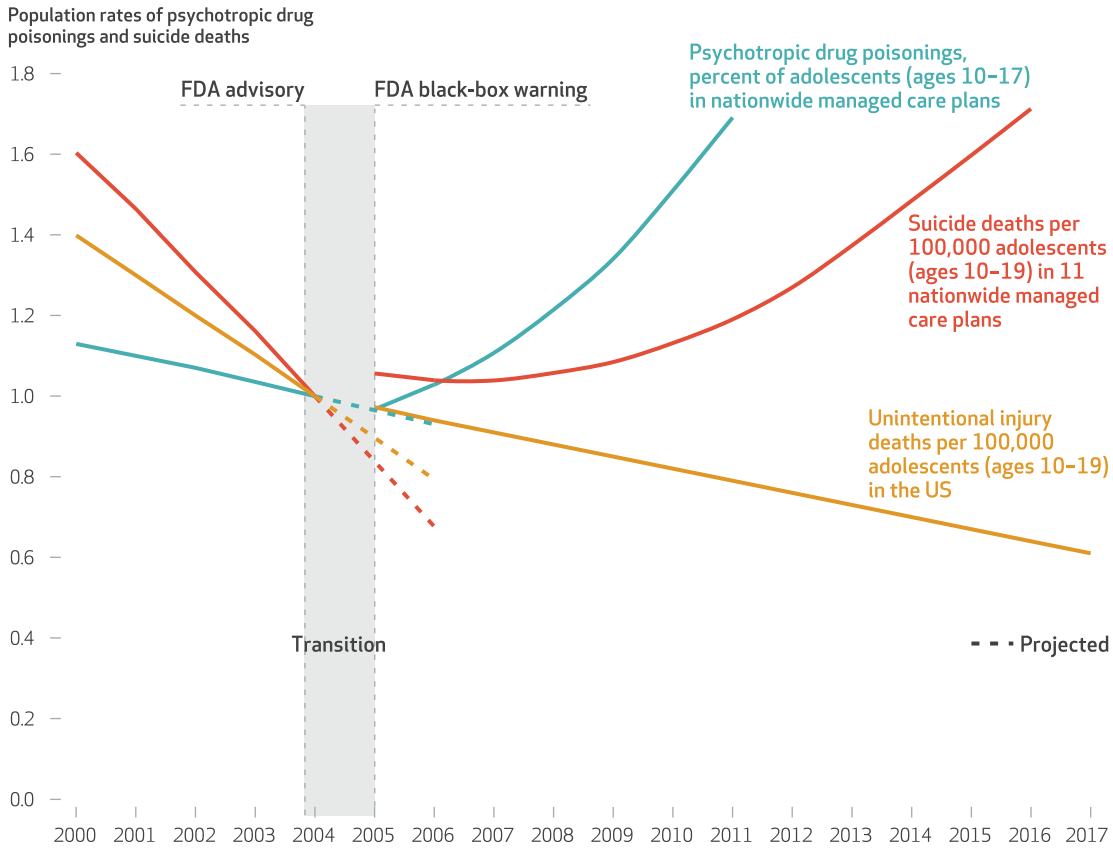
Contrary to the intent of the warnings, fewer than 5 percent of pediatric patients were monitored in accordance with the FDA's recommended contact schedule recommendations after the advisory; this low rate was unchanged from the rate before the warnings. Likewise, there was no increase in monitoring for suicidal thoughts and behaviors in pediatric patients, as defined in the HEDIS monitoring criteria. There was no increase in monitoring in a comparison group of adults who were not targeted by the warnings.

▶ **PHYSICIAN VISITS FOR DEPRESSION, DEPRESSION DIAGNOSES, PSYCHOTHERAPY VISITS:** Four well-designed studies[11,29–31] including a total of more than twelve million patients found consistent evidence of sudden and substantial long-term declines in physician visits for depression and depression diagnoses after the FDA warnings (appendixes 1 and 2, exhibits 2A–2C).[19] These studies showed increases in physician visits for depression and depression diagnoses in the years before the warnings and abrupt, sustained declines, ranging from 20 percent to 45 percent, in visits and diagnoses after the warnings. Some spillover occurred in comparison groups of adults, who were not targeted by the FDA warnings.[11] One national study indicated that reduced diagnosis rates were concentrated among patients treated by pediatricians and other primary care physicians.[11] Of the studies examining psychotherapy visits after the warnings, none found increases. One study found that depression visits decreased among White, Black, and Latino youth after the FDA warnings[29] (appendix 2, exhibit 2.A).[19]

▶ **ANTIDEPRESSANT TREATMENT AND USE:** Seven studies showed evidence that the FDA warnings were followed by abrupt reductions in antidepressant treatment and use, ranging

**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**




**SOURCES** For psychotropic drug poisonings, percent of adolescents (ages 10–17) in nationwide managed care plans ($N = 1.1$ million), Lu CY, et al. (see note 7 in text). For suicide deaths and unintentional injury deaths per 100,000 adolescents (ages 10–19) in 11 nationwide managed care plans and in the US, respectively ($N = 43$ million), Lu CY, et al. (see note 8 in text). **NOTES** The projected lines after the warnings reflect the projection of baseline trends before the FDA advisory and black-box warning. The gray-shaded transition period is defined in the exhibit 1 notes. Psychotropic drug poisonings were used as a proxy measure for suicide attempts. Unintentional injury deaths were used as a comparison outcome because they are unrelated to the stated goal of the FDA warnings. Based on the permissions received from publishers of the cited articles, the exhibit reflects modifications to figures published with the original sources to align pre-post periods consistently across studies and reflect implementation dates of the FDA advisory and black-box warning. In addition, trend lines are standardized to the same unit (1.0) at the date of the 2003 advisory to depict multiple time series in a single exhibit.

from 20 percent to 50 percent.[7,11,29,30,32–34] Most studies showed increasing use of antidepressants in the years before the FDA advisory, followed by abrupt and sustained reductions in use after the warnings. The warnings were associated with declines in rates of overall antidepressant use and treatment of newly diagnosed patients in managed care plans,[11,27,30,31,34] large state Medicaid programs,[29,32] and nationally representative surveys (appendixes 1 and 2, exhibits 3.A–3.K).[19] Relative to the reported declines in antidepressant prescribing and use in the pediatric population, declines were smaller among adults not targeted by the warnings. Several studies showed larger reductions in antidepressant prescribing by generalists, including pediatricians, internists, and family practitioners, than by specialists.[11,34] One study found that after a health maintenance organization attempted to increase monitoring of suicidality after the FDA advisory by requiring preauthorization of antidepressant refills, the proportion of new prescriptions that had any refills declined by about half, and the duration of use declined substantially, contrary to national guidelines.[30]

Two studies suggested modest substitution of an approved antidepressant for youth, fluoxetine, for other selective serotonin reuptake inhibitors (SSRIs) after the FDA warnings; however, this did not offset the overall decline in antidepressant treatment and use.[29,33]

▶ **PSYCHOTROPIC DRUG POISONINGS AND SUICIDE DEATHS:** Three studies found evidence of declining or flat pre-warning trends in psycho-

**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 in text). [a]Increased monitoring for suicidal thoughts and behaviors at the start of antidepressant treatment and reduced suicidal behavior and deaths. [b]Reductions in physician visits for depression, reduced depression diagnoses, reductions in psychotherapy visits, reduced antidepressant treatment and use, and increased psychotropic drug poisonings and suicide deaths. [c]Effects or null effects unrelated to youth suicide risk, such as unchanged physician visits for depression or antidepressant use; no changes in medication supply per prescription; substitution of one approved antidepressant for another agent; and no changes in suicidal behavior or suicide deaths.

tropic drug poisonings (a proxy for suicide attempts) and suicide deaths, followed by abrupt increases in post-warning trends for these outcomes among adolescents who were targeted by the FDA advisory and black-box warning[7,8,35] (appendixes 1 and 2, exhibits 4.A–4.F).[19] No studies found intended/desirable decreases in psychotropic drug poisonings or suicide deaths. On the basis of forty-four quarterly time points from ten years of data in eleven US health plans,[7] a rigorous study demonstrated a 21.7 percent abrupt increase in psychotropic drug poisonings by the second year after the 2005 black-box warning among 1.1 million adolescents and a 33.7 percent spillover increase in the same outcome among 1.4 million young adults who were included in the expanded black-box warning in 2007.[7] Nonsignificant increases in psychotropic drug poisonings among a comparison group of adults not targeted by the warnings were one neutral outcome identified by our review.

A more recent study by Christine Lu and colleagues[8] investigated adolescent and young adult suicide deaths in the US, using data validated by the Centers for Disease Control and Prevention (CDC) over the course of twenty-eight years before and after the 2005 black-box warning.[7] These data suggest that increases in adolescent and young adult suicides exceeded expected trends by nearly 2,500 cases in the three years after the black-box warning among cohorts that averaged forty-three million adolescents and twenty-one million young adults per year. Consistent with results of other studies, pre-warning suicide rates began declining after 1990, soon after SSRIs became available. That trend reversed in 2004: The downward trend immediately flattened and then followed a curvilinear upward trend among adolescents and young adults after the 2005 FDA black-box warning. In contrast to the increased suicide rates described above,[8] there were no simultaneous increases in a comparison outcome (accidental injury deaths among US youth).

A study published in 2008, based on data from the period 1996–2005 using the same CDC suicide data with two years of follow-up, suggested that there were significant increases in adolescent suicides among both males and females and both younger and older teens (ages 10–17 and 18–19), beginning in 2004.[35]

## Discussion

The eleven studies in our systematic review show that the FDA pediatric antidepressant advisory in 2003 and black-box warning in 2005 were associated with unintended outcomes: reduced physician visits for depression, depression diagnoses, psychotherapy visits, and antidepressant treatment and use and increased psychotropic drug poisonings (a proxy for suicide attempts) and suicide deaths. Contrary to the FDA's intent to increase physician monitoring of suicidal

thoughts and behaviors of treated patients, a large longitudinal study suggests that this did not occur.[28] Moreover, a study of eleven million youth in the four largest state Medicaid plans documented that total depression visits declined by almost half in the three years after the black-box warning, which suggests a likely reduction in monitoring of suicidal thoughts and behaviors in youth with depression.[29]

The reduction in physician visits for depression immediately after the warnings may be a stronger intermediate outcome than reduced antidepressant treatment and use in predicting suicidal behavior.[36] Physician visits for depression, depression diagnoses, psychotherapy visits, and antidepressant treatment and use also declined among older populations not targeted by warnings, but to a lesser extent than among youth, who were the target of the warnings.

Primary care physicians, including pediatricians, who frequently provided youth depression treatment after the introduction of SSRIs (which are safer than the earlier tricyclic antidepressants)[37] were more likely than specialists to reduce antidepressant treatment and depression diagnoses after the FDA warnings.[11,34] This trend suggests a reduction in access to care among pediatric patients and fewer opportunities for suicide prevention.

## Conclusion

Rigorous evidence suggests that the FDA's most serious ongoing youth antidepressant warnings have not had the intended outcome of increased monitoring for suicidal thoughts and behaviors. Instead, the warnings were associated with unintended reductions in physician visits for depression, depression diagnoses, antidepressant treatment and use, and psychotherapy visits, as well as increases in psychotropic drug poisonings and increased suicide deaths. It has been more than fifteen years since studies began documenting these outcomes, using the most rigorous quasi-experimental methods.[34] Now, the overwhelming evidence suggests that the ongoing use of these warnings may result in more harms than benefits.

FDA officials should review the totality of evidence and err on the side of caution in acknowledging possible harms of the antidepressant warnings. High-quality studies support reevaluation and possible replacement of the FDA black-box warning with routine warnings in product labeling. Moreover, such warnings should be evaluated rigorously by independent scientists to yield objective evidence on their intended and unintended consequences. ■

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## NOTES


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