Anti-Depressants, Suicide, and Drug Regulation

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Abstract

Policymakers are increasingly concerned that a relatively new class of anti-depressant drugs, selective serotonin re-uptake inhibitors (SSRI), may increase the risk of suicide for at least some patients, particularly children. Prior randomized trials are not informative on this question because of small sample sizes and other limitations. Using variation across countries over time in SSRI sales and suicide, we find that an increase of one pill per capita (a 13 percent increase over 1999 levels) is associated with a 2.5 percent reduction in suicide rates, a relationship that is more pronounced for adults than for children. Our findings suggest that expanding access to SSRIs for adults may be a cost-effective way to save lives, although policymakers are right to remain cautious about pediatric use of SSRIs. © 2005 by the Association for Public Policy Analysis and Management

INTRODUCTION

In June, 2003, the United Kingdom's Department of Health and the United States Food and Drug Administration (FDA) cautioned the public about the use of paroxetine, a member of the selective serotonin re-uptake inhibitors (SSRI) class of antidepressants, for people under 18 years of age (U.K. Department of Health, 2003; FDA, 2003). In December 2003, the U.K. told doctors to stop using all but one type of SSRI for young patients (Goode, 2003a). The motivation for these warnings comes in part from recent unpublished studies that associate paroxetine with increased self-harm and potentially suicidal behavior among children.[1] The result of the warnings has been, as one psychiatrist told the *New York Times,* "anxiety, concern, and questions" about the use of one of the most popular classes of prescrip-

[1] The original source for this concern came from data submitted to the government by GlaxoSmithKline (Harris, 2004). More recently, the FDA ordered a re-analysis of data from a broader set of drug companies and found that SSRI use increases "suicide related events" among treated children compared to controls. One challenge comes from divining intent from potentially ambiguous events; for example, as a recent review notes, "[Dr. Robert Temple of the FDA added] some of the behaviors labeled 'suicidal' were highly suspect and could have been accidents, such as a child 'who hit her head with her hand.' FDA officials acknowledged, however, that some cases classified as 'accidental injury' could be suicide related. Because of this, the FDA has contracted with Columbia University to further study and classify events that might be considered to be suicide related" (Lenzer, 2004, p. 307).

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tion drugs in the United States, which includes Prozac, Paxil, and Zoloft (Goode, 2003b). American doctors, patients, and policymakers seeking additional guidance about whether SSRIs should be used to treat depressed children—or adults, for that matter—will confront a medical and public health research literature about SSRI and suicide that is very limited and not very informative. As a recent Institute of Medicine report on suicide notes, "Although the SSRIs reduce depressive symptoms, their potency in reducing suicide is uncertain" (Goldsmith et al., 2002).

Do SSRIs increase or decrease the risk of suicide? Should health policymakers forbid the use of SSRIs in treating depressed patients, or instead expand access or even subsidize the use of these drugs? And why is available research so uninformative about the treatment of a public health problem that claims around 30,000 lives in the United States each year and another 1 million or so around the world (Goldsmith et al., 2002)? The primary objective of this paper is to answer the first two of these questions, although we do also offer some speculative thoughts about the last question as well, which itself has important implications for health policy more generally.

The possibility that SSRIs could in principle reduce suicide is suggested by the well-established link between depression and suicide. Previous research suggests that 30 to 90 percent of those who complete suicide suffered from a depressive disorder (Goldsmith et al., 2002; Lönnqvist, 2000), and that the suicide rate among those with depression may be up to 21 times the population rate (Harris & Barraclough, 1998). At the same time, previous clinical trials have established the effectiveness of SSRIs in reducing depression (Ryan, 2003; Green, 2003; Vaswani & Ramesh, 2003).[2] For example, in a recent trial, SSRIs were found to nearly double the number of depression-free days compared to placebo (Mallick et al., 2003). While other medications have also been shown to reduce depression, compared to other anti-depressants, the SSRIs are less toxic in overdose and have fewer side effects and so may be prescribed more often and taken for longer durations (Guze, 1996; Lawrenson et al., 2000).

While SSRIs have been shown to reduce depression, a direct link between SSRIs and suicide specifically has to date not been convincingly established. Published results from randomized clinical trials (RCTs) typically provide weak support for an effect of SSRIs on suicide attempts or completions compared to placebo (Beasley et al., 1991; Montgomery et al., 1994; Khan et al., 2000; March et al., 2004). However, for a variety of reasons, previous RCTs are not very informative about the relationship between SSRIs and suicide. For ethical and practical considerations, most clinical trials may avoid enrolling those at highest risk for suicide and typically focus on suicide ideation or "suicide related events" rather than completed suicide. The sample sizes available with most RCTs provided limited statistical power to detect effects on relatively rare events such as suicide. And some trials are further complicated by the provision of mental health services to controls, as well as possible placebo effects (Goldsmith et al., 2002; Kahn et al., 2000, 2001). Given these constraints, it is an open question whether any RCT could ever satisfactorily identify the effects of SSRIs on suicide.

Since randomized trials have not been very informative about the relationship between SSRIs and suicide, a few prior studies have attempted to address this question using nonexperimental methods. However, the research designs used in this literature are quite weak. A number of studies have examined whether suicide rates

[2] A recent meta-analysis of RCTs for SSRI use in children finds an effect on depression of 0.26 standard deviations, although the authors argue this impact is "small" (Jureidini et al., 2004).

are higher or lower after SSRIs enter the market using data from one or a few countries at a time, with mixed results.[3] But each of these before-after comparisons within a given country may confound the causal effects of SSRI use on suicide with other concurrent changes within these countries in other factors that also affect suicide. The difficulties of drawing causal inferences from a single country's time series are highlighted by considering the case of the United States, as in Figure 1, where the vertical line marks the timing of the FDA's approval of the first SSRI for the American market (fluoxetine) in December of 1987 (Goldsmith et al., 2002). While suicide rates are higher in the years just before 1987 than after this point, suicide rates began to decline even before SSRIs came onto the market. On the other hand, the rate of decline in suicide rates appears to have accelerated during the 1990s when SSRI sales increased most dramatically. Our larger point is that a single time-series provides a weak basis for understanding the causal link between SSRIs and suicide.

The two previous studies that are most similar in spirit to ours compare changes in SSRI use and suicide rates over time across areas within a given country. Olfson et al. (2003) focus on changes between 1985–89 and 1995–99 in suicide rates to adolescents within three-digit ZIP code regions. They find that suicide rates for children 10–19 decline more in regions that experience a relatively greater increase in the "antidepressant medication treatment rate," defined as the num-

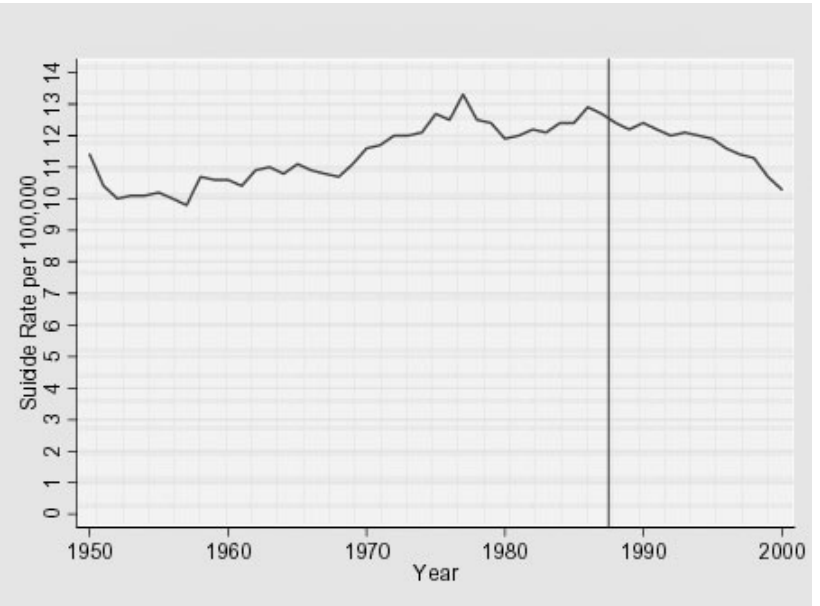


Figure 1. U.S. suicide rates, 1950–2000.

[3] Previous research suggests that national suicide rates declined as SSRI use increased over time in Sweden; similar findings have been obtained for Finland, Norway, and Hungary (Isacsson, 2000; Rihmer et al., 2001; Ohberg et al., 1998). In contrast, Italy did not appear to experience a change in total suicide rates from pre-existing trends following growth in SSRI use (Barbui et al., 1999), while data from Iceland reveals no relationship between the volume of sales of anti-depressant medications more generally and suicide rates (Helgason et al., 2004).

ber of children filling prescriptions for anti-depressant medication divided by the number of children receiving medication of any type (p. 979). One limitation of the study is that any improvements in children's mental or physical health more generally may reduce the number of children receiving any sort of medication (the denominator of their explanatory variable) and thus cause an increase in the anti-depressant medication treatment rate, even without a change in the true rate of anti-depressant use. In contrast, a study from Sweden finds no statistically significant relationship between anti-depressant use and overall suicide rates across counties, although their 95 percent confidence intervals allow for a possible effect in the neighborhood of our own results presented below (Dahlberg & Lundin, 2004).[4]

In what follows, we present new evidence on the relationship between SSRIs and suicide that takes advantage of a "natural experiment" generated by substantial variation across countries over time in when SSRIs were first legally introduced to the market and the rate at which SSRI sales grew over time. While earlier nonexperimental studies focus on one or at most a handful of countries, we draw on annual data for the U.S., Canada, Australia, and 24 European nations collected over a period of nearly 20 years for most countries (1980–2000). We employ a panel-data research design that compares trends in suicide and SSRI use across countries over time that helps rule out a variety of possible confounding factors that may bias previous epidemiological estimates for the SSRI-suicide relationship, such as secular time trends in suicide within or across countries that may coincide with changes in SSRI use.

While our research design represents what is in our view an improvement over most prior nonexperimental studies on this topic, our findings are nonetheless correlational in nature. As with all nonexperimental studies, there necessarily remains some question about whether a true causal relationship has been identified. Nevertheless, given the limits of randomized trials in this application, nonexperimental evidence is likely to be the best guide for health policymakers on this question for the foreseeable future. Our findings on the SSRI-suicide link provide arguably among the best (that is, least imperfect) evidence available to date on this pressing policy question.

Our panel-data analysis suggests that overall suicide rates fell fastest in those countries that experienced the most rapid rate of growth in SSRI sales. In light of the recent actions by the U.K. and U.S. governments, of particular policy interest is whether this relationship differs across age groups. Our ability to identify the SSRI-suicide relationship for particular age groups is limited by the fact that data on SSRI sales (unlike with suicide rates) are only available at the overall country level, not for disaggregated age groups. With this caveat in mind, we find that suicide rates for adults fell most sharply in countries that experienced the greatest increase in overall SSRI sales. In contrast, the relationship between suicide and overall SSRI sales is indeterminate in our data for people under the age of 15. If these findings are correct, the policy community is right to remain cautious about the use of SSRIs with younger patients, while expanding access to SSRIs among adults may be a cost-effective way to save lives.

[4] An alternative approach for using within-country comparison groups is to compare SSRI sales and suicide rates across age groups, to test whether suicide declines are greater for groups that experience relatively larger increases in SSRI use. This approach yields some evidence for a SSRI effect in Australia (Hall et al., 2003), although this is less clear in Swedish data (Dahlberg & Lundin, 2004).

DATA

Annual suicide counts for most countries come from the World Health Organization (WHO), which are in turn obtained from national vital statistics reporting systems. We focus on countries for which we are able to obtain data on SSRI sales (first year of SSRI sales in parentheses): Australia (1990), Austria (1985), Belgium (1985), Belorussia (1997), Bulgaria (1994), Canada (1989), the Czech Republic (1990), Finland (1989), France (1986), Germany (1984), Greece (1990), Hungary (1990), Ireland (1989), Italy (1988), Latvia (1995), Lithuania (1996), Luxembourg (1985), the Netherlands (1985), Norway (1996), Poland (1993), Portugal (1986), the Slovak Republic (1990), Slovenia (1992), Spain (1987), Ukraine (1997), and the United Kingdom (1987). We also included the same suicide information for the United States (1988), obtained from the Centers for Disease Control.

Most of the annual suicide observations in our panel are recorded by national public health systems using the ICD–9 coding system for cause of death, although by the end of our panel some countries used the newer ICD–10 system. While data from the United States suggest that both coding schemes capture suicides in a consistent fashion (Heston, Summers, & Aten, 2002), in our analysis we account for the possibility that a shift from ICD–9 to ICD–10 may produce changes in recorded suicide rates in some countries within our sample.

Data for each country include the annual number of total suicides as well as the number of suicides by gender and by age. We combine information on suicides with data on the total population and population by gender and age group to calculate total as well as gender and age-specific suicide rates per 100,000 people. These data are available through 1999 for all countries, and through 2000 for 13 of our 27 countries. For Germany, we use data only since reunification in 1990. Similarly, in cases like the Czech and Slovak republics, formed by division of pre-existing larger national boundaries, we use data only since the recent borders were formed. In total we have 492 annual suicide observations, for an average of 18.2 observations per country.

We combine suicide data for each of these 27 countries with data on annual sales of all SSRIs, including fluvoxamine, paroxetine, fluoxetine, sertraline, citalopram, and venlafaxine. These sales data were obtained from IMS Health, Inc., a commercial firm that provides data on international pharmaceutical sales to manufacturers and health care providers. In our baseline model we measure SSRI use as the total number of pills sold per capita in each country in a year, which is available from 1990 through 2000.

In principle, the fact that SSRI sales data are not available prior to 1990 will complicate our analysis, although we expect the impact on our results to be quite modest in practice. Nearly half the countries under study here began selling SSRIs in 1990 or later; for the remaining countries, sales often began in the late 1980s. Thus, of the 492 country-year observations in our data file, cases where SSRI sales were legal but SSRI sales data are missing for that country and year account for only 47 country-year observations (9.55 percent of the sample). Moreover, for all countries, growth of SSRI sales appears to be a phenomenon of the 1990s. As seen in Table 1, in 1990 average SSRI sales in our sample equaled only 0.6 pills per capita. From 1990 to 1995 sales, increased by more than a factor of five (from 0.6 to 3.5), and then more than doubled again from 1995 to 1999 (3.5 to 7.4).

Our main results come from imputing pre-1990 SSRI sales in countries that had approved SSRIs for use during that period. Our imputation procedure first calculates annual proportional growth rates for each country using the available sales

Table 1. Descriptive statistics for international panel data.

Variable	Mean	Standard Deviation
Full sample (1980–2000)		
GDP per capita (in 1995 $10,000's)	15.756	6.995
(percent GDP missing)	.152	.360
Divorce rate	36.778	14.556
(percent divorce missing)	.190	.393
Unemployment rate	8.564	3.821
(percent unemployment missing)	.095	.294
Percent population in age group:		
0–14	20.912	2.402
15–24	14.888	1.700
25–34	15.598	1.343
35–44	14.070	1.505
45–54	11.519	1.314
55–64	9.927	1.341
65 and over	13.085	1.733
SSRI doses per capita	1.911	3.235
SSRI kilograms per capita	.038	.073
Suicide rates per 100,000		
Total	13.847	6.605
Male	23.765	10.864
Female	6.897	3.254
Age 10–14	1.145	0.659
Age 15–24	10.216	4.096
Age 25–34	15.216	6.450
Age 35–44	17.675	9.623
Age 45–54	19.872	12.174
Age 55–64	19.695	10.612
Age 65 and over	26.587	15.828
1980		
Suicides per 100,000	12.114	6.647
SSRI doses per capita	0.0	0.0
1985		
Suicides per 100,000	14.089	6.922
SSRI doses per capita	0.003	0.015
1990		
Suicides per 100,000	13.952	5.754
SSRI doses per capita	0.623	0.588
1995		
Suicides per 100,000	14.265	6.807
SSRI doses per capita	3.514	2.868
1999		
Suicides per 100,000	13.179	6.848
SSRI doses per capita	7.436	5.372

Note: Authors' calculations from WHO mortality and SSRI sales data (see text). Calculations are weighted by country population.

data from 1990–2000, and then uses these country-specific SSRI growth rates to estimate the missing pre-1990 sales figures. We demonstrate below that our results are not sensitive to alternative procedures for handling missing data for SSRI sales before 1990.

In our analyses we also control for a number of socio-demographic factors thought to affect suicide rates, including unemployment rates obtained from the Organization for Economic Cooperation and Development, the real per capita gross domestic product (GDP) measured in constant 1985 dollars, the fraction of the population in various age groups (with the fraction ages 0–14 as the referent group), and the number of divorces per 100 marriages.

EMPIRICAL STRATEGY

Our main analysis consists of applying panel-data techniques to pooled annual data from the 27 countries listed above using the 492 country-year observations with valid suicide data available over the period 1980 to 2000. We use these repeated cross-sections to estimate a model as in equation (1), where the outcome is the natural log of country (i)'s suicide rate per 100,000 people in a given year (t), Y_{it}. The key explanatory variable, $SSRI_{it}$, equals the number of pills of SSRIs sold per capita in country (i) in year (t).

$$Y_{it} = b_0 + b_1\, SSRI_{it} + b_2\, X_{it} + d_i + d_t + (t \times d_i) + v_{it} \qquad (1)$$

The model includes a series of control variables for each country by year, X_{it}, including the socio-demographic variables described above and an indicator variable equal to 1 if country (i) in year (t) recorded suicide figures using the ICD–10 system, and equal to 0 if the country recorded suicides using the ICD–9 system. We also include a separate intercept term ("fixed effect") for each country, d_i, to account for the influence of any time-invariant unmeasured factors that cause some countries to have persistently higher suicide rates than other countries, and separate indicator variables for each year in the analytic sample, d_t, to account for changes in suicide rates over time that are common to all countries.

Our preferred model also includes a separate linear trend term for each country, equal to $t \times d_i$, where t is a linear time trend variable and d_i are the country indicators. These country-specific linear trends control for the possibility that countries have distinct trends in suicide rates over time for reasons that are not captured by the covariates or common year fixed effects. The raw data suggest that these country-specific linear terms may be important, given that the countries in our sample experienced quite different suicide trends over our sample period—even before SSRI use became widespread. For example, in Austria the suicide rate was 25.4 per 100,000 in 1980, which then declined to 23.3 by 1990 and 19.0 by 1999. In contrast, the suicide rate in Bulgaria steadily increased from 13.4 in 1980 to 14.5 by 1990, and equaled 15.8 by 1999.

Equation (1) is estimated using weighted-least squares to adjust for heteroskedasticity in the stochastic error term v_{it}, using each country's population as the weight. We account for the possibility of serial correlation in the error term by calculating Huber-White robust standard errors that allow for an arbitrary pattern of autocorrelation within countries over time (Huber, 1967; White, 1980, 1982). This procedure has been shown to perform better than more parametric approaches in panels such as ours, where the number of time periods is fairly modest (Bertrand, Duflo, & Mullainathan, 2004).

Finally, because rates of suicide and depression differ by gender and age (Table 1), it is possible that the effects of SSRIs on suicide may vary along these dimensions, too. To allow for this possibility we re-estimate equation (1) for males and females separately and for individual age groups. However, unlike with our suicide data, information on SSRI sales is only available at the aggregate national level.

RESULTS

The intuition behind our panel data analysis is illustrated by Figure 2. For the figure we divide the 27 countries in our sample into quartiles based on their change in SSRI sales per capita from 1990 to 1999 (horizontal axis),[5] and then show how average suicide rates within each quartile changed from 1990 to 1999 (vertical axis). Figure 2 shows that those countries with the *slowest* growth in SSRI sales on average experienced *increases* in suicide rates. In contrast, the 3rd and 4th quartiles experienced the *fastest* growth in SSRI sales per capita and the largest *declines* in suicide rates.

Figure 2 also helps highlight the advantage of our panel-data research design over previous comparisons that draw on data from only one or a few countries. While every country in our sample experienced increases in SSRI sales during the 1990s, Figure 2 shows that for a variety of reasons some countries experienced increasing suicide rates over this period while others had reductions in suicide. A series of before-after comparisons that examined the experiences of one country at a time

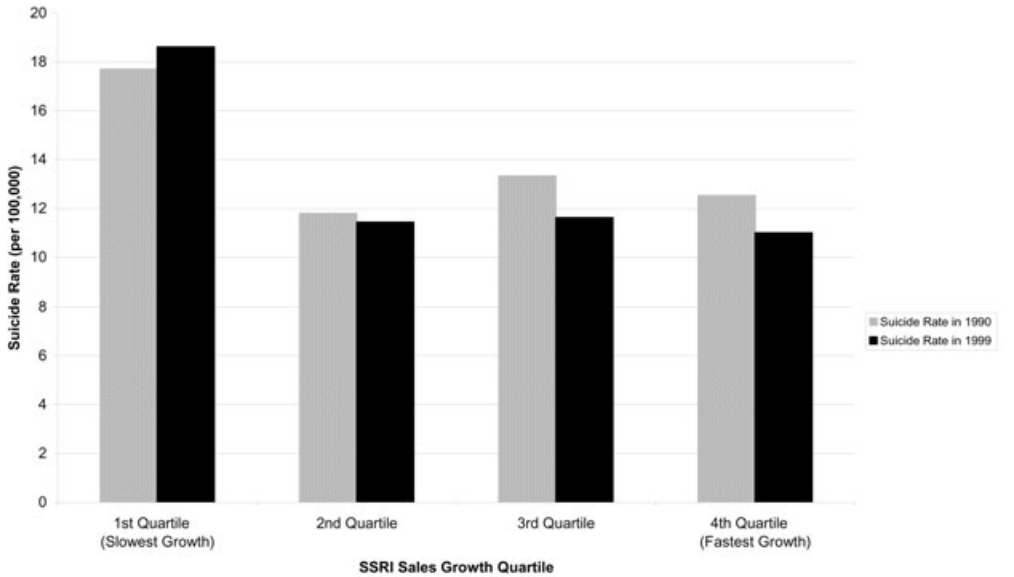


Figure 2. Population weighted suicide rates by rate of growth in SSRI sales: 1990–1999.

[5] The countries that comprise each quartile are as follows: top quartile—United States, Norway, Canada, Australia, Luxembourg; second quartile—Finland, France, United Kingdom, Spain, Portugal, Austria; third quartile—Ireland, Greece, Hungary, Netherlands, Slovenia, Lithuania, Italy; bottom quartile—Czech Republic, Germany, Poland, Latvia, Bulgaria, Ukraine, and Belorussia.

would find mixed results, suggesting that suicide rates declined in most—but not all—countries as SSRI sales increased. This mixed pattern is in fact consistent with what is reported by previous before-after country case studies. Our panel-data analysis instead allows us to compare variation *across* countries over time in SSRI sales with variation in suicide trends. This research design helps rule out, among other things, common trends across countries in suicide rates that are independent of the growth in SSRI use.

Table 2 presents our more formal analysis of the pooled sample of annual country-level observations. The first column shows the results of a parsimonious specification that regresses the natural log of the suicide rate against just the SSRI sales measure and country and year fixed effects. The results of this simple model suggest that an increase in SSRI sales of one pill per capita is associated with a reduction in suicide rates of 1.8 percent, which is statistically significant at the 5 percent level. For purposes of interpretation, a one pill per capita increase in SSRI sales represents a 13 percent increase over 1999 levels. An increase of one pill per capita also represents a 52 percent increase over average sales over our entire sample period, so that the estimated elasticity of suicide with respect to SSRI sales equals –0.03.

Figure 3 provides some additional insight into these results by plotting the relationship between log suicide rates and SSRI sales net of country and year fixed effects.[6] The figure shows that the estimated relationship between log suicide rates and SSRI sales in our international panel (where the slope equals –0.018, as above) is not driven by outliers. For example, excluding the data point in the bottom right corner of Figure 3 (Spain, 2000) produces a coefficient of –0.017, almost identical to the full-sample estimate. More formally, we can also recalculate the fixed-effects estimates shown in the first column of Table 2 excluding each country in turn, which yields 27 separate coefficient estimates for the relationship between SSRI sales and suicide. The standard deviation for these coefficients is just 0.003 with a range of –.028 to –.011.

Our preferred model, shown in the second column of Table 2, is similarly robust to outliers. This preferred baseline specification implies that an increase in SSRI sales of one pill per capita is associated with a reduction in suicide rates of –2.5 percent, nearly 1.5 times the point estimate from the parsimonious specification shown in column 1 of Table 2. The implied elasticity of suicide with respect to SSRI sales from our preferred model equals –0.05. The second column of Table 2 also shows that after controlling for country and year fixed effects as well as country-specific linear trends (coefficients not shown in Table 2 for ease of presentation), the other covariates aside from the country's age distribution typically do not have a statistically significant association with suicide rates.

These findings appear to be robust to a variety of other changes to our basic estimation approach. When we redefine the outcome measure of interest to be each country's actual suicide rate per 100,000 rather than the logged value (column 3 of Table 2), we find that an increase of one pill per capita in SSRI sales is associated with a change in the suicide rate of –0.497 ($p < 0.05$), equal to about a 3.6 percent decline in the mean suicide rate for our sample (Table 1). Column 4 shows the results of estimating a negative binomial maximum-likelihood model, in which the outcome of interest is a suicide count rather than rate and where the country's pop-

[6] Figure 3 is constructed by first running two separate regressions, log suicide rates against country and year fixed effects and a similar regression using SSRI sales as the dependent variable. Figure 3 shows the relationship between the residuals from these two regressions, which is the same as what one obtains from a single regression model where the dependent variable is the actual log suicide rate and the explanatory variables are SSRI sales and country and year fixed effects.

Table 2. Regression estimates for international panel data years 1980 to 2000.

	Outcome Measure = Log (Suicides / 100,000)	Outcome Measure = Log (Suicides / 100,000)	Outcome Measure = (Suicides / 100,000)	Outcome Measure = Suicides
SSRI doses sold per capita	–.018 (.008)**	–0.025 (.007)**	–0.497 (.146)**	0.975 (.004)**
GDP per capita (times 10,000)		0.003 (.002)	0.030 (.480)	0.996 (.002)**
Divorce rate		–0.002 (.001)**	0.005 (.020)	0.999 (.001)
Unemployment rate		0.002 (.002)	0.033 (.040)	1.000 (.001)
Percent population in age group:				
15–24		0.044 (.013)**	0.916 (.350)**	1.051 (.007)**
25–34		0.012 (.023)	0.342 (.250)	1.019 (.011)
35–44		0.032 (.020)	0.832 (.317)**	1.042 (.012)**
45–54		–0.010 (.017)	–0.331 (.308)	0.995 (.010)
55–64		0.020 (.016)	0.341 (.297)	1.021 (.010)**
65 and over		0.008 (.019)	–0.003 (.153)	1.008 (.011)
ICD–10 used for suicide data		0.009 (.023)	0.188 (.337)	0.888 (.020)**
Model specification				
Year indicators?	Yes	Yes	Yes	Yes
Country indicators?	Yes	Yes	Yes	Yes
Socio-demographic controls?	No	Yes	Yes	Yes
Country-specific linear trends?	No	Yes	Yes	Yes
Estimator	Weighted LS	Weighted LS	Weighted LS	Neg Binomial
Sample (N)	492	492	492	492
Adj. R-squared	0.954	0.987	0.981	
Log likelihood				–2922.9

Note: Table reports least squares regression coefficients (columns 1–3) or incidence rate ratios (column 4). Standard errors in parentheses. Regression models in the last three columns also include a constant intercept term and binary indicators for whether GDP, divorce and unemployment rate variables are missing and set equal to zero. Country populations used as weights. For more details on estimation approach see text. * = $p < .10$ ** = $p < .05$.

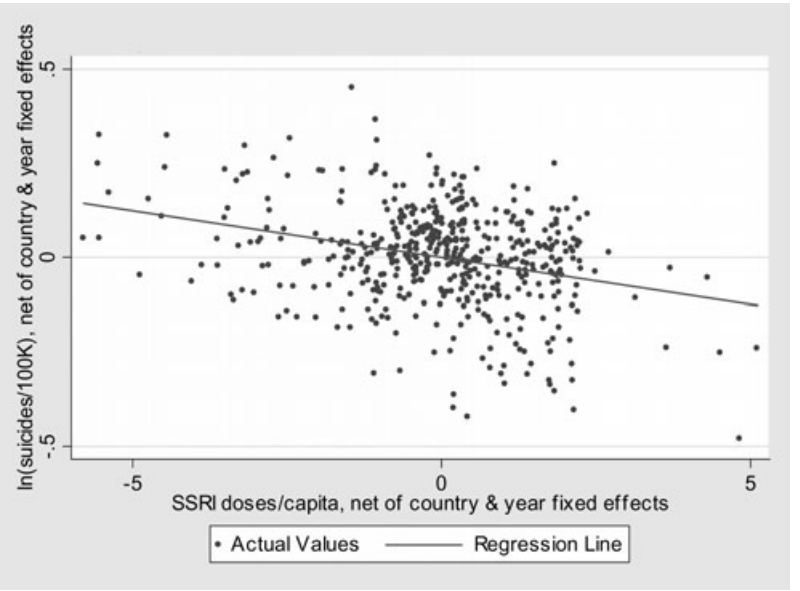


Figure 3. Suicide rates vs. SSRI sales, 1980–2000.

ulation is included as an explanatory variable in the model. The estimated incidence rate ratio from this model equals 0.975, which implies a proportional effect of the same magnitude as our baseline weighted least-squares model. When we re-estimate the model ignoring the problem of serial correlation (not shown), the estimated standard errors are about 30 percent smaller than in our preferred baseline model.

A potential concern with our suicide variable is that most values are recorded by countries using the ICD–9 coding system, although during our panel some countries shifted to the ICD–10. In principle, this coding change could affect recorded suicide rates in some countries, although this does not appear to affect our estimates. As shown in the first column of Table 3, when we drop all country-year observations where countries classify suicides using the ICD–10 system, the estimated coefficient on the SSRI variable equals –0.031.

Measurement problems are also a potential concern with our SSRI variable. In our baseline model we handle missing SSRI sales data prior to 1990 by estimating these figures from available 1990–2000 sales data for each country. To examine whether this affects our results, we replicate our estimates setting SSRI sales figures before 1990 to missing values. Column 2 of Table 3 shows that this change has the effect of reducing the sample from 492 to 445 country-year observations but has little effect on the estimated association between SSRIs and suicide, now equal to –0.021.

One complication with our primary measure of SSRI sales—pills sold per capita—is that drug weights per pill can vary. For example, paroxetine can be sold in both 20 mg and 40 mg pills. To determine whether our results are affected by how we measure SSRI use, we replicate our estimates using the number of kilograms of SSRIs sold per capita in each market as our main explanatory variable of interest. This measure is available for every country in our sample except the United States, and can account for the fact that some pills sold contain a greater dose of SSRI than

Table 3. Multivariate regression results for effects of SSRIs on suicide rates, international panel data.

	Outcome = Log of Suicides/100,000	Outcome = Log of Suicides/100,000	Outcome = Log of Suicides/100,000	Outcome = Log of Suicides/100,000	Outcome = Log of Suicides/100,000
SSRI doses sold per capita	–0.031 (.007)**	–0.021 (.007)**		–0.015 (.007)**	–.026 (.007)**
SSRI kilograms sold per capita			–0.330 (.226)		
Model specification					
Covariates as in Table 2, column 2?	Yes	Yes	Yes	Yes	Yes
Country indicators?	Yes	Yes	Yes	Yes	Yes
Year indicators?	Yes	Yes	Yes	Yes	Yes
Country-specific linear trends?	Yes	Yes	Yes	Yes	Yes
Drop observations that use ICD–10 coding scheme for suicides?	Yes	No	No	No	No
Drop observations with SSRI sales prior to 1990?	No	Yes	No	No	No
Include interactions between Eastern Europe and year indicators for 1990s?	No	No	No	Yes	No
Interact country linear trends with dummy for 1990–2000 period?	No	No	No	No	Yes
Estimation method	Weighted LS	Weighted LS	Weighted LS	Weighted LS	Weighted LS
Sample (N)	436	445	472	492	492
Adj. R-squared	0.988	0.988	0.988	0.988	0.990

Note: Table presents least squares regression coefficients, with standard errors in parentheses. Estimates calculated via weighted least squares (unless otherwise noted) using a model specified by equation (1), using country population as the weighting variable. Sample consists of annual observations for 27 countries (see text). * = $p < .10$ ** = $p < .05$

others. However, like our measure of SSRI pills, this weight measure is also somewhat imperfect because the standard dose can vary across types of SSRI. For example, a typical dose of fluoxetine is 20 mg, while a typical dose of sertraline is 50 mg.

Column 3 of Table 3 shows that when we use our SSRI variable measured in kilograms sold per capita we obtain a coefficient estimate of –0.33, which is not statistically significant at the conventional cutoff ($p = 0.14$). However, recall that the kilogram SSRI measure is not available for the United States. When we re-estimate our basic model without the United States, the regression coefficient for our measure of SSRI pills per capita is –1.9 percent. This implies that when we hold the analytic sample constant (dropping the United States), a one-standard deviation change in SSRI sales measured in KG per capita yields an estimated change in suicide rates equal to around 40 percent of the effect from a one standard deviation increase in SSRI pills per capita (from Table 1, in doses [(sd = 3.235) × (β = –.019) = –.061] versus KG [(sd = .073) × (β = –.330) = –.024]). In our view, the dose per capita measure is the more appropriate indicator for the prevalence of SSRI use within the population, since it better reflects the number of persons undertaking psychopharmacologic treatment. If so, the variable for kilograms of SSRI per capita should be a noisier measure of SSRI use and would yield an estimate that is attenuated toward zero, consistent with the pattern that we find in our data.

The final columns of Table 3 explore the sensitivity of our results to bias from unmeasured variables. One concern is that the countries of Eastern Europe and the former Soviet Union experienced dramatic social changes during the 1990s, which in principle could affect suicide rates. Yet in column 4 of Table 3 we show that when we include interactions between an indicator variable set to one for these countries and separate year indicators for each year from 1990 to 2000, the estimated association between SSRIs and suicide equals –0.015. More generally, we can allow for the fact that the country-specific trends in other unmeasured factors that affect suicide rates may not have been linear over our entire sample period. In the final column of Table 3, we re-estimate our preferred baseline model adding something like a spline term for each country's linear trend. That is, we interact each country-specific linear trend with an indicator variable set equal to 1 for years 1990 to 2000. This model allows country-specific unmeasured variables that change over time to follow different trajectories during the 1980s versus 1990s, and yields an estimate almost identical to our preferred model (final column, Table 3).

As another check on the performance of our regression model, we can estimate the parameters in our preferred specification using data from just 1980 through 1997, and then compare the suicide rates predicted by our parameter estimates for the years 1998–2000 with the values that we actually observe. The average log suicide rate for our sample for the years 1998–2000 equals 2.54. By comparison, the average predicted log suicide rate for 1998–2000 from estimating our model using just 1980–1997 data equals 2.47 with an average standard error of 0.09, implying that the observed values fit quite comfortably within the 95 percent confidence intervals around our model's predictions.

Finally, Table 4 summarizes the results of re-estimating our main model (column 1 of Table 2) for different population sub-groups. We find that the association between SSRI sales and suicide is larger for males than females (–3.0 percent vs. –0.7 percent). The estimated association is also larger for younger and older people compared to middle-age adults (35 to 54). The result for individuals aged 10–14 is not statistically significant at the standard cutoff level, which means that we cannot say much about whether the relationship between overall SSRI sales and suicides for this age group is positive, negative, or zero.

Table 4. Regression estimates for international panel data by gender and age, years 1980 to 2000.

	Log Rate, Males	Log Rate, Females	Log Rate, Ages 10–14	Log Rate, Ages 15–24	Log Rate, Ages 25–34	Log Rate, Ages 35–44	Log Rate, Ages 45–54	Log Rate, Ages 55–64	Log Rate, Ages 65 +
SSRI doses sold per capita	–0.030** (.009)	–0.007 (.008)	–0.033 (.029)	–0.049** (.011)	–0.019 (.013)	–0.008 (.009)	0.002 (.009)	–0.019** (.009)	–0.017** (.008)
Model specification as in column 2 of Table 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample (N)	492	492	472	487	490	489	489	491	477
Adj. R-squared	0.987	0.982	0.967	0.967	0.969	0.980	0.980	0.980	0.988

Note: Table reports least squares regression coefficients, with standard errors in parentheses. Estimates calculated via weighted least squares using a model specified by equation (1), using country population as the weighting variable. A total of 27 country-year observations report no suicides to people in our youngest age group (10–14) during our study period. Since the natural logarithm of zero is undefined, our default is to set these rates equal to log(0.01), although we also experiment with setting these values equal to log(0.1), log(0.001), and to missing values. Sample consists of annual observations for 27 countries (see text). * = $p < .10$ ** = $p < .05$

DISCUSSION

In closing, we return to the three questions raised at the beginning of the paper. We discuss our findings on the question of whether SSRIs increase or reduce suicide rates. We consider what our results imply for health policy and the benefits and costs of government policies to expand SSRI use to combat suicide. And finally, we offer some thoughts about why the existing medical and public health literature has been so uninformative on this question given the number of lives at stake in getting the relevant policy decisions here correct.

Do SSRIs increase or decrease the risk of suicide? While randomized experiments are—appropriately—the gold standard for understanding the causal effects of health, social policy, education, and other public policy interventions on public welfare, in some applications randomized experiments are impossible or uninformative. The effect of SSRIs on suicide appears to be one such application. Given the pressing policy need for useful information, we offer as an improvement over previous nonexperimental research our evaluation of the "natural experiment" generated by substantial variation across countries over time in the introduction and rate of growth in SSRI sales.

Analysis of our international panel data suggests that an increase in SSRI sales of one pill per capita (a 13 percent increase over 1999 levels) is associated with a decline in suicide rates equal to –2.5 percent. Interestingly, our results are generally consistent with what is arguably the best other panel-data study, which uses across-county over-time variation within Sweden in SSRI sales and suicide rates (Dahlberg and Lundin, 2004).[7]

Our own estimate is robust to several changes to our basic estimation approach, including changes in functional form. Our estimates are not susceptible to bias from confounding factors that cause some countries to have persistently higher or lower suicide rates than others, because our analysis controls for country fixed-effects and is identified by comparing changes over time across countries in SSRI use and suicide rates. We also explicitly control for several measures of economic conditions, as well as each country's divorce rate and population age composition. Finally, the inclusion of year fixed-effects and country-specific linear trends in our regression model means that our estimates are not susceptible to bias from any unmeasured cultural, social, or policy factors that change over time and are common across countries, or even unmeasured factors that change uniquely within countries at a constant rate.

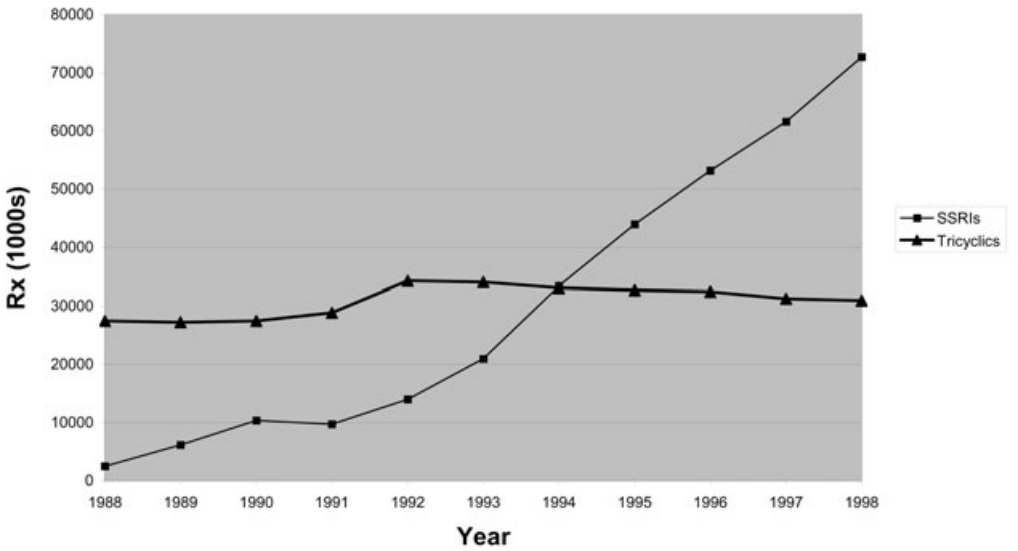
While our findings improve upon most of the previous epidemiological research, all nonexperimental studies are susceptible to bias from omitted variables to some degree. Of particular concern here is the possibility that other forms of mental health treatment may also have become more common during our sample period. However, sales of other anti-depressants seem to have changed gradually and steadily over time and so may be captured by the country-specific linear trends in our regression mod-

[7] The Swedish study does not find a statistically significant relationship overall between SSRI sales and suicide rates. Yet for an increase in SSRI sales of 1 defined daily dose per capita (equal to about a 7 percent increase over the 2000 sales rate), the 95% confidence interval for the implied effect on suicide rates (using the authors' most reliable measure of suicides) ranges from –.0132 to +.0136 (p. 16). The lower bound of this confidence interval suggests that an increase in SSRI sales in Sweden equal to 13 percent over 1999 or 2000 levels (about two defined daily doses per capita) could reduce suicide rates by up to 2.6 percent, consistent with the estimate presented above from our panel of country-level data. The magnitude of our estimate is significantly smaller than what is presented in the study of adolescent suicides by U.S. ZIP code area by Olfson et al. (2003), but as noted above we have significant concerns about the key explanatory variable of interest used in their study.

els. For example, Figure 4 shows that in the United States the number of prescriptions of older tricyclic anti-depressants (TCAs) was fairly steady from 1988 to 1998, with a change of only 12 percent. In contrast, SSRI prescriptions increased by more than 2,800 percent from 1988 to 1998. Note that the country-specific linear trend terms do not eliminate the effect of SSRIs on suicide because SSRI sales increase at an increasing (that is, nonlinear) rate over our entire sample period, in part because SSRI sales were zero for most countries during most of the 1980s.[8]

A related possibility is that the availability of SSRIs are associated with broader changes in how medical professionals treat mental illness. For example, the availability of an anti-depressant with fewer side effects and less toxicity in overdose could increase the willingness of physicians to prescribe anti-depressant medications and in turn also increase community awareness of depression as an illness.[9] Further, growing awareness of depression may have had the effect of improving psychosocial supports and therapeutic strategies available to alleviate it (Lesage, 2004). Unfortunately, our data do not enable us to explore such possibilities. However, to the extent to which SSRI availability stimulates such changes in mental health treatment, these ancillary changes should arguably be counted as part of "the" effect of SSRIs on suicide.

A different challenge comes from the difficulty of measuring suicide rates across countries (Douglas, 1967), although we believe that our analytic approach should



Source: IMS Health.

Figure 4. New prescriptions of SSRIs and tricyclic anti-depressants in the United States, 1988–1998.

[8] Unfortunately, we are constrained to this period because we do not have data on TCA sales prior to 1988 for the United States. A similar pattern seems to hold for the U.K.: Between 1991 and 1996, prescriptions of older tricyclic antidepressants (TCAs) increased by 40 percent, while those for SSRIs increased by 460 percent (Lawrenson et al., 2000).

[9] Thanks to an anonymous referee for this observation.

control for many of the problems that may arise in recording suicides. The inclusion of country fixed-effects in our analysis will control for persistent under-reporting of suicides in some countries over time, for example in those countries where the act carries a relatively greater stigma over our sample period. Changes in stigma or improvements in vital statistics reporting within a country may be captured by our inclusion of country-specific linear time trends. And the inclusion of year fixed-effects controls for sharp changes over time in stigma, vital statistics reporting or other factors that are common to all of the countries in our sample.

A final series of potential challenges for our analysis come from limitations with the SSRI sales data that are currently available. The most obvious concern is that SSRI sales data are not available prior to 1990. However, this does not appear to materially affect our results, because we obtain quite similar findings to those from our baseline model when we drop observations for countries with missing SSRI sales information prior to 1990.

We find that measuring SSRI sales on the basis of kilograms rather than pills sold per capita yields an estimated association between SSRI sales and suicide that is about two-fifths as large as our baseline estimates. In our view, the measure of pills per capita is a more appropriate indicator for the prevalence of SSRI use within the population, since it is a better indicator of the number of persons undertaking psychopharmacologic treatment. If this view is correct, then the variable for kilograms of SSRI per capita should be a noisier measure of SSRI use and would yield an estimate that is attenuated toward zero, consistent with the pattern in our results.

A final limitation with our SSRI sales data is that they are available only at the national level for our full sample of countries and not disaggregated by population sub-groups. This means that we have more confidence in our estimates for the association between SSRI sales and total suicide rates than for the association of overall SSRI sales with suicide among particular gender or age groups. Obtaining more detailed SSRI sales data would enable future investigators to determine whether the more pronounced reductions in suicide rates reported here for males than females and for young adults and seniors compared to those in middle age, come from disproportionately large increases in SSRI use among these groups, from unusually pronounced responsiveness to SSRI treatment, or some other reason.

Unfortunately, the available data on patterns of SSRI use are somewhat limited. A study of physicians' prescribing practices in the United States using the National Ambulatory Medical Care Survey (Olfson et al., 1998) and data from Sweden (Dahlberg & Lundin, 2004) indicate that anti-depressant use increases steadily with age. The likelihood American physicians mentioned anti-depressant therapy during an office visit also has been found to increase monotonically with age (Bernstein et al., 2003). These patterns could help explain why the estimated SSRI effect on suicide is larger for older people than for those in middle age, although this cannot explain why the estimated SSRI coefficient is larger for young people than middle-aged people. The Swedish data also indicate that the level and change (in absolute terms) in SSRI usage is greater for females than for males. The U.S. data, however, find the level of anti-depressant use only slightly higher among women, and the change larger for males. These data taken together cannot rule out the possibility of differential responses to SSRI use across population sub-groups.

Learning more about potential heterogeneity in the population's response to SSRIs is particularly important in light of ongoing controversies about whether SSRI use increases the risk of suicide among youth. The 95 percent confidence interval estimated here for the association between SSRIs and suicides to those 10–14 years old includes both positive and negative values, but is negative for sui-

cides to those 15–24 and to those 55 and older. If our results are correct, then recent U.S. and U.K. government recommendations against pediatric use of SSRIs should not affect SSRI use by adults, since our estimates suggest that increases in overall SSRI sales is associated with reductions in suicide rates for these groups.

In principle, even our estimates for the relationship between changes in total suicide rates and SSRI use could suffer from the ecological fallacy if the decline in suicides that is associated with increases in SSRI sales occurs among those who are not taking SSRIs (Robinson, 1950). Of course, this interpretation of our findings requires some alternative explanation for why suicides would decline most sharply in our panel among non-SSRI users in countries where SSRI sales increase the most. Our controls for country and year fixed-effects, economic conditions, divorce, and even country-specific linear trends would seem to eliminate many candidate explanations.

In order to examine whether declines in suicide rates were concentrated among people who were being treated with SSRIs, the ideal nonexperimental study would employ detailed micro-level data across countries over time on individual decedents, including information about their cause of death, psychological history, and mental health treatment, paired with population survey data that could support estimates for SSRI use among specific population sub-groups. The truly ideal study would also specify a clear source of identifying variation in SSRI use across countries over time. We hypothesize that the variation in SSRI use within our panel may be driven in part by differences across countries in the speed with which the relevant government agencies approve new drugs for public use, together with differences in private- and public-sector policies and practices that affect the use of drugs more generally. Unfortunately the data necessary to implement the type of ideal study described here are currently not readily available.

Should health policymakers limit access to SSRIs for depressed patients? With an increase of SSRI use from 1990 to 1999 of 0.623 to 7.436 pills per capita on average (Table 1), our estimates imply that, all else equal, the suicide rate in 1999 would have been about 17 percent higher than what was actually observed had there not been a nearly 1,100 percent increase in SSRI use from 1990 levels. Doubling the rate of SSRI use again from 1999 levels would still leave a suicide rate of nearly 11 per 100,000, suggesting that complementary approaches to reducing suicide remain important.

In any case, if taken literally, our estimates imply that SSRIs may be a relatively cost-effective means for saving lives. The results shown in Table 2 suggest that 1 suicide is averted for about every 300,000 SSRI pills sold. Some indication for the cost per life saved comes from considering that citalopram, a commonly used SSRI within the United States, can currently be had for $3.33 per 20 mg or 40 mg tablet. Using this price, the cost per life saved implied by our estimates is on the order of $1 million in current (2003) U.S. dollars. It is important to note that this calculation ignores other possible benefits from expansions in SSRI use, such as those from a reduction in nonfatal suicide attempts. In any case, by way of comparison a review of regulatory interventions designed to improve health and well-being finds that fully 54 of the 76 regulations reviewed cost more than $1 million per statistical life saved (Morrall, 2003).

One possible objection to this type of calculation is that suicidal individuals by definition place an unusually low value on their own lives. This challenge raises difficult conceptual and practical questions about which preferences to give standing from a policy perspective. One solution is suggested by the approach that federal agencies use—they simply ignore variation across people in attitudes about mortality risks, and use a uniform value per statistical life for everyone (Sunstein, 2004). The value per statistical life used by government agencies, which does not vary

across people or risks within a given agency's calculations but does vary across agencies, ranges from $1.5 to $6.5 million. Expanding the use of SSRIs would appear to pass the type of benefit-cost test that federal agencies regularly conduct, assuming that expenditures for SSRIs account for most of the cost of expanding the use of these drugs.

If one wishes to instead take people's preferences about mortality risks seriously, it is worth noting that some suicide attempts are impulsive and many survivors of suicide attempts do not attempt to take their own lives again. In addition, family and friends may be willing to pay significant sums to reduce the risk of suicide to a loved one. In any case, existing estimates for the value per life typically range from $3.8 to $9 million (Viscusi & Aldy, 2003; Sunstein, 2004). This range in estimates may reflect in part variation across individuals in their aversion to the risk of physical injury or death. If so, then the "true" preferences of the average depressed individual and their loved ones would need to be nearly four times less averse to the risk of death than the least risk-averse sample of workers studied to date in order for an expansion of SSRIs to fail a benefit-cost test.

Beyond the implication that SSRI use may be a relatively cost-effective life-saving intervention, our findings are consistent with previous research suggesting that many people with major depressive episodes receive inadequate treatment for their depression (Kessler et al., 2003). Table 1 reports an average of 7.4 SSRI pills sold per person per year in the year 2000, which suggests just over 2 person-years of daily SSRI treatment per 100 people. This figure is far lower than the estimated proportion of adults suffering from depression in countries such as the United States (Goldsmith et al., 2002). At the same time, the SSRI usage rates are relatively high in an absolute sense, which lends credence to the idea that levels and changes in SSRI use can affect country-level suicide rates. The Institute of Medicine's recent report on suicide recommends improving access to mental health care services by reducing the number of uninsured persons, providing insurance parity to mental health treatment and improving the ability of health care providers to identify those at high risk for attempting suicide (Goldsmith et al., 2002). If our findings are correct, such measures could save lives if they are successful in expanding access to and use of SSRIs.

Why has previous medical and public health research been so uninformative about the effects of SSRIs on suicide? Suicide has long been an important national and international health problem. The advent of SSRIs provided clinicians with a potentially highly effective treatment for a disease—depression—that greatly increases the risk of suicide. Given the number of lives and pressing policy questions at stake, why has previous medical and public health been unable to resolve the question of whether SSRI treatment affects suicide risk?

One part of the problem is surely that much of the research on the effects of drug therapies is proprietary. Consequently, there may be instances in which the results of studies funded by pharmaceutical companies are not made public if the findings show limited efficacy or negative side effects. Such selective reporting would, of course, hamper the ability of doctors, medical researchers, and consumers to draw conclusions. There has been substantial and growing concern about this possibility within the medical research community, prompting editors of the major medical journals to begin requiring researchers to register clinical trials in advance of enrollment (DeAngelis et al., 2004).

An additional problem may be that understanding the impact of therapeutic interventions has almost exclusively been the domain of the medical research community, although this community is generally not well equipped to answer empirical questions that cannot be answered using randomized clinical trials or clinical

case studies. These two methods of inquiry account for the vast majority of empirical work in the medical research literature. For example, in our review of articles published in 2003 in the *New England Journal of Medicine* and the *Journal of the American Medical Association,* of the 191 studies of the effects of health interventions fully 132 rely on randomized trials, while 25 are clinical case studies and only 29 use some sort of other nonexperimental, epidemiological research design.

Neither the production nor consumption of either the randomized trial or the clinical case study requires much statistical experience or skill in the construction of valid counterfactuals. RCTs by their nature provide a highly credible counterfactual for the treatment of interest, so that interpreting or judging the quality of RCT findings does not require much statistical sophistication. However, as we have argued above, there are applications that cannot be answered through the use of RCTs. Clinical case reports provide clinicians' observations about treatment response or side effects among one or a handful of patients. Case reports can offer suggestive evidence about treatment and outcomes or side effects. Indeed, clinical case reports shortly after the introduction of SSRIs were often cited in litigation against pharmaceutical companies by families of patients who committed suicide while undergoing treatment. However, clinical case reports are limited in their ability to resolve questions about drug effects because no such observations are made on those not undergoing treatment. In any case, clinical case reports do not require much judgment about constructing credible counterfactuals because the only counterfactual available is the pre-treatment state of patients.

For questions that cannot be answered through RCTs or clinical case reports, nonexperimental methods may be the only source of guidance for health policymakers. Yet the training of most actors within the medical research community does not appear to be targeted toward the analysis of nonexperimental data.[10] And in fact the medical community appears to eschew nonexperimental evidence in applications where randomized trials are possible,[11] perhaps (as one medical journal editor suggested to us) out of concern that future RCTs may overturn the findings of nonexperimental evidence. This risk is suggested by the medical community's recent experience with hormone replacement therapy[12] and is exacerbated in cases where a research community is not well-equipped to distinguish between strong and weak nonexperimental research designs.

Regardless of the reasons for the medical community's reluctance to examine nonexperimental evidence for therapeutic interventions, we believe that health policymakers who are charged with regulating the use of SSRIs will have to rely on such findings. While our results are necessarily less convincing than the ideal randomized

[10] For example, of all articles published in the *New England Journal of Medicine* and the *Journal of the American Medical Association* during 2003, 75 percent of lead authors hold either the Medical Doctorate degree alone, or the M.D. together with a Master's degree in Public Health. (We acknowledge that secondary co-authors could have different backgrounds.) This training is also true for 83 percent of the editorial board of NEJM and 89 percent of the editorial board of JAMA. The statistics training of most MDs or MD/MPHs may be perfectly adequate for interpreting the results of RCTs or clinical case studies, but, as most policy analysts know, the discriminating consumption of non-experimental evidence requires specialized training and often seasoned experience as well.

[11] For example, a review of the 2003 issues of JAMA and NEJM revealed that only 12 percent of studies of drug therapies used non-experimental methods.

[12] While previous non-experimental studies of hormone replacement therapy in postmenopausal women had suggested that such treatment provided cardiovascular benefits (Grady et al., 1992; Barrett-Connor & Grady, 1998; Grodstein et al., 2000), recent evidence from randomized trials suggested that such treatment instead increases the risk for cardiovascular disease and breast cancer (Hulley et al., 1998; Women's Health Initiative, 2002).

clinical trial would be, an informative RCT on this topic is not likely to be available in the foreseeable future, if ever. Our findings provide policymakers with suggestive evidence that is supportive of recent government warnings about the use of SSRIs with younger patients, while at the same time consistent with the recent IOM's recommendation to expand access to SSRIs for other depressed people at risk of suicide. The more general lesson here is that there may be an important role for policy analysts in answering a variety of pressing health policy questions that have traditionally been the domain of the medical research community, but which cannot be answered through that community's traditional methods of empirical inquiry. The SSRI-suicide application seems to highlight the value of what might be called "econometric epidemiology," as well as other applications of the traditional tools of policy analysis to regulations that affect the use of therapeutic interventions.[13]

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[13] Tomas Philipson (2000) discusses the growing field of what he terms "economic epidemiology," which is characterized in part by considering the effects of individual private decisions on the impacts of large-scale public health interventions. We are arguing in part that there is also value in applying the conceptual and empirical tools of economics and policy analysis more generally to clinical, therapeutic interventions as well as to broader public health programs.

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