Effect of the FDA Black Box Suicidality Warnings for Antidepressants on Suicide Rates in the USA : Signal or Noise?

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Abstract

Background: Some authors claimed that the FDA black box warning on treatment-emergent suicidality with antidepressants in adolescents (issued 2004) and young adults (issued 2006) led to an increase of suicides, based on the analyses of ecological data with debatable assumptions about putative changes in suicide rates.

Aims: To explore if putative changes in suicide rates in adolescents and young adults at the time of the FDA warnings is a detectable signal in the data or compatibly with noise.

Method: We applied different changepoint analyses for US adolescent and young adult suicide rates 1981-2019.

Results: No changepoint analysis supported a detrimental effect of the FDA warnings. The downward trend of suicides reversed years after the warning for adolescents (2007-2009) and years before for young adults (1999-2001). Wide confidence intervals hint at noisy data.

Limitations: Our analyses cannot rule out detrimental effects of the FDA warnings. However, even if there was such an effect, it was likely small and indistinguishable from the noise in the available suicide data.

Conclusion: There is no detectable change of trend in adolescent or young adult suicide rates in line with a detrimental effect of the FDA black box warnings on treatment-emergent suicidality.

Key Words: suicide, antidepressants, adolescents, FDA, black box warning

Introduction

In October 2004, the US Food and Drug Administration (FDA) issued a black box warning for the treatment of adolescents with antidepressants because clinical trials found an increased risk for suicidal ideation and behavior (Hammad, Laughren, & Racoosin, 2006). The warning was enacted in 2005 and was then extended to young adults aged 18-24 in December 2006 (Stone et al., 2009). Similar warnings were issued in other countries, too (Wheeler, Metcalfe, Martin, & Gunnell, 2009). Since then, there is an ongoing debate as to whether the warning led to an unintended increase of suicides among young people, resulting from fewer antidepressant prescriptions or lack of treatment in general (Lu et al., 2018; Lu et al., 2014; Spielmans, Spence-Sing, & Parry, 2020; Stone, 2014, 2018). On the one hand, data from clinical trials and observational studies confirmed the increase of suicide risk associated with antidepressant treatment (Dragioti et al., 2019; Hetrick et al., 2021; Sharma, Guski, Freund, & Gotzsche, 2016; Stone et al., 2009). On the other hand, some authors based their studies on ecological data using interrupted time series, which found a change of trend of suicides after the warning (Lu et al., 2018; Lu et al., 2020; Lu et al., 2014). Indeed, for adolescents, a visual inspection of the time-series may suggest an unusual upshift from 2003 to 2004 for adolescents, and for young adults, there seems to be a halt of the declining suicide rates around 2006 (see Figures 1ab). In this article, we explore if these putative changes are a true signal of a trend change, detectable with changepoint analyses, or if these interrupted time-series are compatible with noise, that is, random variation of yearly suicide rates. Assuming a true signal, we expected changepoints at the time or shortly after the FDA warnings 2004-2005 for adolescents, and 2006-2007 for young adults. We used extended time frames before and after the warnings to investigate the long-term trends and to increase the statistical information for the changepoint analyses. We also inspected the long-term trends of antidepressant prescriptions to bring our findings into context.

Method

We obtained all available yearly US suicide rates for adolescent (10-19 years) and young adults (20-24 years) from the CDC WISQARS (1981-1998) and WONDER (1999-2019) databases.

To detect changepoints in the time-series of suicide rates, we used a variety of statistical procedures available for R (R Core Team, 2020) (Table 1). Changepoint analyses can detect changes in trends (change of slope of a regression model), changes in the mean (change of the intercept in a regression model), or changes in variance. Some changepoint analyses require a pre-specified number of changepoints, and some automatically estimate the optimal number of changepoints. Some analyses are designed to detect only single changepoints, and here we used an additional time frame restricted from 1990 to 2017, similar to the one in Lu et al. (2020). We did this because there was an obvious changepoint around 1990 and perhaps a changepoint in 2017, what may have prevented the detection of a less obvious changepoint in between 1990 and 2017.

For simplicity, we mainly describe the results of two selected changepoint analyses. First, we report the results from a segmented regression with R's "segmented" package (Muggeo, 2008). The segmented regression model breaks the time-series into linear segments (broken-lines), with a pre-specified number of changepoints. We used a bootstrap restarting procedure for initial values of the changepoints. The segmented regression with 5 changepoints had excellent fit and more changepoints did not increase the fit. Second, we report the results from a Bayesian changepoint analysis with the "bcp" package (Erdman & Emerson, 2007). This Bayesian analysis provides continuous posterior probabilities of changepoints and not only binary decisions about the presence of changepoints.

Additional changepoint analyses included the following: the "changepoint" package uses popular algorithms to detect changes of mean and/or variance. We only used the change of mean (cpt.mean) function for this paper, with the single changepoint (AMOC), multiple changepoints using exact (PELT and segmented neighborhoods), and the approximate (binary

segmentation) search algorithms. The "strucchange" package gives estimations of multiple changepoints for changes of means or change of trends (without joint regression lines), together with confidence intervals. The "EnvCpt" package automatically fits 12 different models, of which we report on the change of mean and change of trend results (further results for autoregressive models are available online). The "trend" package provides the Buishand U-test, a non-parametric test to detect one single changepoints for a change of mean. Finally, as an alternative way, we used the "tree" package for a regression tree, where recursive partitioning is used to split the data in order to maximize the reduction in impurity.

Based on the comments of an anonymous reviewer, we also included a segmented regression analysis using the Joinpoint software from the National Cancer Institute (2020). We used a Poisson model with the number of suicides and the size of the population and a maximum number of 9 changepoints.

Antidepressant prescriptions rates were estimated using the Medical Expenditure Panel Survey (MEPS), a representative sample of civilian noninstitutionalized population of the US. For each available year (1996 to 2018), we linked the full year consolidated data file with the prescribed medicine data file. The MEPS codes antidepressants according to the Multum Lexicon. We coded a person as using antidepressants if there was any purchase of antidepressants in the respective year. We used a complex sampling design to generate the prevalence of antidepressant use for each year among adolescents (10-19 years) and young adults (20-24 years).

All data and statistical code are available online on the Open Science Framework *(link provided upon publication)*.

Results

For adolescents, the segmented regression analysis estimated changepoints in 1989, 2002, 2007, 2015, and 2017 (Figure 1a). The changepoint in 2007 indicates a reversal from a declining trend to an increase in suicides, paralleling a change of trend in antidepressant prescriptions, which likewise started to rise again in 2007. The Bayesian analysis detected changepoints with posterior probabilities exceeding 0.7 in 1984, 1998, and 2016. The posterior probability of a changepoint between 2004 and 2005 was below 0.1 (Figure 1a). Other changepoint analyses either detected changepoints other than 2004/2005, no changepoints at all, or changepoints with wide confidence intervals.

For young adults, the segmented regression analysis estimated changepoints in 1992, 1994, 1997, 2001, and 2013. A reversal of the trend in suicides (from a decrease to an increase) already occurred in 2001. There was no change of trend in suicides in accordance with the reversal of antidepressant prescriptions in 2003 (from an increase to a decrease) or in 2006 (from a decrease to an increase). The Bayesian analysis detected changepoints in 1995, 2009, and 2014 (Figure 1b). The posterior probabilities of changepoints in 2006 or 2007 were very low (0.05). Other changepoint analyses either detected changepoints other than 2006/2007 or with wide confidence intervals.

- Table 1 about here -

Discussion

None of the changepoint analyses detected changes of suicide trends occurring at the time of the FDA black box suicidality warnings for antidepressants. For adolescents, segmented regression changepoint analyses suggested a reversal of previously declining suicide rates in 2007, which was at a time when antidepressant prescriptions also started to increase again (Kafali, Progovac, Hou, & Cook, 2018). For young adults, segmented regression suggested a reversal of suicide trends already in 2001, thus well before the black box warning in late

2006. Furthermore, the Bayesian analyses indicated that the probability of a changepoint is close to zero at the time of the FDA black box warnings. Other changepoint analyses likewise could not reliably detect changepoints at the time of the FDA warnings.

Therefore, the conclusion by Lu et al drawn from interrupted time-series analyses that the FDA warning reversed a downwards trend of suicides is not supported by the data. This is not to say that there certainly is no iatrogenic or beneficial effect, but if there is a related effect, it is too small to be distinguishable from the noise in the data. That the data is noisy is also supported by the findings that some changepoint analyses could not detect changepoints at all or only with wide confidence intervals.

Our findings are largely in line with the literature. Various theoretical arguments and empirical findings are at odds with the assumption that the FDA warnings resulted in increased suicide rates. The short-lived decline in antidepressant prescriptions in the mid-2000s not just in young people but in all age groups may have been caused by other reasons than the FDA warnings, such as reduced advertising by the major pharmaceutical companies (Stone, 2014). Moreover, as pointed out by Stone (2018), the assumptions in studies such as Lu et al. (2018) are largely arbitrary, with substantial degrees of freedom. This concerns the assumed timing when the FDA warnings should have had an effect, the selection of the time frame before and after the FDA warnings for the analyses, or the selection of the outcome. For example, using a flawed outcome such as psychotropic drug poisoning with unspecified intent as proxy for suicidal behavior (Lu et al., 2014) is misleading and leads to very different results than using valid outcomes such as actual suicide attempts or suicides (Stone, 2014, 2018).

It is also problematic to attribute an increase in adolescent suicide rates starting 2007 to a black box warning from 2004. A safety warning cannot directly cause suicides. People do not suicide because a drug regulator warns about treatment-emergent suicidality with antidepressants. If the black box suicidality warning for antidepressants was causally related

to suicides, it would be indirectly through an underuse of antidepressants in adolescents with serious mental health problems (further assuming that antidepressant treatment reduces the suicide risk in these people). That is, in theory the black box warning can only be responsible for increased suicide rates when suicide rates are negatively correlated with antidepressant prescription rates. However, as shown in Figure 1, antidepressant prescriptions steeply increased as of 2007 in line with increasing suicide rates (positive correlation), thus the conclusion is flawed. In addition, the assumption that antidepressant prescriptions reduce national suicide rates is also implausible, because randomized controlled trials of antidepressant treatment in adolescents and young adults found an increase of suicidal behavior with new generation antidepressants (Hetrick et al., 2021; Stone et al., 2009).

In accordance, international data neither support the claim that increased antidepressant prescriptions reduced national suicide rates (Amendola, Ploderl, & Hengartner, 2021; Hogberg & Bremberg, 2019), nor that regulatory warnings consistently lead to an increase of suicides (Wheeler et al., 2009). This is also supported by our data: suicide rates among adolescents and young adults decreased since the introduction and increased prescription of antidepressants until 2003, resulting in a large negative correlation. However, this correlation reversed from 2004 to 2018 (large positive correlations), despite an increase of antidepressant prescriptions from around 2007 to an all-time high in recent years (see Figure 1 and the online supplement for the correlations). It is surprising that Lu et al. never discussed these conflicting findings in their publications. Furthermore, the correlation between year to year changes of suicides and antidepressant prescriptions was more often positive than negative (Stone, 2018), thus not supporting a suicide preventive role of antidepressants.

Interestingly, when ecological studies found that increasing antidepressant prescriptions were associated with reduced suicide rates, several publications in high-ranked journals interpreted this finding as evidence for the potentially suicide preventive role of

antidepressants (e.g., Grunebaum, Ellis, Li, Oquendo, & Mann, 2004; Isacsson, 2000). However, in more recent years, when ecological studies detected an increase in both suicide rates and antidepressant prescriptions among young people, the possible suicidogenic role of antidepressants was rarely discussed in related publications (e.g., Padmanathan, Bould, Winstone, Moran, & Gunnell, 2020; Ruch et al., 2019).

Our study has several limitations. First, there are more changepoint analyses than the one we presented, perhaps leading to different results. However, we think it is unlikely that other statistical procedures will find changepoints especially at the time of the FDA warnings, given that none of our analyses detected changepoints here. Even if some did, it would rather point towards statistical artifacts, given the large inconsistency and variability in results generated by different methods. Second, there may be more options for fitting statistical models than using linear segmentations of time-series (such as fitting quadratic or cubic lines). However, with the noisy data at hand, these strategies may likely risk being over-fitted. Third, the results from different changepoint analysis are only partly replicating, hinting that the data is indeed noisy and prone to statistical artifacts (i.e. false-positive chance findings).

To conclude, the changes of trends in suicide rates detected by several changepoint analyses do not support the notion that the FDA black box suicidality warning led to increased suicide rates. It is problematic to interpret fluctuations of suicide rates at the time of the warning as reflecting an underlying causal process. Instead, the fluctuations after the FDA warnings are perfectly compatible with random variations in yearly suicide rates.

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Conflicts of interest

None.

Ethical standards

Not applicable (analysis of national suicide rates)

Availability of data and materials

The data and R-code is available via the OSF (provided upon publication)

Caption to Figure 1.

Main results from the changepoint analyses. Black dots are the yearly suicide rates. The blue lines are the fitted values from the segmented regression analyses. The gray continuous lines are the posterior probabilities for the Bayesian changepoint analysis. The dotted black lines are rates of antidepressant prescriptions, with the 95% confidence intervals as dotted gray lines. The vertical red line denotes the timing of the FDA black box suicidality warnings (2004 and 2006, respectively, for adolescents and young adults).

References

Amendola, S., Ploderl, M., & Hengartner, M. P. (2021). Did the introduction and increased prescribing of antidepressants lead to changes in long-term trends of suicide rates? *Eur J Public Health, 31*(2), 291-297. doi:10.1093/eurpub/ckaa204

Dragioti, E., Solmi, M., Favaro, A., Fusar-Poli, P., Dazzan, P., Thompson, T., . . . Evangelou, E. (2019). Association of Antidepressant Use With Adverse Health Outcomes: A Systematic Umbrella Review. *JAMA Psychiatry, 76*(12), 1241-1255. doi:10.1001/jamapsychiatry.2019.2859

Erdman, C., & Emerson, J. W. (2007). bcp: An R Package for Performing a Bayesian Analysis of Change Point Problems. *Journal of Statistical Software, 23*(3), 1-13.

Grunebaum, M. F., Ellis, S. P., Li, S., Oquendo, M. A., & Mann, J. J. (2004). Antidepressants and suicide risk in the United States, 1985-1999. *Journal of Clinical Psychiatry, 65*(11), 1456-1462. doi:10.4088/jcp.v65n1103

Hammad, T. A., Laughren, T., & Racoosin, J. (2006). Suicidality in pediatric patients treated with antidepressant drugs. *Archives of Generl Psychiatry, 63*(3), 332-339. doi:10.1001/archpsyc.63.3.332

Hetrick, S. E., McKenzie, J. E., Bailey, A. P., Sharma, V., Moller, C. I., Badcock, P. B., . . . Meader, N. (2021). New generation antidepressants for depression in children and adolescents: a network meta-analysis. *Cochrane Database of Systematic Reviews, 5*, CD013674. doi:10.1002/14651858.CD013674.pub2

Hogberg, G. N., & Bremberg, S. G. (2019). Antidepressant medication might increase the risk of self-harm injuries: findings in 17 OECD countries. *Eur J Public Health, 29*(2), 365-367. doi:10.1093/eurpub/cky268

Isacsson, G. (2000). Suicide prevention--a medical breakthrough? *Acta psychiatrica Scandinavica, 102*(2), 113-117. doi:10.1034/j.1600-0447.2000.102002113.x

Kafali, N., Progovac, A., Hou, S. S., & Cook, B. L. (2018). Long-Run Trends in Antidepressant Use Among Youths After the FDA Black Box Warning. *Psychiatric services, 69*(4), 389-395. doi:10.1176/appi.ps.201700089

Lu, C. Y., Penfold, R. B., Toh, S., Sturtevant, J. L., Madden, J. M., Simon, G., . . . Kulldorff, M. (2018). Near Real-time Surveillance for Consequences of Health Policies Using Sequential Analysis. *Medical Care, 56*(5), 365-372. doi:10.1097/MLR.0000000000000893

Lu, C. Y., Penfold, R. B., Wallace, J., Lupton, C., Libby, A. M., & Soumerai, S. B. (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. doi:10.1176/appi.prcp.20200012

Lu, C. Y., Zhang, F., Lakoma, M. D., Madden, J. M., Rusinak, D., Penfold, R. B., . . . Soumerai, S. B. (2014). Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. *BMJ, 348*. doi:10.1136/bmj.g3596

Muggeo, V. M. J. R. n. (2008). Segmented: an R package to fit regression models with broken-line relationships. *8*(1), 20-25.

National Cancer Institute. (2020). Joinpoint Regression Program, Version 4.8.0.1. In: Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute.

Padmanathan, P., Bould, H., Winstone, L., Moran, P., & Gunnell, D. (2020). Social media use, economic recession and income inequality in relation to trends in youth suicide in high-income countries: a time trends analysis. *Journal of affective disorders, 275*, 58-65. doi:10.1016/j.jad.2020.05.057

R Core Team. (2020). R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org/

Ruch, D. A., Sheftall, A. H., Schlagbaum, P., Rausch, J., Campo, J. V., & Bridge, J. A. (2019). Trends in Suicide Among Youth Aged 10 to 19 Years in the United States, 1975 to 2016. *Jama Network Open, 2*(5). doi:10.1001/jamanetworkopen.2019.3886

Sharma, T., Guski, L. S., Freund, N., & Gotzsche, P. C. (2016). Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ, 352*, i65. doi:10.1136/bmj.i65

Spielmans, G. I., Spence-Sing, T., & Parry, P. (2020). Duty to Warn: Antidepressant Black Box Suicidality Warning Is Empirically Justified. *Frontiers in Psychiatry, 11*. doi:10.3389/fpsyt.2020.00018

Stone, M. B. (2014). The FDA warning on antidepressants and suicidality--why the controversy? *New England Journal of Medicine, 371*(18), 1668-1671. doi:10.1056/NEJMp1411138

Stone, M. B. (2018). In Search of a Pony: Sources, Methods, Outcomes, and Motivated Reasoning. *Medical Care, 56*(5), 375-381. doi:10.1097/MLR.0000000000000895

Stone, M. B., Laughren, T., Jones, M. L., Levenson, M., Holland, P. C., Hughes, A., . . . Rochester, G. (2009). Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ, 339*, b2880. doi:10.1136/bmj.b2880

Wheeler, B. W., Metcalfe, C., Martin, R. M., & Gunnell, D. (2009). International impacts of regulatory action to limit antidepressant prescribing on rates of suicide in young people. *Pharmacoepidemiol and Drug Safety, 18*(7), 579-588. doi:10.1002/pds.1753