

**Antidepressant prescription rates and suicide attempt rates
from 2004 to 2016 in a nationally representative sample of
adolescents in the United States**

Journal:	<i>Epidemiology and Psychiatric Sciences</i>
Manuscript ID	EPS-LE-2018-0036.R1
Manuscript Type:	Letter to the Editor
Date Submitted by the Author:	n/a
Complete List of Authors:	Plöderl, Martin; Christian-Doppler-Klinik, Dept. of Clinical Psychology and Dept. for Crisis Intervention and Suicide Prevention, University Clinic for Psychiatry, Psychotherapy, and Psychosomatics; Paracelsus Medizinische Privatuniversität, Hengartner, Michael; Zurich University of Applied Sciences (ZHAW), Department of Applied Psychology
Keywords:	



Antidepressant prescription rates and suicide attempt rates from 2004 to 2016 in a nationally representative sample of adolescents in the United States

Meta-analyses of randomized controlled trials (RCTs) (Hammad *et al.* 2006, Hetrick *et al.* 2012, Sharma *et al.* 2016) and observational studies (Barbui *et al.* 2009) suggest that antidepressants may increase the suicide risk in youth, which justifies the decision of the FDA to issue a black box warning. Contesting that controversial decision, some authors used ecological data to allegedly show that there was an increase in suicide risk after the introduction of the FDA warning in 2004 (e.g. Gibbons *et al.* 2007). However, that specific study in question and some other research were criticised for being severely flawed (Stone, 2014) and surprisingly, there are no recent replications of these critical studies. In particular, to avoid biases owing to random fluctuations in suicide attempt rates during short time intervals, long observation periods are necessary. Therefore, here we focus on antidepressant prescriptions and suicide attempt rates from 2004 to 2016 in adolescents aged 12-17 years.

Method

Our analysis is based on the public use data from the annual National Survey on Drug Use and Health (NSDUH) extracted from <http://pdas.samhsa.gov>. The NSDUH is a nationally representative survey among the civilian, non-institutionalised US population. Data were assessed by interviewers during in-person visits to households and non-institutional group quarters (detailed information online <https://www.samhsa.gov/data/population-data-nsduh/reports>). If participants screened positive on gate questions on depressed mood, they were asked nine specific symptoms of depression and were categorized as having past year major depression if they had at least five depression symptoms several days or longer in the past year (see, for example, Appendix F in the 2016 codebook). Participants were also asked

if they took prescribed medication for their mood problems in the past year. No more details were given about the specific medication, but since prescriptions for mood problems are most likely antidepressants, we used this variable as proxy for antidepressant medication. Participants who screened positive on the gate questions were also asked specific items on suicidality, from suicide ideation to suicide attempts. The item on suicide attempt was “Did you make a suicide attempt or try to kill yourself?” No information on the specific timing of the suicide attempt was given. However, this suicide attempt variable seemed to be valid of actual past year suicide risk, since it correlated high and significant with the yearly suicide rates of the same age group, $r=0.75$, 95%-CI 0.33 – 0.92 (yearly suicide rates retrieved from the CDC website, <https://webappa.cdc.gov/sasweb/ncipc/mortrate.html>). We cross-tabulated the relevant variables for each year, using the survey package in R and a validated R-code to account for the complex sampling design. Pearson correlations were used to quantify associations between variables. The R-code and the extracted data can be obtained upon request from the authors.

Results

Figure 1 shows the rate of suicide attempts and self-reported prescriptions for mood disorders (most likely antidepressants) for persons with and without major depression (MD). Both prescription and suicide attempt rates decreased after the FDA warning in 2004 but increased in recent years. If antidepressants cause suicidality, then the reversal of the prescription trend should precede the reversal of the suicidality trend. This was confirmed with a Buishand U-Test that revealed a changepoint for antidepressants rates most likely at 2012 ($U=0.41$, $p=0.05$) and for suicide attempt rates most likely in 2013 ($U=0.45$, $p<0.05$). The correlation between suicide attempt rates and prescription rates was $r=0.83$ (95%-CI: 0.51 - 0.95; $p<0.01$) for all adolescents, $r=0.41$ (-0.18 – 0.78; $p=0.16$) for those with MD, and $r=0.76$ (0.37 – 0.93; $p<0.01$) for those without MD.

Please Insert Figure 1 here

Figure 1: Suicide attempt and antidepressant prescription rates in adolescents aged 12-17 years with and without major depression

Discussion

Suicidality is a core feature of MD, and MD is commonly treated with antidepressants, hence producing at least in part a spurious correlation. However, persons without MD are rarely suicidal, therefore, in these youths the strong correlation between suicide attempts and antidepressant prescriptions is hardly explained by indication alone. Also, antidepressant prescription rates increased before the suicide attempt rates, which accords to individual person data demonstrating that the suicide risk is highest *after* initiation of antidepressant pharmacotherapy (Bjorkenstam *et al.* 2013). This is an important finding, because temporality is a necessary but not sufficient prerequisite for causality (Hill, 1965). Additional research has revealed that the antidepressant-suicidality association is most likely dose-dependent (Courtet *et al.* 2014, Miller *et al.* 2014), which is another key aspect of causality (Hill, 1965).

Our study is limited because we could not determine the exact medication and the exact time of the suicide attempt. Moreover, all data relied on self-reports, which may bias estimates of both suicide attempts and antidepressant prescriptions. However, in line with the meta-analytic evidence from RCTs (Hammad *et al.* 2006, Hetrick *et al.* 2012, Sharma *et al.* 2016), one interpretation of our findings is that antidepressants may cause suicidality in some adolescents.

Efforts to deliver mental health care for adolescents and young adults are of highest public health significance to reduce the suicide risk, but we want to caution against the

indiscriminate use of antidepressant drugs, which may worsen the problem they are supposed to treat. Based on our findings we stress that the FDA decision to issue a black box warning was justified and necessary.

Proof

Acknowledgements:

Both authors declare that they have no conflicts of interest. No funding was received for this publication. We thank Anthony Damico for providing R-code to use the NSDUH data

<https://github.com/abresler/usgsd/blob/master/National%20Survey%20on%20Drug%20Use%20and%20Health/replicate%20samhsa%20puf.R>

Financial support:

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest:

None.

Availability of Data and Materials:

The R-code is available upon request from the authors. The data is available publicly (see Methods section for link).

Proof

References

- Barbui C, Esposito E, Cipriani A** (2009). Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. *CMAJ*, **180**, 291-297.
- Bjorkenstam C, Moller J, Ringback G, Salmi P, Hallqvist J, Ljung R** (2013). An association between initiation of selective serotonin reuptake inhibitors and suicide - a nationwide register-based case-crossover study. *PLoS One*, **8**, e73973.
- Courtet P, Lopez-Castroman J, Jaussent I, Gorwood PA** (2014). Antidepressant dosage and suicidal ideation. *JAMA Internal Medicine*, **174**, 1863-1865.
- Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, Herings RM, Mann JJ** (2007). Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *American Journal of Psychiatry*, **164**, 1356-1363.
- Hammad TA, Laughren T, Racoosin J** (2006). Suicidality in pediatric patients treated with antidepressant drugs. *Archives of General Psychiatry*, **63**, 332-339.
- Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN** (2012). Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, **11**, CD004851.
- Hill AB** (1965). The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine*, **58**, 295-300.
- Miller M, Swanson SA, Azrael D, Pate V, Sturmer T** (2014). Antidepressant dose, age, and the risk of deliberate self-harm. *JAMA Internal Medicine*, **174**, 899-909.
- Sharma T, Guski LS, Freund N, Gotzsche PC** (2016). Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ*, **352**, i65.
- Stone MB** (2014). The FDA warning on antidepressants and suicidality--why the controversy? *New England Journal of Medicine*, **371**, 1668-1671.

