

## Do rising rates of antidepressant prescription translate into lower rates of suicide?

*Professor James Coyne discusses his recent research into the correlation between the growing use of prescription antidepressants and decreasing suicide rates, with evidence drawn from 29 countries.*

According to **media reports**, trace amounts of antidepressants are now being found in the drinking water. Apparently the drugs get into the sewage water, presumably flushed down the toilet, and then they make it intact through waste water filtering and processing into the water supply. These minuscule amounts are not of clinical and public health importance, except as just another indication of the high rates of prescription of antidepressants in the United States and other industrialized countries. A **2011 data brief** from the US Center for Disease Control and Prevention indicates that antidepressant use in the United States had increased 400% from 1988 – 2008. Antidepressants are now the most commonly prescribed drugs for persons aged 18 to 44.

Questions can be raised as to just what public health benefits are being obtained by this costly increase in prescription of antidepressants. Claims that widespread use of the newer antidepressants has decreased rates of suicide have found considerable support, but have been met with controversy. Just when all the press was describing the serotonin reuptake inhibitor *fluoxetine* (tradename *Prozac*) as a wonder drug, Martin Teicher and his colleagues attracted considerable attention with claims that the drug precipitated “**intense suicidal preoccupation.**” These observations were based on six cases. In hindsight, these adverse reactions were probably idiosyncratic and relatively rare and were not replicated in a **subsequent meta-analysis** of a larger sample.

In a **recent PLOS One article**, I joined an international group in examining whether a signal could be found that increasing rates of antidepressant prescription were having a payoff in decreasing rates of suicide in data obtained from 29 European countries. It had already been noticed that that an *increase* in antidepressant prescriptions had been occurring in the past decade, as well as an overall *decrease* in rates of suicide in most of these countries. But the question that we wanted to address was whether the two trends could be linked. Basically, we obtained administrative data concerning both these trends and examined them in ecological analyses, a study design that I will explain later in the blog post.

The strongest test of whether antidepressants reduce suicide would be a randomized trial, but there are practical limitations on such a study being conducted. Suicide is indeed a public health problem with devastating consequences to persons who commit suicide and their family members, and suicide carries a lot of associated social costs in terms of a wasted life. Yet suicide occurs infrequently enough that so that would be difficult to have a clinical trial that had sufficient statistical power to demonstrate an effect—that the intervention group had a statistically significant reduction versus the number of suicides occurring in the control group. **Isaacson** estimated that given the infrequency of suicide, a randomized trial would have to have a combined intervention and control group of 20,000 persons.

In the late 90s, US **Senator Harry Reid** nonetheless requested that NIMH solicit applications for a clinical trial that would test whether intervening with primary care physicians could conceivably reduce suicides in the elderly. Contrary to the myths about suicide, elderly males, particularly those living alone, are among the highest risk populations. Senator Reid had a personal stake in the matter. His father had committed suicide just after a visit to his primary care physician, and Senator Reid reasoned that if the primary care physician had been alert to his father’s mental state, his father’s life may have been saved.




I was a professor in the departments of family medicine and psychiatry at the University of Michigan study and depression in primary care at the time, and I was approached by a NIMH program officer to submit a proposal responsive to Senator Reid's requests. I was sympathetic to the senator's concern, but I declined, telling the program officer that it would be unlikely a clinical trial targeting the vigilance of primary care physicians concerning risk of suicide would be able to show any effect. I calculated that typical primary care physicians would probably encounter a clinical situation only about every 18 months in which their actions could conceivably make a decisive difference in whether a patient committed suicide.

NIMH was nonetheless anxious to meet Senator Reid's request, and so they funded a study that became known as **PROSPECT**, the Prevention of Suicide in Primary Care Elderly: Collaborative Trial. The study evaluated an intervention that involved putting depression care managers into primary care practices to improve the delivery of depression care to older patients, mainly antidepressants, but with interpersonal therapy offered as a supplement. In writing their successful proposal, the investigators realized that suicide could not be the primary outcome if they were expecting a positive trial. Instead, they selected a clinically significant reduction in suicidal ideation, that is, patient reports of self harm or thoughts they would be better off dead. This is a surrogate outcome, not the same as suicide, but maybe reducing suicidal ideation could be seen as a step along the way to reducing suicide. Of course, this depends on the strength of the relationship between measures of suicidal ideation and the patient subsequently committing suicide being sufficiently strong.

**I have noted** that expressions of serious suicidal ideation are relatively uncommon among primary care patients, with most endorsements not carrying much thread of lethality. So such self-reports do not really tell us much whether we are dealing with the likelihood of a death by suicide. That is the main reason why the **United States Preventive Services Task Force does not recommend** screening primary care patients for suicidality.

Belatedly, the PROSPECT investigators discovered this problem in the base rate of suicidal ideation, as I noted in a recent **BMJ Rapid Response**. The investigators had recruited 18 primary care practices and were screening patients for depression and suicidal ideation. They administered a standardized, clinician-rated measure of suicidal ideation, the Scale for Suicidal Ideation (SSI), and immediately discovered that that the primary care patients were not reporting much suicidal ideation. In order to salvage their trial, they changed their primary outcome to whether primary care patients endorsed any suicidal ideation versus whether they endorsed none. Thus, to be designated as having suicidal ideation, patients only had to indicate not having a moderate or strong wish to live or that they would leave life/death choice to chance rather than taking precautions to save their life. Still, when the investigators had collected baseline data from the 589 patients who were randomized with a depressive diagnosis, only about a quarter were rated as having endorsed any suicidal ideation whatsoever. And when actual results of the PROSPECT study were reported, only two patients, one in the intervention group and one in the control group who completed suicide. In effect, PROSPECT did not end up being about reducing clinically significant suicidal ideation and certainly not about suicidality.

Can we reasonably expect any intervention study to demonstrate a significant reduction in suicidality? The **Nuremberg Alliance against Depression (NAD)** got off to a promising start by implementing a multilevel intervention program in the city of Nuremberg with 480,000 inhabitants and used Wuertzburg with 270,000 inhabitants as a control group. The intervention involved providing primary care physicians with training and support in dealing with depression and suicidality, but also mobilizing community facilitators (teachers, priests, and local media), a public relations campaign and support for self-help activities. The outcome was whether there was a two-year reduction in the number of suicidal acts (attempted suicides plus completions) in the intervention versus control group. A significant reduction was indeed observed, but there were no significant differences between the two regions for completed suicides. The number of suicides in Nuremberg fell from 100 at baseline to 75 during the first and 89 during the second year of the intervention, but in the control region Wuertzburg from 58 baseline to 42 in the first year and 40 in the second year. Basically, high annual fluctuations in suicides in both regions swallowed **any** 

possible effect of the intervention. Figure 4 from the report of the NAD, which demonstrates this fluctuation going back to eight years before the trial was implemented, captures this.

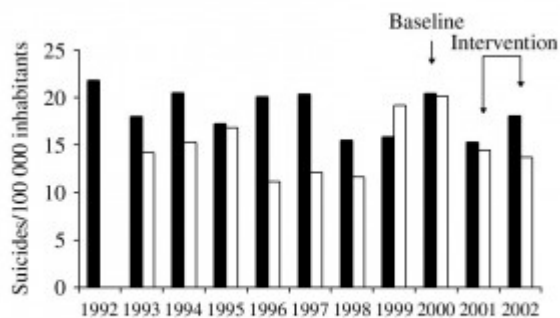


FIG. 4. Suicide rates in Nuremberg (■) and Wuerzburg (□) from 1992 to 2002.

So, keep in mind the bottom line as I discuss our study in PLOS One and call attention to the study's limitations. Suicide is an important public health issue, but it is difficult to demonstrate any effects of an intervention aimed at reducing it. In conducting our study, our first aim was to determine whether we could detect an effect of the increased use of antidepressants on European suicide rates and to explore the plausibility of some competing explanations. Our second aim was to see if there was patterning over time, such that declining rates of suicide preceded or followed upon the increased use of antidepressants.

## What we did

Our study was observational, correlating the trend in increasing rate of antidepressant prescription with trends in suicide across 29 European countries. We obtained data concerning completed suicides from the WHO European Region Health for All Database. Country level data for prescription of antidepressants were obtained from both the **IMS** and **Organization for Economic Cooperation and Development** (OECD) wherever possible, but for some countries only IMS data were available. We standardized our measures of both suicide and antidepressant to control for size of population, yielding a **standardized death rate (SDR)** for suicide per thousand persons per day and **defined daily dosage (DDD)** per thousand persons per day for antidepressant prescription. The SDR is a nifty weighted average of age-specific death rates that allows comparisons between countries that differ in their age structure. The DDD allows comparisons across different antidepressants. We introduced statistical controls for alcohol consumption, unemployment and divorce and gross national product (GNP).

## What we found

There were marked differences in suicide SDR/thousand persons/day rates across Europe, but also high consistency in those countries with the lowest and highest rates of suicide over the study period.

The greatest reductions in suicide rates tended to occur in European countries where there had been a greater increase in prescription of antidepressants.

Portugal was the only country where there was a positive correlation over time between antidepressant utilization and suicide. Perhaps this result might be explained by a lack of precision in the Portuguese suicide registry, with some overestimate of undetermined violent deaths at the expense of estimates of suicide.

The results held when the control variables were introduced.

Overall, our analyses indicated that for 15 years of data on average for the 29 countries included in our study, the use of antidepressants increased by 20% per year by the end of this time period.

for the whole study area and there had been an average increase of 40.33 units of DDD per thousand people per day. Over a mean period of 28 years the overall SDR for suicide decreased at a rate of .81% per year.

What does this mean in practical terms? For each additional person per 1000 population who receives a defined daily dose of antidepressant, the age-adjusted absolute risk of death from suicide in that 1000 population decreases by a small but significant 0.088 fewer deaths. Put differently, providing 650 persons at risk for suicide with antidepressants could save one life. While we cannot talk about causality, within the limits of our methods, our results provide an endorsement of a role for antidepressant prescriptions in reducing rates of suicide on a public health basis.

### What were the limitations of our study?

There are lots of limitations to our study starting with it being an **ecological study**, which is

an epidemiologic study in which the unit of analysis is a population rather than an individual. For instance, an ecological study may look at the association between smoking and lung cancer deaths in different countries.

An ecological study can be distinguished from a case-control study in which we compare people who ultimately committed suicide to those who did not in terms of whether they had been taking an antidepressant. Ecological studies are subject to the **ecological fallacy**, if we are not careful in making interpretations.

The classic example of a potential ecological fallacy in suicide research is interpreting **Emile Durkheim's** finding that suicide rates were higher in Protestant countries than in Catholic countries in terms of individual Protestants being more likely to commit suicide than Catholics. With only country level data, we could not necessarily determine that some or all of the effect could be due to Catholics in Protestant countries being more likely to commit suicide.

We have potential for an ecological fallacy in our own study. The countries with the highest economic disruption and unemployment had the lowest rates of suicide, but that doesn't necessarily say anything about the likelihood of an unemployed person in these countries committing suicide.

So, with epidemiologic studies, we always need to caution that correlation does not equal causality. Yet, further, with ecological studies we need to additionally caution that ecological correlations, and in our case correlations within and between countries do not necessarily equate with correlations for individuals.

We assume that the suicide recording procedures remained the same in the countries involved throughout the study period, that is, the criteria for deciding what is a suicide versus an unexplained death and the accuracy with which cause of death was being preserved. If it happened to be a period in which suicide was being stigmatized, relative rates of deaths being attributed to suicide could have been increasing.

It is possible that the long term trends in suicide reduction we picked up in our time frame were already occurring before the introduction of newer antidepressants and so the antidepressants cannot serve as an explanation.

We did not take receipt of psychotherapy into account, which is undoubtedly important, but cannot be so readily measured on a population basis



We only controlled for a limited number of confounding factors and missed a lot. For instance, the same period in which antidepressant prescriptions were increasing was also a period in which there was considerable campaigning to educate and improve the performance of primary care physicians in dealing with depression. We cannot separate out the independent influences of the increase in prescriptions and the increased priority being given to physicians treating depression.

Perhaps the most questionable assumption of our study is that we can assume much of a relationship between dispensing antidepressants and the right people receiving them in an appropriate dosage with appropriate follow-up. As I have mentioned in previous blogs, most antidepressants are dispensed in primary care, where routine care for depression is notoriously bad. We can assume that many of the antidepressants were dispensed without a proper diagnosis being made and many of the patients receiving them had little or no further contact with their prescribing physician. As many as 40% of patients receiving an antidepressant primary care get no more benefit than if they had would remained on a waiting list.

If we try to take these factors into account, and attach some credibility to our results, then improving the quality of routine care for depression in primary care can have an added payoff for reducing suicide. But just try to demonstrate that in an intervention trial.

## Acknowledgments

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## Conflict of Interest Statement

I served as a consultant to PROSPECT, but was not involved in the revision of the primary outcome of that study. I also served as external scientific advisor to the Nuremberg Alliance against Depression and to a decade of successor projects financed by the European Union modeled after it.

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