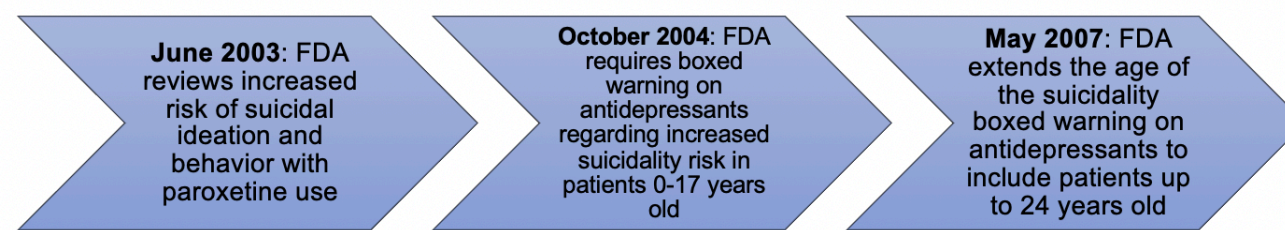


Impact of an FDA Antidepressant Boxed Warning on Rates of Suicides and Suicide Attempts in Pediatrics and Young Adults

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Background

- Suicide was the tenth leading cause of death in the United States and the third leading cause of death among U.S. children and adolescents (1-19 years old) in 2017.^{1,2} From 2000 to 2014, the number of suicides from poisoning increased by 38.5%, with around 90% of those deaths involving medications.^{3,4}
- In October 2004, the U.S. Food and Drug Administration (FDA) required antidepressants to include a boxed warning that suggested an increased risk of suicidal ideation and behavior in pediatric patients (0-17 years old) with psychiatric disorders.⁵ In May 2007, the FDA extended the age range to include young adults up to 24 years old.⁶
- Assessing the effectiveness of this warning and age extension is crucial for reducing preventable suicides and suicide attempts involving antidepressants in the pediatric and young adult populations.



Objectives

To examine the impacts of:

1. The October 2004 FDA boxed warning on the rates of suicides and suicide attempts involving antidepressants in pediatrics (0-17 years old)
2. The May 2007 age extension on the rates of suicides and suicide attempts in pediatrics and young adults (0-24 years old).

Methods

Data Sources

- 23,473 cases of suicides and suicide attempts involving a single antidepressant for all ages reported from January 2000 to July 2016 were extracted from the California Poison Control System (CPCS) database.
- Analysis populations: pediatrics only (0-17 years old), combined pediatrics and young adult (0-24 years old)

Statistical Approach

- Primary outcome: Monthly suicide rate ratio

$$\text{Rate} = \frac{\# \text{ of suicides and suicide attempts}}{\text{U.S. Census California population}} * 1,000,000$$

$$\text{Rate Ratio} = \frac{\text{Rate in analysis population}}{\text{Rate among all age groups}}$$

- Cumulative sum (CUSUM) control chart tests identified the months when suicide rate ratios changed significantly, and they were used as intervention time points in interrupted time series analyses (ITSAs).
- Linear and nonparametric polynomial smoother regression models graphically presented changes in the monthly suicide rate ratios in relation to the significant time points.
- Natural logs of the monthly suicide rate ratios ensured assumptions for the CUSUM tests and ITSAs were met.

Results – CUSUM Test Outputs

Table 1. Pediatrics only population

Row	Confidence Interval	Conf. Level	From	To	Level
27	(4, 36)	100%	-0.13903	0.022092	2
90	(79, 106)	99%	0.022092	-0.12447	6
123	(111, 134)	100%	-0.12447	0.055933	5
165	(162, 168)	100%	0.055933	0.34224	4

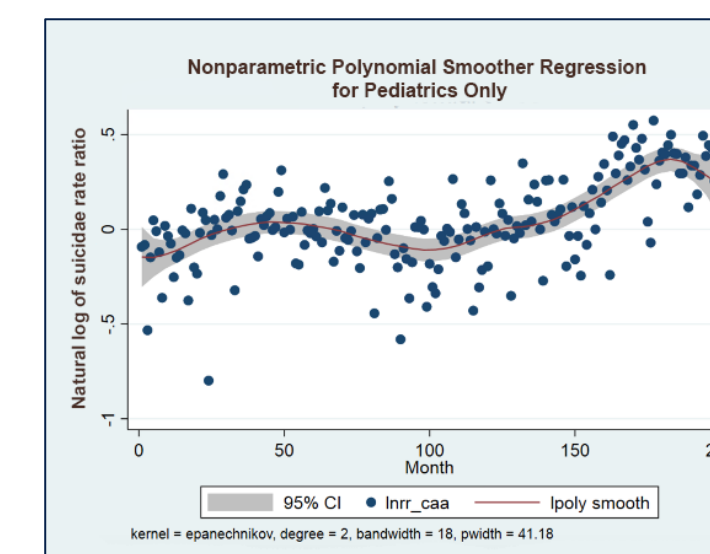
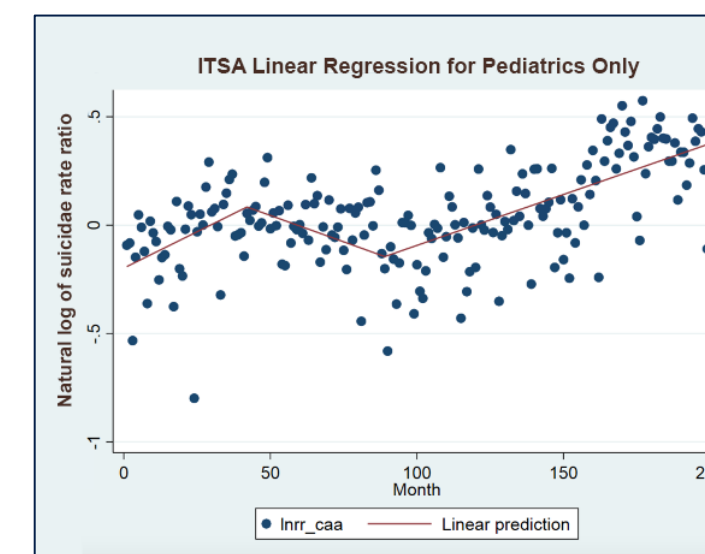
Table 2. Pediatrics and young adult population

Row	Confidence Interval	Conf. Level	From	To	Level
99	(5, 119)	91%	0.24522	0.19958	4
123	(116, 128)	100%	0.19958	0.32069	2
160	(155, 164)	100%	0.32069	0.46382	1
184	(161, 190)	90%	0.46382	0.5429	2

Results - Regressions

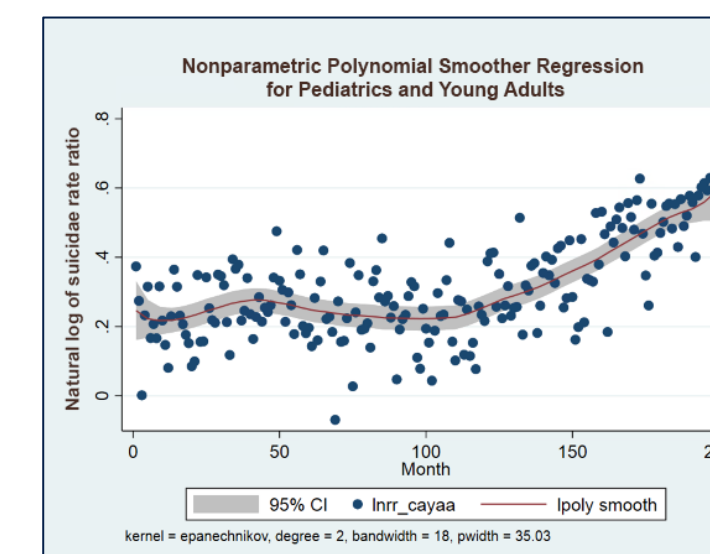
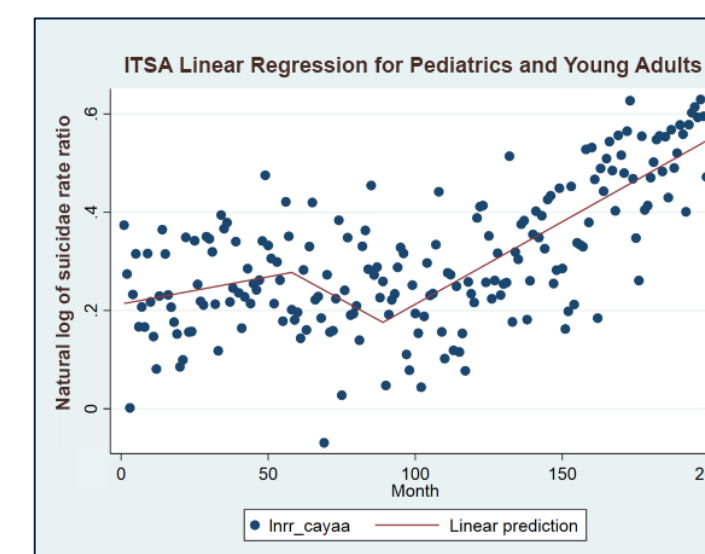
Figures 1 and 2. Pediatrics Only

- Significant changes in suicide rate ratios detected close to June 2003 (row 42) and May 2007 (row 89). [Table 1]
- Monthly suicide rate ratios significantly decreased after June 2003 (P<0.0001) but significantly increased after May 2007 (P<0.0001).



Figures 3 and 4. Pediatrics and Young Adults

- Significant change in suicide rate ratios detected close to May 2007 (row 89). Confidence interval included October 2004 (row 58). [Table 2]
- Monthly suicide rate ratios significantly decreased after October 2004 (P=0.002) but significantly increased after May 2007 (P<0.0001).



Conclusion

- In the short-term, monthly rates of suicides and suicide attempts in pediatric patients and young adults significantly decreased after the FDA implemented the suicidality boxed warning on antidepressants in October 2004. However, the May 2007 age extension to include young adults was followed by a significant increase in monthly rates of suicides and suicide attempts.
- More research is needed to understand, monitor, and reduce possible unintended effects of FDA actions and warnings.

Discussion

- The October 2004 FDA boxed warning may have had less of an effect on suicides and suicide attempts with antidepressants in pediatrics compared to the FDA's announcement in June 2003 regarding their review of paroxetine use and increased suicidal ideation and behavior.
- While our study suggests there are risks associated with the FDA boxed warning and age extension, it is difficult to conclude whether this was the result of the FDA's actions, media coverage of the boxed warning, or other causes.⁷

Limitations

- Because reports to the CPCS are voluntary, true rates of suicides and suicide attempts involving antidepressants were potentially underestimated.
- Recall and response biases could have contributed to misclassification of cases in the CPCS database.
- This study was limited to generalizing results in the California pediatric and young adult populations.

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