# Trends in suicide rates and antidepressants prescribing by sex and race/ethnicity in the United States of America, 1999-2020


## Abstract

*Background*. Previous ecological studies reported that increasing antidepressant prescriptions were associated with decreasing suicide rates.

*Aim*. To determine whether antidepressant prescription prevalence is negatively associated with suicide rates (i.e., as antidepressant prescribing increases, suicide rates decrease) between 1999 and 2020.

*Method*. The study protocol was pre-registered on the Open Science Framework (https://osf.io/978sk/). Publicly available data from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiological Research (CDC WONDER) and Medical Expenditure Panel Survey (MEPS) were used.

*Results*. Overall, both the antidepressant prescription prevalence and suicide rate were increasing from 1990 to 2020 in the US. Positive trends for both outcomes were also evident when analyses were stratified according to sex and/or race/ethnicity. Pearson's correlation analyses consistently found positive associations between antidepressant prescription prevalence and suicide rates.

*Limitations*. Population-level analysis; no clarification of the causal nature of the association observed.

*Conclusion*. The results of our analysis consistently demonstrated positive trends for both antidepressant prescription prevalence and suicide rates overtime as well as positive associations between them. These findings update those from previous studies and are at odds with the notion that, at a population level, more antidepressant prescriptions would lead to lower suicide rates. However, it needs to be acknowledged that ecological studies provide insufficient evidence to infer causality.


**Keywords**: suicide, antidepressants, psychopharmacology, epidemiology.

## Introduction

Various ecological studies from the USA (e.g. Grunebaum et al., 2004) and different European countries (e.g. Gusmao et al., 2013) reported that increasing antidepressant prescriptions were associated with a decrease in suicide rates during the late 1980s and 1990s. These ecological correlations were causally interpreted as suicide-preventive effects of antidepressant treatment (Isacsson et al., 2010) and were also used in influential reviews to support the claim that antidepressants prevent suicides (Mann et al., 2005; Zalsman et al., 2016). However, at least two reviews of ecological studies concluded that the literature does not support the claim that increased antidepressant prescriptions were causally related to lower suicide rates (Baldessarini et al., 2007; Safer and Zito, 2007). These reviews noted the considerable fluctuations in long-term suicide rates, a lack of falling suicide rates in many countries where antidepressant prescription rates have also increased, and that, in most countries, suicide rates started to decline (typically in the mid-1980s) many years before antidepressant prescription rates steeply increased (in the early 1990s). In accordance, in a previous study on long-term suicide trends in Switzerland, Italy, and Austria from about 1950 to 2015, we found no evidence for change of trends in suicide rates related to the introduction of the first antidepressants in clinical practice around 1960 and the beginning of wide-spread antidepressant prescribing with the introduction of the serotonin reuptake inhibitor class of drugs around 1990 (Amendola et al., 2021). In another study, antidepressant prescription rates in US adolescents from 2004 to 2016 were examined and a strong positive correlation (r=0.83) with self-reported suicide attempt rates over that time period was found, indicating that when antidepressant prescription rates fell, so did suicide attempt rates, and when prescriptions rates increased again, suicide attempt rates also increased (Plöderl and Hengartner, 2019). Since the early 2000s suicide rates have consistently been increasing in the US until very recently (Hedegaard et al., 2018; Miron et al., 2019), but to the best of our knowledge, no study has examined this national trend in association with antidepressant prescription rates in the general population.

The aim of the present study is thus to expand previous work in US adolescents by focusing on both adolescents and adults, by considering a longer and more recent observation period, and by

examining associations between antidepressant prescriptions and suicide rates stratified by sex and race/ethnicity. If it is true that antidepressant prescribing is negatively associated with suicide rates (i.e., as antidepressant prescribing increases, suicide rates decrease) and this reflects a causal pharmacological mechanism, then, we should find evidence for such a relationship overall as well as according to sex and race/ethnicity over a long period of observation, that is, from 1999 to 2020.

## Materials & methods

### Data sources and procedure

Our analysis is based on publicly available data from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiological Research (CDC WONDER) and Medical Expenditure Panel Survey (MEPS) databases on suicide rates and antidepressant prescribing, respectively. The reference period for the analysis of the study is 1999-2020, the longest time-period where relevant information for our study is available in both databases. The CDC WONDER database provides yearly age-adjusted suicide rates (per 100,000 persons) and standard errors for the period of interest. Regarding antidepressant prescribing, we linked the full-year consolidated data file with the prescribed medicine data file of the MEPS database and used a complex sampling design to obtain yearly weighted prevalence estimates of antidepressant prescribing reported as percentages (i.e., percentage of persons who obtained or purchased at least one prescription during each MEPS round).

In line with the aims of the study, we generated data for the whole population, and according to sex, race/ethnicity (i.e., Hispanic, non-Hispanic American Indian or Alaska Native (AI-AN), non-Hispanic Asian or Pacific Islander (A-PI), non-Hispanic Black, non-Hispanic White), and both sex and race/ethnicity. Then, trends in the suicide rate and antidepressant prescription prevalence were compared. We expected a higher degree of variability in estimates of the AI-AN group compared to those of the other groups due to relatively small sample size and, therefore, decreased power to compute reliable antidepressant prescription estimates. This may particularly

occur when stratifying by both sex and race/ethnicity, also for the A-PI group. Thus, we interpret the study findings for these groups with caution.

According to Swiss law, the study was exempt from approval by an ethics committee because all data were de-identified and publicly available.

**Statistical analysis**

To detect changepoints in the time series of the suicide rate and antidepressant prescribing prevalence, we used a segmented regression analysis using the Joinpoint software from the National Cancer Institute (National Cancer Institute, 2022). To fit a Joinpoint regression model, we assumed that the errors were heteroscedastic and/or correlated by performing weighted least squares (WLS) analysis (i.e., using the Standard Error (Provided) option). We specified a first-order autocorrelation estimated from the data as an error model to fit. Further, we chose a log-linear model. This model was used to estimate the annual percent change (APC) in suicide rate and antidepressant prescribing prevalence as well as the number and location of joinpoints, based on linear regression with the log suicide rate and antidepressant prescribing prevalence as dependent variables and the year as independent variable. As recommended by the National Cancer Institute (National Cancer Institute, 2022), the default maximum number $N$=4 Joinpoints for $N$=22 observations (from 1999 to 2020) was used. The permutation test was used for choosing the model with the best fit to the data because it produces parsimonious results, that is, it detects fewer joinpoints than other approaches, especially if the slope changes are small (Kim et al., 2000, National Cancer Institute, 2022). In the final model, joinpoints indicate the points in time when changes in long-term trends occur. The APC, based on the slope of the line segment, describes a positive trend (positive APC value) or negative trend (negative APC value).

Moreover, we carried out comparability tests to compare suicide rates and antidepressant prescribing prevalence again using the Joinpoint software. Specifically, we tested whether the two regression mean functions were parallel (test of parallelism). In doing so, we used all the above specifications except for an uncorrelated error model to fit because autocorrelated error models are not available with the comparability tests. Errors of the two compared series may be considered

uncorrelated or only partially correlated because estimates come from different sources of the same population (i.e., antidepressant prescribing from a national survey and suicide rates from data based on death certificates for US residents). The objective of the test is in comparing the slopes and change points (not in the intercepts) and it is conducted under $K_{max}$ joinpoints, where $K_{max}$ is the maximum of the estimated number of joinpoints for each group fit separately, and for the two groups fit together under the assumption of parallelism (Kim et al., 2004; National Cancer Institute, 2022). The test for parallelism is then performed after the three models are fitted.

Finally, we carried out different tests of association as part of a sensitivity analysis examining the relationship between the variables of interest overtime. Pearson's correlation analysis, linear regression model (controlling for the effect of time), partial correlation analysis (controlling for the effect of time), correlation of annual change (after detrending by differencing), mixed model controlling for autocorrelation and covarying for the effect of time, and mixed model controlling for autocorrelation and using detrended data were applied.

The study protocol was preregistered online on the Open Science Framework (https://osf.io/978sk/).

## Results

### Trends in antidepressant prescription prevalence and suicide rate in the USA population

Four joinpoints were detected for antidepressant prescription prevalence and two for suicide rate (Table 1, Figure 1). Antidepressant prescription prevalence significantly increased between 1999 and 2002 by 11.9% per year. Later, the trend was mainly stable until 2007 when a new significant increase by 3.6% per year until 2012 was detected. Thereafter, antidepressant prescription prevalence was stable until 2017 when a new positive trend began. Antidepressant prescription prevalence significantly increased by 3.3% between 2017 and 2020.

Suicide rate significantly increased by 0.8% per year between 1999 and 2006. Afterwards, a stronger positive trend was shown with an increase of 2.1% per year until 2018, when a decline emerged.

Even though both antidepressant prescription prevalence and suicide rate consistently rose between 1999 and 2020, the hypothesis of parallelism of the two joinpoint regression models was rejected ($p$= 0.001).

[insert table 1 about here]

[insert figure 1 about here]

**Trends in antidepressant prescription prevalence and suicide rate stratified by sex**

Overall, trends in antidepressant prescription and suicide rate were positive in both females and males, as shown in Figure 2.

Regarding female sex, three joinpoints were detected for both antidepressant prescription prevalence and suicide rate (Table 1, Figure 2a). Antidepressant prescription prevalence significantly increased by 9.1% per year between 1999 and 2003. The trend between 2003 and 2010 was mainly stable, despite characterized by a decrease of 2.6% per year until 2007 and an increase of 4.9% afterwards. A significant positive trend was detected between 2010 and 2020 with an increase of antidepressant prescription of 1.1% per year. Suicide rate significantly increased between 1999 and 2015 by 2% and 3.3% per year until 2008 and 2015, respectively. Then, suicide rate was mainly stable between 2015 and 2018. Thereafter, a significant decrease by 5.2% per year was observed until 2020. The hypothesis of parallelism of the two joinpoint regression models was rejected ($p$<0.001).

Regarding male sex, one joinpoint was detected for antidepressant prescription prevalence while three for suicide rate emerged (Figure 2b). Antidepressant prescription prevalence constantly increased overall. Indeed, a significantly positive trend by 1.8% per year was found between 2001 and 2020. Similarly, suicide rate was mainly stable between 1999 and 2006. Thereafter, it significantly increased by 1.6% per year until 2015. An increase of 2.6% per year was shown

between 2015 and 2018, followed by a decrease of 1.8% until 2020. The hypothesis of parallelism of the two joinpoint regression models was not rejected ($p$=0.13).

[insert figure 2 about here]

**Trends in antidepressant prescription prevalence and suicide rate stratified by race/ethnicity**

Overall, trends in antidepressant prescription and suicide rate were positive in all race/ethnicity groups with more pronounced increases for the AI-AN and White groups and less pronounced for the A-PI group (Table 2, Figure 3).

In the Hispanic group, four joinpoints were found for antidepressant prescription prevalence and one for suicide rate (Figure 3a). Antidepressant prescription prevalence increased by 11.8% per year until 2001 and thereafter by 4% until 2005. Between 2005 and 2008 it decreased by 3.5% per year. Afterwards, antidepressant prescription prevalence significantly increased by 3.1% per year until 2018. Similarly, suicide rate was mainly stable between 1999 and 2012. Then, it constantly rose by 3.8% per year until 2020. The hypothesis of parallelism of the two joinpoint regression models was rejected ($p$=0.02).

[insert Table 2 about here]

Regarding the AI-AN group, four joinpoints were detected for antidepressant prescription prevalence while no joinpoint was found for suicide rate (Figure 3b). Antidepressant prescription prevalence increased by 121.9% per year between 1999 and 2001. Then, it significantly decreased by 11.7% per year until 2007 when it rose by 19.8% per year until 2011. Between 2011 and 2014, antidepressant prescription prevalence decreased by 13.7% per year. Thereafter, it significantly increased by 12.1% per year until 2020. Conversely, a constantly positive trend in suicide rate was detected. It increased by 3.3% per year over the entire period of the study. The hypothesis of parallelism of the two joinpoint regression models was rejected ($p$=0.02).

In the A-PI group, one joinpoint was shown for both antidepressant prescription prevalence and suicide rate (Figure 3c). Antidepressant prescription prevalence decreased by 3.3 per year between 1999 and 2009 whereas it significantly increased thereafter by 4.4% until 2020. Similarly, suicide rate was mainly stable until 2005. Then, it increased by 1.7% per year until 2020. The hypothesis of parallelism of the two joinpoint regression models was not rejected ($p$=0.14).

Regarding antidepressant prescription and suicide rate in non-Hispanic Blacks, three joinpoints were detected for both (Figure 3d). Antidepressant prescription prevalence significantly increased by 20.5% per year between 1999 and 2002. Afterwards, it was mainly stable except for a positive trend between 2009 and 2012 due to an increase of 8.3% per year. Suicide rate significantly decreased by 1.1% per year between 1999 and 2007. Thereafter, it consistently increased by 1.4% per year until 2015 and 7.6% between 2015 and 2018. Then it increased by 2.6% until 2020. The hypothesis of parallelism of the two joinpoint regression models was rejected ($p$=0.001).

In non-Hispanic Whites, three joinpoints were highlighted for antidepressant prescription prevalence and four for suicide rate. Both antidepressant prescription and suicide rate significantly increased until 2002 by 12.1% and 2.6% per year, respectively. Afterwards, they were mainly stable until 2005/2007. Then, significant positive trends emerged , and antidepressant prescription significantly increased by 1.8% per year between 2011 and 2020. Suicide rate increased by 2-3% per year until 2018 when a decrease of 3.2% per year was observed until 2020. The hypothesis of parallelism of the two joinpoint regression models was rejected ($p$=0.02).

[insert figure 3 about here]

Results stratified by race/ethnicity and sex are reported in Table S1 and Figure S1 (Supplementary material). Results for American Indian and Alaska Native and Asian or Pacific Islander groups stratified by sex were unreliable due to huge variability in the data and should be interpreted with caution.

**Sensitivity analysis**

The results of the sensitivity analysis are reported in Table S2 (Supplementary material). Pearson's correlation analyses consistently found positive associations between antidepressant prescription

prevalence and suicide rates, with *r* values ranging from 0.94 (White group) to 0.01 (AI-AN male subgroup). More parsimonious analyses considering the effect of linear trend in the data and/or autocorrelation demonstrated lower coefficients compared to the results of Pearson's correlation analysis. However, those results still pointed to a positive association, if any, between the two variables with few exceptions due to the AI-AN, A-PI, and Black subgroups, characterized by less representative sample size compared to Hispanic and White groups.

## Discussion

In this study, we investigated the association between suicide rates and antidepressant prescription prevalence at the population level in the USA over a long period of time (1999-2020) and applied stratification by sex and/or race/ethnicity. We tested whether antidepressant prescription prevalence was negatively associated with suicide rate (i.e., as antidepressant prescribing increases, suicide rate decrease), as supported by findings of previous studies mostly focusing on the 1990s and early 2000s (Grunebaum et al., 2004; Gusmao et al., 2013). This led some authors to conclude that, at a population level, prescribing more antidepressants would causally lower the suicide rate (Isacsson et al., 2010). By examining more recent suicide and prescription data, our findings did not provide evidence for such an inverse causal relationship. On the contrary, the results of our analysis consistently demonstrated positive trends for both antidepressant prescription prevalence and suicide rates overtime as well as positive associations between them.

In line with findings of previous reviews (Baldessarini et al., 2007; Safer & Zito, 2007) and various ecological studies (Amendola et al., 2021; Dahlberg & Lundin, 2005; Ploderl & Hengartner, 2019; Zahl et al., 2010), our findings are at odds with the notion that increased antidepressant prescribing is causally related to decreased suicide rate. Indeed, the findings of previous studies showing negative associations were limited by short observation periods or by not considering that declining (negative) suicide trends preceded the huge increase in antidepressant prescriptions in the '90s (clearly visible in near all, if not all, subfigures shown in Gusmao et al., 2013), therefore, leading to

the detection of spurious negative correlations. This points to the importance of considering long-term trends (Amendola et al., 2021; Reseland et al., 2006). Our analyses showed that, when considering the effect of linear trend in the data and/or autocorrelation, estimates of the associations were lower compared to the high Pearson's correlation coefficients. However, those results overall still pointed to a positive association between antidepressant prescription prevalence and suicide rate.

Our findings are also consistent with the results of many meta-analyses of observational studies and clinical trials. These do not indicate that antidepressants prevent suicides, in fact there is even some evidence that they might increase the suicide risk (Baldessarini et al., 2017; Braun et al., 2016; Hengartner et al., 2021; Hengartner & Ploderl, 2019; Ploderl et al., 2020; Stone et al., 2009). The strong emphasis put on the results of selected ecological studies that putatively demonstrate a causal suicide-preventive effect of antidepressants (see Isacsson et al., 2010) is thus not warranted and conflicts with all other lines of evidence.

Some limitations should be considered when interpreting the findings of our study. First, we examined trends and ecological correlations at the population level. Thus, our results should not be interpreted at the individual level. Further, they cannot clarify the causal nature of the association observed, i.e., whether the increase in suicide rate is a consequence of increased antidepressant prescription or, conversely, the increase in antidepressant prescription is due to increased suicide rate in the population. An alternative explanation points to the role of different external factors influencing antidepressant prescription and suicide rates, such as economic/financial crises (Huikari et al., 2019; Luo et al., 2011). Finally, the test of parallelism does not provide information on where differences in two series occur when parallelism is rejected, limiting the interpretability of the associated results.

## Conclusion

Our analysis of antidepressant prescribing prevalence and suicide rate in the USA from 1999 to 2020 does not support the notion that, at a population level, more antidepressant prescriptions would lead to lower suicide rate. Both antidepressant prescription and suicide rate showed upward

trends, and although tests of parallel trends were mostly negative, Pearson correlations indicated significant positive associations in most subgroups. Nevertheless, no causal conclusions should be drawn from these data.

**Electronic Supplementary Material**

ESM 1. Tables S1–S2, Figure S1. The tables and figure show information on trends in antidepressant prescription prevalence and suicide rate stratified by race/ethnicity and sex.

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**Table 1.** Annual Percentage Change (APC) in antidepressant prescription prevalence and suicide rate according to joinpoint regression models, overall and stratified by sex.

| Sex | Variable | Period | APC (95% CI) |
|---|---|---|---|
| All | Antidepressant prescription | 1999 - 2002 | 11.9 (8.1, 15.8) |
| | | 2002 - 2007 | -0.6 (-2.3, 1.0) |
| | | 2007 - 2012 | 3.6 (1.7, 5.5) |
| | | 2012 - 2017 | 0.5 (-1.4, 2.5) |
| | | 2017 - 2020 | 3.3 (0.2, 6.4) |
| | Suicide | 1999 - 2006 | 0.8 (0.5, 1.1) |
| | | 2006 - 2018 | 2.1 (1.9, 2.2) |
| | | 2018 - 2020 | -2.3 (-4.7, 0.2) |
| Female | Antidepressant prescription | 1999 - 2003 | 9.1 (6.5, 11.8) |
| | | 2003 - 2007 | -2.6 (-6.3, 1.3) |
| | | 2007 - 2010 | 4.9 (-3.4, 13.9) |
| | | 2010 - 2020 | 1.6 (1.1, 2.2) |
| | Suicide | 1999 - 2008 | 2.0 (1.7, 2.3) |
| | | 2008 - 2015 | 3.3 (3, 3.8) |
| | | 2015 - 2018 | 1.5 (-1.5, 4.6) |
| | | 2018 - 2020 | -5.2 (-8.5, -1.8) |
| Male | Antidepressant prescription | 1999 - 2001 | 16.2 (-4.9, 42) |
| | | 2001 - 2020 | 1.8 (1.4, 2.1) |
| | Suicide | 1999 - 2006 | 0.3 (-0.2, 0.8) |
| | | 2006 - 2015 | 1.6 (1.2, 2.0) |
| | | 2015 - 2018 | 2.6 (-0.7, 6.0) |
| | | 2018 - 2020 | -1.8 (-4.9, 1.4) |

**Table 2.** Annual Percentage Change (APC) in AD prescription prevalence and suicide rate according to joinpoint regression models, stratified by race/ethnicity.

| Race/Ethnicity | Variable | Period | APC (95% CI) |
|---|---|---|---|
| Hispanic | Antidepressant prescription | 1999 - 2001 | 11.8 (-9.9, 38.8) |
| | | 2001 - 2005 | 4.0 (-1.0, 9.2) |
| | | 2005 - 2008 | -3.5 (-16.6, 11.6) |
| | | 2008 - 2018 | 3.1 (2.4, 3.8) |
| | | 2018 - 2020 | -3.9 (-18.8, 13.8) |
| | Suicide | 1999 - 2012 | 0.0 (-0.4, 0.4) |
| | | 2012 - 2020 | 3.8 (3.1, 4.4) |
| AI-AN | Antidepressant prescription | 1999 - 2001 | 121.9 (-24, 547.7) |
| | | 2001 - 2007 | -11.7 (-18.9, -3.7) |
| | | 2007 - 2011 | 19.8 (-6.6, 53.6) |
| | | 2011 - 2014 | -13.7 (-50, 49) |
| | | 2014 - 2020 | 12.1 (4.6, 20.2) |
| | Suicide | 1999 - 2020 | 3.3 (3.1, 3.6) |
| A-PI | Antidepressant prescription | 1999 - 2005 | -0.5 (-2.3, 1.3) |
| | | 2005 - 2020 | 1.7 (1.4, 2.1) |
| | Suicide | 1999 - 2009 | -3.3 (-6.8, 0.3) |
| | | 2009 - 2020 | 4.4 (1.9, 7.0) |
| Black | Antidepressant prescription | 1999 - 2002 | 20.5 (9.0, 33.4) |
| | | 2002 - 2009 | -0.6 (-3.2, 2.1) |
| | | 2009 - 2012 | 8.3 (-5.7, 24.3) |
| | | 2012 - 2020 | -0.6 (-2.0, 0.8) |
| | Suicide | 1999 - 2007 | -1.1 (-1.5, -0.6) |
| | | 2007 - 2015 | 1.4 (0.8, 2.1) |
| | | 2015 - 2018 | 7.6 (2.6, 12.8) |
| | | 2018 - 2020 | 2.6 (-1.6, 7.0) |
| White | Antidepressant prescription | 1999 - 2002 | 12.1 (6.4, 18.2) |
| | | 2002 - 2007 | -0.1 (-2.7, 2.7) |
| | | 2007 - 2011 | 4.6 (-0.4, 9.8) |
| | | 2011 - 2020 | 1.8 (1.0, 2.6) |
| | Suicide | 1999 - 2002 | 2.6 (0.7, 4.5) |
| | | 2002 - 2005 | 0.5 (-3.7, 4.8) |
| | | 2005 - 2010 | 2.9 (2.0, 3.8) |
| | | 2010 - 2018 | 2.3 (2.1, 2.6) |
| | | 2018 - 2020 | -3.2 (-6.6, 0.3) |

*AI-AN:* non-Hispanic American Indian or Alaska Native, *A-PI:* non-Hispanic Asian or Pacific Islander.

**Figures**

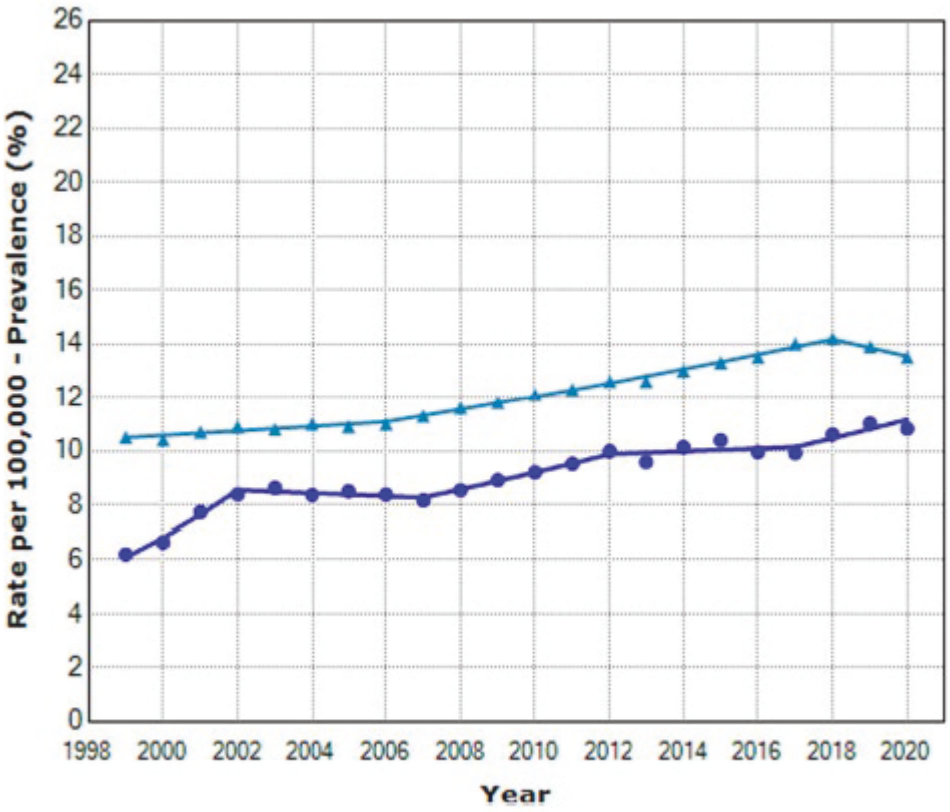


**Figure 1.** Trends in antidepressant prescription prevalence (dots) and suicide rate (triangles) in the USA, 1999-2020.

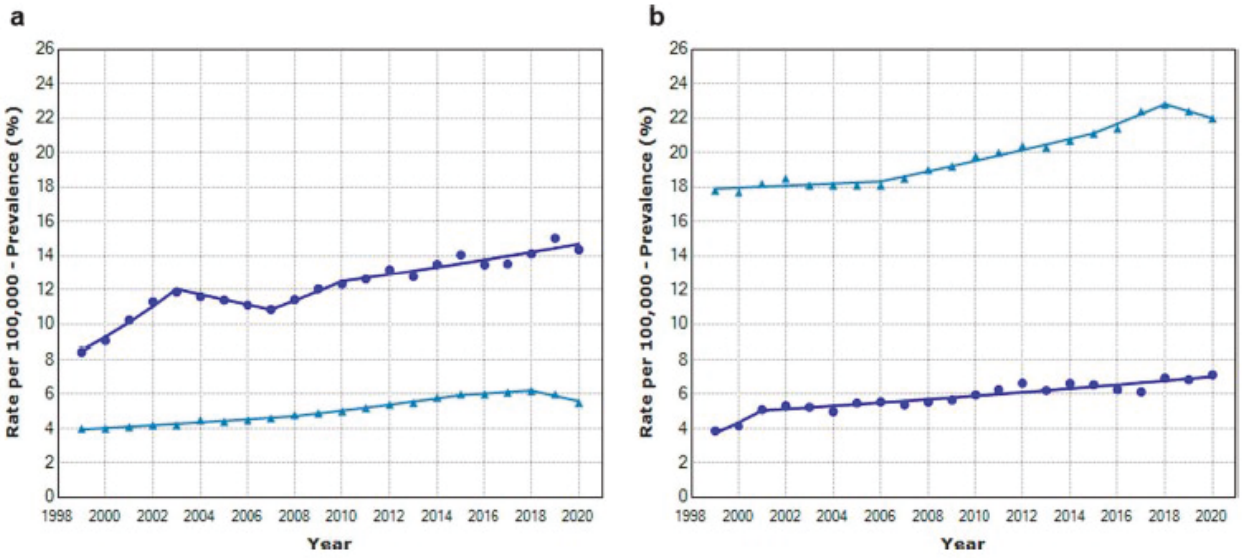


**Figure 2.** Trends in antidepressant prescription prevalence (dots) and suicide rate (triangles) in the USA stratified by sex (female in 2a, male in 2b), 1999-2020.

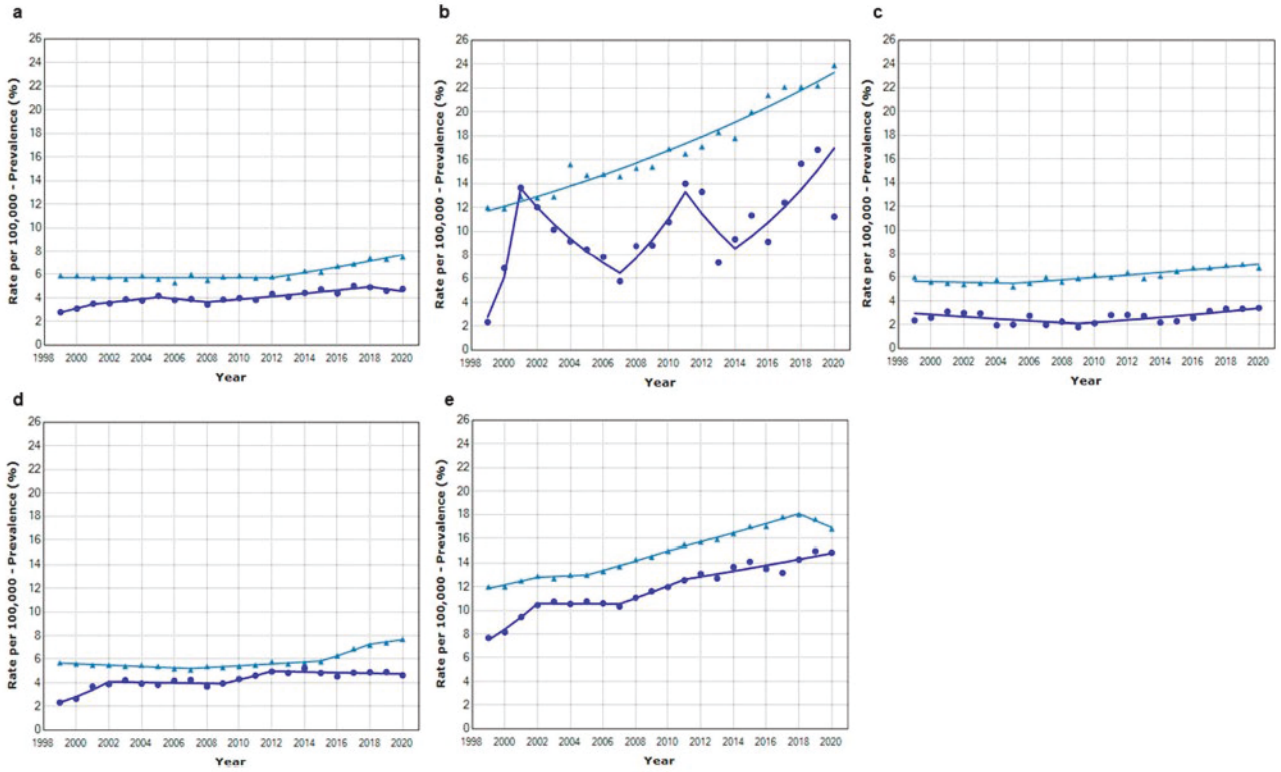


**Figure 3.** Trends in antidepressant prescription prevalence (dots) and suicide rate (triangles) in the USA stratified by race/ethnicity (Hispanic in 3a, AI-AN in 3b, A-PI in 3c, Black in 3d, and White in 3e), 1999-2020.