HEALTH & MEDICINE

Barriers to Care Remain

The authors maintain that the boxed warning has deterred care.

BY ARIF KHAN, ANSHU ARORA, AISHWARYA PRASAD, AND MICHELE FORNARO

Despite the preceding critique by Stone et al. (2026), we stand by Khan et al. (2026). The fact of the matter is that physicians and statisticians can argue over the findings of the 2004 and 2006 Food and Drug Administration advisory committee meetings (concerning trials that were never intended to evaluate suicidality in the first place). Instead, we need to focus our attention on what the decision to place the boxed warning on antidepressants means for young patients, their families, and their physicians.

We do not advocate the indiscriminate prescribing of antidepressants, but we maintain the boxed warning has in practice created barriers to care, deterring physicians wary of malpractice liability from using their clinical judgment and expertise to provide for their patients and alarming families at the very moment their children need treatment. We know several anecdotes supporting this. In this context, as emphasized by the American Academy of Child and Adolescent Psychiatry,

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a comprehensive, evidence-based approach that integrates psychotherapy with medication when clinically indicated remains the recommended standard for treating depression in children and adolescents.

While establishing a direct causal relationship between the boxed warning and suicide rates in the United States is methodologically difficult, the warning itself functions as the independent variable in this equation. The only way to determine whether it is producing detrimental effects at the population level is to remove the boxed warning, allow prescribing patterns to normalize, and observe whether outcomes change as new data emerge. Until then, we can examine what has occurred over the past two decades following FDA adoption of the boxed warning for pediatric antidepressants and try to draw lessons. We do that below.

THE EUROPEAN ANGLE

Actions taken by the European Union regarding antidepressant use in children and adolescents support our position. On April 25, 2005, the European Medicines Agency concluded that warnings should be incorporated into Section 4 ("Clinical Particulars") of antidepressant drug labels (EMA 2005). For example, Section 4.4 ("Special Warnings and Precautions for Use") of the label for sertraline (the branded drug Zoloft), as published in the United Kingdom's Electronic Medicines Compendium, states that "sertraline should not be used in the treatment of children and adolescents under the age of 18 years.... If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms, especially in early treatment." Comparable language appears in the European labels for fluoxetine (Prozac), citalopram (Celexa), fluvoxamine (Luvox), venlafaxine (Effexor), and mirtazapine (Remeron).

Two features of this approach are worth noting. First, the warning is placed within the standard precautions section rather than in a boxed warning, avoiding unnecessary alarm for patients and families. Second, the language explicitly preserves clinical discretion, allowing physicians to treat them based on individual clinical need without undue regulatory constraint. As Stone et al. note, Eurostat (2025) shows that suicide rates in Europe have either stayed the same or decreased since the introduction of the US boxed warning, a stark contrast to the suicide rates in the United States. Bertuccio et al. (2024), which evaluates a longer timeline of self-inflicted harm in Europe, affirms this. This has occurred without a European boxed warning about youth and suicidality on antidepressant labels.

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As we argued in our initial publication, we support the FDA relocating the perceived risk of suicidal ideation information from the boxed warning to the "Warnings and Precautions" section of the US label, an approach consistent with the framework Europe has adopted.

Available pharmacoepidemiologic data indicate that antidepressants continued to be prescribed to European youth after the EMA warning and, in several countries, prescribing increased. Bachmann et al. (2016) examined antidepressant use among children and adolescents aged 0–19 years in Denmark, Germany, the Netherlands, the United Kingdom, and the United States from 2005–2006 through 2012. In the European cohorts, annual antidepressant-use prevalence increased from 0.7 to 1.1 percent in the UK, from 0.6 to 1.0 percent in Denmark, from 0.5 to 0.6 percent in the Netherlands, and from 0.3 to 0.5 percent in Germany. The authors concluded that, although antidepressant use declined immediately after the regulatory warnings, that decline did not persist and antidepressant use subsequently increased in youth cohorts from all five countries (Bachmann et al. 2016).

More recent European data are consis-

Table 1

Risk Ratio for Suicidal Behavior or Ideation

Pediatric antidepressant trials for patients indicating Major Depressive Disorder (MDD) and patients with all indications.

Drug	Number of Trials	Overall Risk Ratio	95% Confidence Interval
Celexa	2	1.37	0.53 to 3.50
Luvox	1	5.52	0.27 to 112.55
Paxil	5	2.65	1.00 to 7.02
Prozac*	5	1.52	0.75 to 3.09
Zoloft	3	1.48	0.42 to 5.24
Effexor XR	4	4.97	1.09 to 22.72
Remeron	1	1.58	0.06 to 38.37
Serzone	2	No events	n/a
Wellbutrin	2	No events	n/a
Overall (MDD Trials) **	10 trials	1.6	0.82 to 2.97
Overall (all indications)	25 trials	1.95	1.28 to 2.98

* Including TADS trial, which was funded by the NIMH and conducted at Duke University.
**MDD: Major Depressive Disorder; these trials included one trial for Celexa, two trials for Effexor XR, three trials for Paxil, two trials for Prozac, and two trials for Zoloft – almost none of which were remotely statistically significant.

tent with continued antidepressant utilization in young people. A systematic review of European studies covering Austria, Denmark, Finland, France, Italy, Norway, Spain, and Sweden found relative increases in youth antidepressant use during the COVID-19 period ranging from 23 to 52 percent (Fassmer et al. 2026). During overlapping periods, European youth suicide trends were generally stable or declining, although with substantial country-level heterogeneity and important exceptions, including unfavorable trends in the UK (Bertuccio et al. 2024).

NEED FOR THE DATA

In 2005 and 2006, while the original FDA advisory committees were convening to deliberate on the antidepressant boxed warning for young adults, one of us (Khan) requested from Stone access to the data underlying his analysis, so as to conduct an independent review. That request was denied. At one of the Annual Meetings of the American Society of Clinical Psychopharmacology around 2010, Stone presented these data. When approached by Khan and others requesting access to the original data, Stone informed us that the data were obtained by him from unknown pharmaceutical companies and were confidential. Furthermore, he made it clear that they were not available via the federal Freedom of Information Act. Stone has continued to rely on statistical argumentation to justify the boxed warning rather than uphold transparency in the process.

In the venlafaxine extended-release trials (Emslie et al. 2007), the authors noted that the FDA's analysis identified two additional subjects with events classified as suicidal ideation. Stone et al. attributed this discrepancy to differences between the FDA's criteria for identifying suicidal ideation and behavior and the classification system used in the original trials, which did not specify whether events such as hostility involved suicidal intent.

Despite this broadened classification, the FDA's analysis failed to demonstrate statistically significant findings for several individual antidepressants. Table 1 summarizes data from a slide deck Hammad presented to the 2004 FDA advisory committee (FDA 2004). It shows that analysis using the data from trials for the branded drugs Celexa, Luvox, Paxil, Prozac, Remeron, and Zoloft, estimating the risk ratio of suicide behavior, produced a 95 percent confidence interval that includes 1 (Paxil is borderline), suggesting that the null hypothesis cannot be rejected. In the case of Wellbutrin, the FDA's own analysis found no incidents of suicidal ideation, yet the product still bears the class-wide boxed warning.

Delayed effect / Stone et al. argue that the lag between adoption of the boxed warning and the increase in youth suicide is too large to indicate causation. But regulatory action takes time to implement. While there was a brief downturn in deaths caused by suicide from 2005 to 2007, this does not justify the continued implementation of a barrier between patients and treatment. Indeed, the downturn may be a continuation of the downward trend in suicides prior to the boxed warning. When updates are made to a drug label, existing bottles already dispensed to patients carry the old label and are not recalled or replaced. Pharmacies may continue dispensing remaining inventory with outdated labeling until stock turns over, meaning the practical effect of a labeling change can lag months to years behind the regulatory decision date (ERG 2012).

This delay has been corroborated by multiple independent sources, including neutral third-party CDC suicide rate data cited in our original publication and a 2024 analysis drawing on insurance data (Soumerai et al. 2024). The latter describes a transition period following boxed warning implementation characterized by declining depression diagnoses, reduced physician visits for depression, and a subsequent delayed rise in adolescent suicide deaths.

NEXT STEPS

Khan et al. (2026) was not without precedent. A substantial and growing body of peer-reviewed and clinical literature has raised concerns about the implementation of the antidepressant boxed warning (Gibbons et al. 2007; Kurian et al. 2007; Bridge et al. 2008; Rob & Foster 2009; Lu et al. 2014; Carson et al. 2017; Kafali et al., 2018; Lu et al. 2018; Lu et al. 2020; Soumerai et al. 2024; Soumerai & Lu 2026). We note that Stone has published formal criticism of several of these works (Stone 2014; Stone 2018a; Stone 2018b).

The decision by Stone et al. (2026) to focus on methodological objections while relying on findings that remain unverified and unavailable for independent review, all while ignoring the real-world detrimental effects this regulatory decision may be having on patients, is the embodiment of the old saw, "I wouldn't have seen it if I hadn't believed it."

We should note that our previous article anonymously quoted from some direct feedback that Stone et al. provided us of an earlier paper. Because the quotation was anonymous, we did not seek their permission to use the material and we have since learned they disagree with our decision. Also, our wording suggested that, when they provided that feedback, they were all affiliated with the FDA; in fact, at least some of them were not, though Stone made similar criticisms in articles while he was with the FDA. We also note that, in some previous writings about the boxed warning, some of them failed to disclose their involvement with the FDA decision.

CONCLUSION

We want to make clear that we have no financial or nonfinancial conflicts of interest regarding the pediatric antidepressant boxed warning. We reaffirm the recommendation of Khan et al. (2026): The boxed warning information should be relocated to the "Warnings and Precautions" section of the label. The central aim of our argument is to advocate for patients and their right to access treatment.

In this response, we have examined the dilemma that physicians and families face because of the boxed warning. As stated in Khan et al. 2026, we support patients developing a full understanding of the medications they take: the benefits, the risks, and the uncertainties. That does not require patients and their families to be alarmed by a warning resting on limited evidence, derived from an analysis not designed for detecting suicidality, and never made available for independent validation. *R*

READINGS:

- Bachmann, Christian J., Lise Aagaard, Mehmet Burcu, et al., 2016, "Trends and Patterns of Antidepressant Use in Children and Adolescents from Five Western Countries, 2005–2012," *European Neuropsychopharmacology* 26(3): 411–419.
- Bertuccio, Paola, Andrea Amerio, Enrico Grande, et al., 2024, "Global Trends in Youth Suicide from 1990 to 2020: An Analysis of Data from the WHO Mortality Database," *eClinicalMedicine* 70:102506.
- Bridge, Jeffrey A., Joel B. Greenhouse, Arielle H. Weldon, et al., 2008, "Suicide Trends Among Youths Aged 10 to 19 Years in the United States, 1996–2005," *JAMA* 300(9): 1025–1026.
- Carson, Nicholas J., Ana M. Progovac, Ye Wang, et al., 2017, "A Decline in Depression Treatment Following FDA Antidepressant Warnings Largely Explains Racial/Ethnic Disparities in Prescription Fills," *Depression and Anxiety* 34(12): 1147–1156.
- EMA (European Medicines Agency), 2005, "European Medicines Agency Finalises Review of Antidepressants in Children and Adolescents," EMEA/CHMP/128918/2005, April 25.
- Emslie, Graham J., Robert L. Findling, Paul P. Yeung, et al., 2007, "Venlafaxine ER for the Treatment of Pediatric Subjects with Depression: The Results of Two Placebo-Controlled Trials," *Journal of the American Academy of Child & Adolescent Psychiatry* 46(4): 479–488.
- ERG (Eastern Research Group), 2012, "Analysis of the Feasibility of Safety Labeling Changes Implementation Timeline," prepared for the FDA, June 22.
- Eurostat, 2025, "Young People—Health," *Statistics Explained*, European Commission.
- Fassmer, Alexander M., Kathrin Wandscher, Aida Bedri, et al., 2026, "Change of Antidepressant Utilization in Children, Adolescents and Young Adults in Europe before and during the COVID-19 Pandemic: A Systematic Review," *European Child & Adolescent Psychiatry* 35: 3–16.
- FDA (US Food and Drug Administration), 2004, "Psychopharmacologic Drugs Advisory Committee," CDER 2004 meeting documents, accessed April 29, 2026.
- Fornaro, Michele, Annalisa Anastasia, Alessandro Valchera, et al., 2019, "The FDA 'Black Box' Warning on Antidepressant Suicide Risk in Young Adults: More Harm than Benefits?" *Frontiers in Psychiatry* 10:294.
- Gibbons, Robert D., 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(9): 1356–1363.
- Kafali, N., C. Hendricks Brown, Kwan Hur, et al., 2018, "Long-Run Trends in Antidepressant Use Among Youths after the FDA Black Box Warning," *Psychiatric Services* 69(4): 389–395.
- Khan, Arif, Anshu Arara, & Aishwarya Prasad, 2026, "A Tragic Unintended Consequence," *Regulation* 49(1): 26–29.
- Kurian, Benji T., Wayne A. Ray, Patrick G. Arbogast, et al., 2007, "Effect of Regulatory Warnings on Antidepressant Prescribing for Children and Adolescents," *Archives of Pediatrics & Adolescent Medicine* 161(7): 690–696.
- Lu, Christine Y., Fang Zhang, Matthew D. Lakoma, et al., 2014, "Changes in Antidepressant Use by Young People and Suicidal Behavior after FDA Warnings and Media Coverage: Quasi-Experimental Study," *BMJ* 348:g3596.
- Lu, Christine Y., Robert B. Penfold, Sengwee Toh, et al., 2018, "Near Real-Time Surveillance for Consequences of Health Policies Using Sequential Analysis," *Medical Care* 56(5): 365–372.
- Lu, Christine Y., Robert B. Penfold, Jamie Wallace, et al., 2020, "Increases in Suicide Deaths among Adolescents and Young Adults following US Food and Drug Administration Antidepressant Boxed Warnings and Declines in Depression Care," *Psychiatric Research and Clinical Practice* 2(2): 43–52.
- Robb, Adelaide S., & Leia Foster, 2009, "The Black Box Warning and Its Unintended Consequences," *Child and Adolescent Psychopharmacology News* 14(1): 6–9.
- Soumerai, Stephen B., & Christine Y. Lu, 2026, "RFK Jr.'s War on Antidepressants Is Coming—and It Will Cost Lives," *STAT News*, January 7.
- Soumerai, Stephen B., Ross Koppel, Huseyin Naci, et al., 2024, "Intended and Unintended Outcomes after FDA Pediatric Antidepressant Warnings: A Systematic Review," *Health Affairs* 43(10): 1360–1369.
- Stone, Marc B., 2014, "The FDA Warning on Antidepressants and Suicidality—Why the Controversy?" *New England Journal of Medicine* 371(18): 1668–1671.
- Stone, Marc B., 2018a, "In Search of a Pony," *Medical Care* 56(5): 375–381, May.
- Stone, Marc B., 2018b, "Honest Opinion versus Dishonest Analysis," *Medical Care* 56(5): 391–393, May.
- Stone, Marc B., Andrew Mosholder, and Tarek Hammad, 2026, "In Defense of the Boxed Warning," *Regulation* 49(2): 38–44.