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Jens Ludwig
Georgetown University and NBER

Dave E. Marcotte
UMBC

Karen Norberg
Washington University, St. Louis and NBER

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Comments can be directed to any of the paper's authors at ludwigj@georgetown.edu, marcotte@umbc.edu, or norberg@nber.org. Any errors and all opinions are of course our own.

Anti-Depressants and Suicide

Abstract

Does drug treatment for depression with selective serotonin reuptake inhibitors (SSRIs) increase or decrease the risk of completed suicide? The question is important in part because of the substantial social costs associated with severe depression and suicide, and by plausible clinical and behavioral arguments that SSRIs could have either positive or negative effects on suicide mortality. Randomized clinical trials on this topic have not been very informative because of small samples and other problems. In this paper we use data from 27 countries for up to 20 years to estimate the association between SSRI sales and suicide mortality using just the variation across countries in the timing of when SSRIs were first sold that can be explained by differences in the speed with which countries approve new drugs for sale more generally. This source of variation is plausibly unrelated to unmeasured mental health conditions or other factors that may influence both SSRI sales and suicide outcomes. We find that an increase in SSRI sales of 1 pill per capita (about a 13% increase over 1999 sales levels) is associated with a decline in suicide mortality of around 3-4%. These estimates imply a cost per statistical life saved of around $66,000, far below most other government interventions to improve health outcomes.

I. Introduction

Does anti-depressant drug treatment increase or decrease the risk of completed suicide? Recent estimates suggest the lifetime prevalence of major depressive disorders is on the order of 17% (Kessler, Berglund et al., 2005). Since depression is a leading risk factor for suicide, and anti-depressant drugs are effective in treating depression (Goldsmith et al., 2002), these drugs are widely prescribed to improve quality of life and reduce the risk of self harm. However concern that antidepressants might increase rather than decrease suicide date back to the introduction of these drugs in the late 1950s. Early classes of antidepressants were highly toxic in overdose. If what Hamermesh and Soss (1974) term the "distaste for suicide" is affected by access to a painless but effective method of suicide – if the "demand" for suicide attempts is elastic with respect to the ease of access, pain or lethality of different methods – then access to potentially lethal doses of an antidepressant might increase the risk of suicide. And heterogeneity in pharmacological effects may increase impulsivity, aggression or suicidal thoughts among some patients, such as those with unrecognized bipolar disorder (Akiskal et al., 2005).

Of particular concern has been the possibility that the risk of suicide may be increased by the introduction in 1984 of a newer class of anti-depressant drugs, the selective serotonin reuptake inhibitors. SSRIs appear to be similar to the older anti-depressants in their ability to reduce depression,[1] but are much less toxic in overdose with fewer side effects and so were prescribed for a wider range of patients by a wider range of practitioners (Guze, 1996, Lawrenson et al., 2000). Concerns about the effects of SSRIs on suicide have led to warnings in

[1] For example Trindade et al. (1998), Mallick et al., (2003), Ryan (2003), Green (2003), Vaswani et al. (2003). There have been fewer studies of the safety and efficacy of SSRIs in children, but a recent meta-analysis of RCTs for SSRI use in children finds an effect on depression of 0.26 standard deviations, an impact the authors argue is "small" (Jureidini et al., 2004). Perhaps the most comprehensive individual study on the topic was the NIMH funded Treatment for Adolescents with Depression Study, which found that a combination of fluoxetine and cognitive behavior therapy (CBT) was superior to placebo, but either CBT or medication alone was not (March et al., 2004).

the United Kingdom and the United States about the use of SSRIs in people under 18 years of age (U.K. Department of Health, 2003, FDA, 2003, 2004, Goode, 2003a). In June, 2005, the FDA also issued a public health advisory raising concern about a link between SSRIs and suicide in adults (FDA, 2005). The result of these warnings has been, as one psychiatrist told the *New York Times*, "anxiety, concern, and questions" about one of the most popular classes of prescription drugs in the world (Goode, 2003b). In the US, SSRI sales accounted for about 12% of the increase in spending on prescription drugs between 1993 and 1998 (NIHCM, 1999), and 3 of the 11 best-selling drugs in 2000 were SSRIs (Prozac, Zoloft and Paxil), which together accounted for nearly $7 billion in sales (Frank et al., 2002).

This topic is of interest to economists for two reasons. First, it is important. Suicide is the third leading cause of death among persons age 15-24 in the United States and an important cause of death in all age groups, claiming the lives of around 30,000 Americans every year and another 1 million or so worldwide (Goldsmith et al., 2002). Depression and other mental health disorders impose substantial social costs by affecting human capital accumulation, employment, productivity, crime, child abuse, accidents, homelessness and divorce (Frank and McGuire, 2000; Marcotte and Wilcox-Gök, 2001; Currie and Stabile, 2004). Given these social costs, governments have typically been more involved in providing and regulating treatment of mental than physical health (Frank and McGuire, 2000).

Understanding the net effect on suicide from treatment with SSRIs and other anti-depressant drugs is particularly important for government regulation. Policy discussions in the medical or public health literatures often assume that the primary or even exclusive goal of government policy is to reduce mortality.[2] However adopting a broader economic perspective of

[2] For example the American Academy of Pediatrics (2000) statement on gun violence argues: "The AAP affirms that the most effective measure to prevent firearm-related injuries to children and adolescents is the absence of guns

social welfare highlights the difficult tradeoff that would confront regulators if SSRIs do in fact increase suicide – crucial in this case would be careful empirical estimates that would allow policymakers to weigh the benefits from SSRIs from improved mental health against the costs from increased suicide mortality. If SSRIs instead *reduce* the risk of suicide completion, empirical estimates for the magnitude of the effect on suicide are still important for determining whether (or how much) the government should subsidize or otherwise encourage SSRI use. Despite a large increase in mental health treatment rates in the U.S. during the 1990s, between 2001 and 2003 only around one-third of those with serious mental disorders received treatment (Kessler, Demler et al., 2005).

A second reason why the effect of SSRI anti-depressants on suicide is of interest to economists is that the standard empirical tools of medical and public health research have not been very informative on the questions of greatest interest. Randomized clinical trials (RCTs) have sample sizes that are too small to detect effects on rare health outcomes such as suicide completion. Recent reports from several meta-analyses of randomized clinical trials indicating a risk of increased suicidal behavior were in fact using some (vaguely defined) measures of non-lethal "suicidality" (e.g., Fergusson et al., 2005; Hammad et al., 2006). In addition the subjects enrolled in RCTs typically exclude those at highest risk for suicide, and the conditions under which treatment subjects in clinical trials use SSRIs may differ from the standard level of care provided to patients outside of such trials.

Analyses of population-level data could in principle shed light on this issue by providing adequate statistical power to detect relationships between measures of SSRI use and suicide

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from homes and communities. Firearm regulation, to include bans of handguns and assault weapons, is the most effective way to reduce firearm-related injuries" (p. 893). We are not arguing for or against the AAP position, but rather simply intend to note that the AAP statement does not include discussion about how to weigh the benefits from reduced gun injuries against the costs from lost recreational benefits or defensive gun use against criminal attack or property loss.

mortality. However existing epidemiological studies have employed weak research designs, typically before-after comparisons using data from one or a few countries, which provide limited power to rule out the influence of confounding factors. More recently a few studies have applied basic panel-data techniques to county- or country-level data to at least control for year and jurisdiction-specific fixed effects (Dahlberg and Lundin, 2005; Gibbons et al., 2005; Ludwig and Marcotte, 2005). However in a standard panel-data analysis, variation in SSRI drug sales over time across countries is likely to be driven in part by local trends in demand (e.g., the prevalence of mental disorders). Even the timing of when SSRIs are first approved for sale in each country may be endogenous: previous research suggests that approval times are lower for important drugs for high-visibility health problems (Dranove and Meltzer, 1994; Carpenter, 2002), so changes within a country in the prevalence of important mental disorders like severe depression may affect approval timing for SSRIs. To date no study has tried to identify the SSRI-suicide relationship in population data using a clearly defined source of exogenous variation.

Our goal in this paper is to use country-level data on 27 countries for up to 25 years to identify the effect of SSRI sales on suicide completion rates, using just the variation across countries over time in SSRI sales that can be explained by differences in how quickly countries approve for sale new drugs in general. The efficiency of these drug review systems seems to be related to institutional factors such specific requirements for RCTs and the degree to which countries collect user fees from drug companies (Berndt et al., 2005), and is plausibly orthogonal to changes in mental disorders or other determinants of suicide rates across countries over time.

We estimate that an increase in SSRI sales of 1 pill per capita (around a 13% increase over 1999 sales levels) would reduce suicide mortality rates by around 3-4%. These estimates imply that around 1 suicide is averted for every 200,000 pills sold. Commonly used SSRIs can

currently be obtained in the United States for around $0.33 per pill, which suggests a cost per statistical life saved from increasing SSRI use of around $66,000 – far below most other government regulations or policies to improve health. Suicide prevention strategies that focus on restricting access to methods of self harm raise difficult conceptual questions about the appropriate way to value the life of someone who subjectively prefers death. If SSRIs reduce the risk of suicide by reducing access to a painless method of self harm, then the suicidal person may or may not experience a switch to SSRIs as a net benefit, depending on the transience or permanence of their state of pain. On the other hand if SSRIs reduce the risk of suicide by improving the subjective utility of life, then persons at risk for suicide, and the family and friends of those at risk for suicide, should have considerable willingness to pay for such an intervention.

The remainder of the paper is organized as follows. The next section develops a simple conceptual framework to help understand the mechanisms of action through which SSRIs may affect suicide. The third section briefly summarizes previous empirical work in this area, while sections 4 and 5 outline our data and analytic approach. Section 6 presents our empirical estimates while the final section discusses the scientific and policy implications of the results.

II. Conceptual Framework

To motivate the question of how anti-depressant drugs may affect suicide, consider the basic economic model of suicidal behavior, laid out by Hamermesh and Soss (1974). A person will commit suicide at age *a*, if the present value of expected lifetime utility falls below their "distaste for suicide" (*b*):

$$(1) \qquad Z(a,I) = \int_{a}^{d} e^{-r(m-a)} U[(C(m,I) - K(m)]P(m)dm < b$$

Among the determinants of the expected value of remaining lifetime utility (*Z)* are income that could be devoted to consumption (*I*), and health maintenance costs (*K*). P*(m)* is the

probability of living to age *m*, given living to age *a*.[3] Among the determinants of (K) are the current state of health and the marginal improvement in health that can be achieved by investing a unit of income. Among the determinants of (b) are certain kinds of fear (eg, fear of heights, fear of pain, fear of the unknown), altruistic concern about how a suicide might affect others, and the costs and risks associated with gaining access to various methods of self-harm.

Depression and treatment with new anti-depressant agents may affect the likelihood of suicide in a variety of ways. First, these new drugs could increase *Z* by reducing health maintenance costs. Prior to the introduction of anti-depressant drugs the primary means of treating depression came from psychotherapy or other forms of "talk" therapy, which were extremely costly in terms of time and money. Anti-depressant drug treatment may be faster, cheaper or more effective than talk therapy alone in treating depression, and so the introduction of these drugs may increase the prevalence of those with mental disorders who receive treatment as well as increase the effectiveness of treatment for the treated.

Alternatively, treatment for depression can be thought of as increasing *Z* by increasing the marginal utility of permanent income, i.e., by changing preferences. People suffering from severe depression have a more difficult time deriving enjoyment from anything in life than those without this condition. People with severe depression may also be less future-oriented and so more heavily discount future utility.

The important point here is that regardless of whether it operates on suicide is by changing the arguments of the utility function, changing its shape, or changing the discount rate, all else equal anti-depressant drug treatment would reduce suicide attempts.

Economists have expanded treatment of suicide beyond the Hamermesh and Soss "rational" or "depression" model, to recognize that not everyone who attempts suicide may do so

[3] Here d is the maximum life expectancy, and r is the discount rate.

with the intent to end their own life. Some people may injure themselves as a signal of unhappiness, with the intent of changing the behavior of others, or of punishing them (Rosenthal, 1993, Cutler, Glaeser and Norberg, 2001, Marcotte, 2003). We would expect strategic suicide attempts to be more common among those who are relatively powerless – like youth. The determinants of non-lethal self-injury may be different from the determinants of completed suicide, but like the "rational" model, the 'strategic' model predicts a positive relationship between unhappiness and suicide attempts, so by reducing depression, anti-depressant drugs should reduce strategic suicide attempts as well.

There are two mechanisms through which anti-depressant drug treatment could *increase* the risk of suicide. The first comes from heterogeneity in the effects of anti-depressant drug treatment on mental health (that is, on Z): antidepressants could reduce the risk of suicide among most patients, but heighten the risk of suicide among a few. In this case, the net effect of drug treatment would depend on the prevalence of the two types of patient, and clinicians' ability or inability to distinguish between them.

A second mechanism through which anti-depressants may increase the risk of suicide arises because the older tricylic anti-depressants are highly toxic in overdose, which means that prescriptions for these drugs provides access to a lethal and painless method for attempting suicide. The instrumentality hypothesis predicts that risk of suicide increases with access to methods of suicide that reduce (b), the "distaste for suicide" in the Hamermesh-Soss model of equation (1). This hypothesis assumes that the "demand" for self harm attempts is elastic to the time, money, risk or other challenges – what Mark Moore (1973) in a different context termed the "effective price" – of attempting suicide by particular means. This hypothesis also assumes

that suicide methods are not perfectly substitutable and that some methods are not widely available (that is, an almost perfectly elastic supply schedule set at a very low effective price).

Empirical evidence available from other contexts provides some support for the idea that instrumentality effects may be a concern. Suicide methods may not be perfect substitutes in part because of considerable variability in skill required, physical pain, likelihood of rescue, likelihood of a fatal outcome, and likelihood of permanent injury if the outcome is not fatal. Different methods of suicide are not readily available to everyone at all times – for example, "only" around one-third of American households own guns (Cook and Ludwig, 1996), and tall buildings or bridges are more common in some places than others. Existing research provides at least qualified support for the idea that changing access to particular methods of suicide – such as reduced access to firearms, or reducing the carbon monoxide content of domestic gas – may achieve at least temporary reductions in suicide mortality (Ludwig and Cook, 2000, Goldsmith et al., 2002, Duggan, 2003).

Within this framework, how might the introduction of SSRI drugs affect suicide? First, SSRIs have increased the prevalence of anti-depressant drug treatment., which may reduce suicide mortality by reducing the fraction of people with very low expected lifetime utility (Z). But the introduction of SSRIs may also reduce patients' access to a painless, lethal method of injury. The increase in drug treatment rates could also lead to an increase in the absolute number of patients with adverse treatment responses, and the lower toxicity in overdose may cause a paradoxical increase in mortality as an unintended consequence of an increase in suicide attempts among people (eg, children and youth) who use self-injury as a signal of distress.

III. Previous Empirical Research

While SSRIs have been shown to reduce depression, a direct link between SSRIs and suicides has 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; Ferguson et al., 2005).

There are several reasons why RCTs are not very informative about the relationship between SSRIs and suicide. First, the feasible sample sizes for RCTs are too small to detect effects on suicide and other relatively rare outcomes (Deyo, 2004), and so instead focus on other outcomes such as suicidal ideation or other "suicide related events." For example a recent meta-analysis of data from 702 separate RCTs, which together involved a total of 87,650 patients, found just 24 completed suicides , and so focused instead on an outcome measure that pools together fatal and non-fatal attempts (Fergusson et al., 2005). This study found a statistically significant increase in the risk of (lethal plus non-lethal) suicide attempts for patients receiving SSRI's compared to placebo, and no difference in the risk of suicide attempts between patients receiving SSRI's and tricyclic antidepressants. Similarly, a recent FDA meta-analysis of 20 RCTs also found a modest positive association between SSRI use rather than placebo for non-lethal "suicidality" in children and adolescents (Hammad et al., 2006. However as Baldessarini et al. (2006, p. 246-7) argue, only a small fraction of patients with suicidal thoughts attempt suicide, few attempts prove to be fatal, and risk factors for suicide attempts and completions differ markedly.

The second problem is that the patients enrolled in RCTs may be unrepresentative of the average patient, and the treatments offered in RCTs may be unrepresentative of the usual community levels of care. For ethical and practical reasons, most clinical trials avoid enrolling

subjects with prior histories of suicide attempts or current histories of suicidal ideation (Person et al., 2001); thus, these studies exclude those at highest risk for suicide (Goldsmith et al., 2002; Zimmerman et al, 2002; Baldessarini, 2005, Ferguson et al., 2005, Baldessarini et al., 2006, Kahn et al., 2000, 2001).

In response to the limitations of RCTs, previous investigators have employed a variety of "non-experimental" research designs to study the link between SSRI's and suicide.. Several authors have concluded that the most promising designs for identifying treatment effects on suicidal behavior would be whole-population based studies However, most previous population-based studies have used research designs with limited ability to rule out the influence of competing explanations.

Most population-based studies of SSRIs and suicide have compared suicide rates before and after SSRIs become available in a particular jurisdiction. Studies of Sweden, Finland, Norway, Hungary and Australia using this "interrupted time series" design have found that national suicide rates declined as SSRI use increased over time (Isacsson, 2000, Rihmer, Belso, and Kalmar, 2001, Ohberg et al., 1998, Hall et.al., 2003), although a study in Italy found no noticeable effect (Barbui et al., 1999).

Unfortunately, the independent effects of SSRI use are difficult to infer from studies that rely on simple before-and-after comparisons within a given country. The overall problem with this study design is that it cannot distinguish the effects of the policy change – in this case, the introduction of SSRIs – from the effects of the myriad of other factors that might be changing in that population over the same period of time.

The difficulties with simple pre-post designs are highlighted by the case of the United States; see Figure 1. A comparison of suicide rates before and after SSRIs were introduced to

the American market reveals that suicide rates were higher in the years just before 1987 than in the years just after. This might suggest that SSRI's played a role in reducing risk of suicide. But a more careful examination shows that suicide rates began to decline even before SSRIs came onto the market, which argues against assigning much causal role to SSRIs. On yet another hand, the rate of decline in suicide seems to have accelerated during the 1990s, when SSRI sales increased most dramatically, and this would seem to argue in favor of a protective effect of SSRIs. Our point is that a single time-series provides a weak basis for divining the causal link between SSRIs and suicide. This basic problem makes it difficult to draw causal inferences from studies that use a simple before-and-after research design.

One way to improve on this before-and-after design is to compare suicide outcomes across multiple jurisdictions that have changed their policies regarding SSRI use at different times. This approach enables investigators to use standard panel-data techniques to control for unmeasured confounding variables that are common to a given country in all time periods (country fixed effects) or common to all countries at a given point in time (year fixed effects).

Two studies have used this basic panel setup to examine variation in SSRI sales across time and space within a single country. Using data for the U.S. for the years 1996 to 1998, Gibbons et al. (2005) find that increases in prescriptions for SSRIs and other newer anti-depressants are associated with lower suicide rates both within and between counties. The authors note that this is consistent with anti-depressant efficacy and low toxicity in the event of a suicide attempt, but also with the possibility that local SSRI sales levels may be positively correlated with the quality of local mental health care. Dahlberg and Lundin (2005) examine variation in SSRI sales across counties and age groups in Sweden, and find no significant association between SSRI sales and suicide rates.

A third study using this same basic approach examines variation in use of SSRIs across countries over time. Ludwig and Marcotte (2005) use data from 27 countries over 20 years, and condition on country-specific linear trends as well as country and year fixed effects. They find that an increase in SSRI sales of one pill per capita is associated with a 2.5 percent decline in suicide rates. This study serves as the launching-off point for the current research.

An important remaining problem is that SSRI sales may be influenced by other factors that affect suicide mortality. There are several reasons why this could be true. For example, if therapy prevents suicide, and if countries with improving mental health systems also have increasing access to psychiatric medications, then any deleterious effects of SSRI sales on suicide risk might be masked by a protective effect of access to general mental health treatment. Or, rising suicide rates may drive increased anti-depressant drug sales, or cause government regulators to bring SSRIs to market sooner. Previous research suggests that more important drugs that address more high-visibility health problems seem to be approved by the FDA more quickly (Kaitin et al., 1991 ; Dranove and Meltzer, 1994 ; Carpenter, 2002). In this case, a beneficial effect of SSRI sales on suicide risk might be masked by the positive correlation between suicide rates and market demand for treatment of depression. In the present study, we seek to overcome this source of bias by using an instrumental variables approach, using just the variation in SSRI sales that can be predicted from the sales of non-psychiatric medications introduced during the same time period.

IV. Data

The present study builds on the data from Ludwig and Marcotte (2005). We examine annual suicide counts from 27 separate countries for which we have data on SSRI sales: Australia, Austria, Belgium, Belorussia, Bulgaria, Canada, the Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Portugal, the Slovak Republic, Slovenia, Spain, Ukraine, the United Kingdom, and the United States. The annual suicide observations in this panel are from the Centers for Disease Control in the United States, and for other countries from the World Health Organization (WHO), which in turn obtained them from national vital statistics reporting systems.

Most of these suicide reports were based on the ICD-9 coding system for cause of death, although by the end of the panel some countries used the newer ICD-10 system. While data from the United States suggests that both coding schemes capture suicides in a consistent fashion (Anderson et al., 2001), in our analysis we accounted 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. Our analytical methods also account for the possibility of 'fixed' cultural or institutional differences across countries in their coding practices around suicide.

Data for each country included the annual number of total suicides and by gender and age, as well as relevant population counts. We have these data for at least 1980 through 1999 for all countries, and have been able to extend the panel back to 1975 and up through 2000 for at least half of our 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 obtained information for each of these 27 countries about dates of approval and annual sales of all SSRIs, including fluvoxamine, paroxetine, fluoxetine, sertraline, citalopram and venlafaxine These 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 initially measured SSRI use as the total number of pills sold per capita in each country in a year.

In principle, the fact that data on 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).

To implement our IV strategy we obtained information about dates of introduction for the 8 best-selling drug classes in 1998-2000, which include SSRIs. The non-SSRI drug classes are summarized in Table 2: Statins, a class of drugs designed to lower LDL ("bad") cholesterol; proton pump inhibitors (PPIs), which are used to treat stomach and duodenal ulcers; Cox-2 anti-inflammatory drugs; alternative anti-convulsant agents, used to treat seizures; two drug classes used to treat hypertension, calcium channel blockers (CCBs) and angiotensin-converting enzyme (ACE) inhibitors; and atypical anti-psychotics used to treat schizophrenia.

In our analyses we also controlled 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. Descriptive statistics for these and other measures are presented in Table 1.

V. Empirical Approach

To describe the empirical approach used in the present paper we begin with the standard panel-data setup as in equation (1), used by Ludwig and Marcotte (2005). The outcome is the natural log of country *i*'s suicide rate per 100,000 people in a given year *t*, denoted as Y_{it}. The key explanatory variable, $SSRI_{it}$, equals the number of pills of SSRIs sold per capita in country *i* in year *t*, while v_{it} represents a stochastic residual ("error") term.

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

The model includes a series of control variables for each country by year, X_{it}, including the socio-demographic variables, the proportion of the population in different age groups, 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. The model also includes a separate intercept term for each country, d_i, to account for the influence of unmeasured factors – for example, religious or cultural traditions- that might 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 of the countries in the sample. The model also includes a separate linear trend term for each country, equal to $t \times d_i$, where t indicates a linear time trend and d_i are

the country indicators. These country-specific linear trends control for the possibility that countries have distinct (but linear) trends in suicide rates for reasons that are not captured by the covariates or common year fixed effects.[4]

The obvious problem with this standard panel-data approach is that SSRI sales may be endogenous to the conditions that influence suicide. For example, if mental health conditions change within a country in a way that leads to increased depression, we might see an increase in SSRI sales and an increase in suicide rates, which would lead estimates from the standard analysis (equation 2, above) to understate (in absolute value) any protective association between SSRI sales and suicide mortality. On the other hand, countries that are improving overall access to mental health services might experience an increase in SSRI sales and a reduction in suicide rates, leading the standard analysis to overstate an apparent protective association between SSRI's and suicide

As a way to understand the intuition behind our preferred IV estimator, consider first a research design that would estimate the SSRI-suicide relationship using just the variation in sales across countries over time that can be explained by the fact that some countries approved SSRIs for sale earlier than others. This type of IV design uses the date that SSRI's are first adopted in each country, and "throws away" variation in SSRI sales that is due to differences across countries in the rate at which SSRI sales grow over time, once these drugs are on the market, The SSRI-suicide relationship is identified under the assumption that the timing of adoption of SSRIs is independent of other determinants of suicide.

[4] The raw data suggested that these country-specific linear terms may be important, because the countries in our sample were experiencing quite different suicide trends over our sample period even before SSRI use became widespread. For example, in Austria the suicide rate declined from 25.4 per 100,000 in 1980 to 23.3 by 1990 and 19.0 by 1999. In contrast, the suicide rate in Bulgaria increased steadily from 13.4 in 1980 to 14.5 by 1990, and15.8 by 1999.

Mechanically, this initial IV design would be estimated using the standard two-stage least squares setup, where the first stage involves regressing SSRI sales in each country and year against the covariates, country and year fixed effects and country-specific linear trends, as well as our instruments, Z_{it} indicating how many years SSRIs had been on the market in each country and year (equal to 0 for country-year observations where SSRIs had not yet been approved).

(3) $SSRI_{it} = a_0 + a_1 X_{it} + a_2 Z_{it} + d_i + d_t + (t \times d_i) + v_{2it}$

Specifically, the instrumental variables that we are use in our initial design consist of a series of binary indicator variables equal to 1 if calendar year *t* in country *i* is the Nth year that the country has had SSRIs on the market and equal to 0 otherwise. For example $Z(1)_{it}$ is equal to 1 if year *t* is the first year that country *i* had SSRIs on the market, and equal to 0 for all other country-year observations in our panel dataset, and so on.

In a model without other covariates, this first stage regression will assign predicted SSRI sales to each country during the Kth year that SSRIs are on the market in that country using the average sales volume of SSRI sales observed across all countries during the Kth year that each country was selling SSRIs. The approach in that sense "throws away" all of the variation across countries over time in the rate of growth in SSRI sales once they are approved for sale. By replacing the actual with the predicted value of SSRI sales in the second-stage equation (4), we would identify the coefficient b_1 using just the variation in SSRI sales in the panel that can be explained by differences in the timing of SSRI drug adoption across countries.

(4) $Y_{it} = b_0 + b_1 SSRI_{it} + b_2 X_{it} + d_i + d_t + (t \times d_i) + v_{3it}$

Our *preferred* IV estimator is motivated by the possibility that the process through which a country approves SSRIs could itself be endogenous to the determinants of mental health and suicidality. Instead of using the *actual* date of adoption of SSRIs to instrument for SSRI sales,

we use the *predicted* date of adoption of SSRIs, based on the lag with which countries approve other new drugs for public use.

There are many cultural and institutional reasons why drug approval times might vary across countries. To take just one example, the U.S. Prescription Drug User Fee Acts (PDUFA) was intended to provide additional resources to FDA to speed up drug approvals by charging drug companies user fees, user fees from drug companies varies considerably – for example the United Kingdom's Medicine and Healthcare Products Regulatory Agency receives 100% of funding from user fees, while Japan's Koseisho regulatory agency does not charge any user fees (Berndt et al., 2005). Sociological factors may also influence patterns of technology adoption. For example, Skinner and Staiger (2005) found that some states in the US consistently adopted effective new technologies, whether hybrid corn, tractors, or heart attack treatments, earlier than other states. They also found that early adoption was closely associated with social capital and state-level 1928 high school graduation rates, but not per capita income, density, or (in the case of Beta Blockers) expenditures on heart attack patients.

To illustrate our 'preferred' research design, consider Statins, which like SSRIs were introduced in the 1980s as a new agent to treat a common illness, with fewer side effects compared to previous drugs. Both types of medication had high sales volumes once introduced to the market, and were often prescribed by general practitioners. However, *unlike* with SSRIs, we expect the government approval process for Statins to be orthogonal to the underlying determinants of suicidality. We can therefore use the lag time from when Statins were first introduced anywhere in the world market to when Statins were adopted in a particular country to as an estimate for the lag time to adoption of SSRI's, if SSRI adoption were independent of risk factors for suicide.

The vector of instruments for equation (3), Z_{it}, will now contain a series of indicator variables, $Z(N)_{it}$, equal to 1 if country i in year t is predicted to have had SSRIs on the market for N years based on the lag with which country i first brought Statins to market, and equal to 0 otherwise (for N=1 to 25). That is, for each country we predict the year of predicted adoption of SSRIs as being equal to 1984 (the first year that SSRI's became available anywhere), plus the number of years that it took, on average, for each country to bring Statins to market compared to the year that some first country sold each particular drug in our sample. The indicator for the first year of SSRI sales in country i equals 1 in the year that is equal to this predicted adoption year, and equals 0 otherwise. The indicator for the second year of predicted SSRI sales equals 1 in the year following the predicted adoption year, and equals 0 otherwise; and so forth.[5]

This IV strategy takes advantage of the fact that SSRI sales vary across countries over time in part because some countries approve these drugs for sale sooner than others, but ignores the variation in SSRI sales that comes from expedited approval of SSRIs in countries with particularly pressing mental health problems. This design also takes advantage of the fact that SSRI sales grow over time within countries as a function of time since SSRIs have been on the market, but throws away variation in SSRI sales that comes from the fact that SSRI sales grew faster in some countries than in others once these drugs were on the market.

Table 3 illustrates the basic idea. The first column shows the difference in years between when SSRIs were first sold by *any* country in the sample, and when *each particular country* first allowed SSRIs to be sold. Countries are listed in order of their date of first sale of SSRIs. For

[5] For example, SSRIs were actually first sold in Belgium in 1985, one year after their introduction anywhere in the world. But Belgium first sold Statins two years after they were first sold anywhere. So in our preferred IV design the instrument $Z(1)_{it}$ equals 1 for Belgium in 1986, $Z(2)_{it}$ equals 1 for Belgium in 1987, and so on. In a two stage least squares setup without other covariates the first stage equation described by (3) would assign Belgium SSRI sales of zero up through and including 1985, then in 1986 assign Belgium the average SSRI sales level for all countries in the first year they are predicted to have had SSRIs on the market based on implementation lag of Statins, and so on.

example SSRIs were first brought to market anywhere in this sample in 1984 in Germany, while in the United States the first SSRI sales occurred four years later in 1988. The next column shows the number of years between when Statins were first sold anywhere in the sample, and when they were first sold in each particular country. The lags for SSRIs are very similar to the lags in time-to-first sale for Statins, with a correlation between the lags from first sale anywhere to first sale in each country equal to +0.53. That these correlations are positive is consistent with the idea that some countries are generally slower to bring new drugs to market than others. However the fact that the correlations are less than perfect is consistent with our concern that some countries may bring SSRIs to market more quickly than others, in response to short-term changes in conditions correlated with the country's suicide rates.

For illustrative purposes we have focused our discussion here and our initial empirical results below on an instrument constructed from first-sale lags for just a single drug class, Statins. However we demonstrate below that our estimates are robust to using the average first-sale lag observed for all of the other top-selling drugs that were introduced during the 1980s and are unrelated to the treatment of mental health, or to using an instrument constructed individually from any of these other drugs.

The other critical identifying assumption for our empirical strategy is that countries that are usually "early approvers" of new drugs do not experience sharp changes in suicide rates in any consistent direction, compared with countries that are usually "late approvers." It might seem that we have a problem: countries that are early adopters for Statins and PPIs might be different in enduring ways from countries that are late adopters (Skinner and Staiger, 2005), and these differences might be associated with different baseline suicide rates. But we take account of enduring or even slowly-changing features of the society by using country-fixed-effects and

country-specific linear trends; any baseline country-specific propensities to suicide are conditioned out of the analysis.

VI. Results

In what follows we first show that a standard panel-data setup generates an estimated negative and statistically significant association between SSRI sales and suicide rates, replicating Ludwig and Marcotte (2005). We then provide some evidence that variation in both the rate of growth in SSRI sales once these drugs are approved, and the timing of when SSRIs are first sold, are both endogenous. We conclude by presenting results from our preferred IV estimator, which show a larger negative association between SSRI sales and suicide rates and which do not appear to be sensitive to a variety of changes in our basic estimation approach.

A. Baseline Estimates

Table 4 presents the results of estimating the standard panel-data setup described by equation (2) above. 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 suggests that an increase in SSRI sales of 1 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.

Our preferred model, shown in the second column of Table 4, implies that an increase in SSRI sales of 1 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 the first

column. The implied elasticity of suicide with respect to SSRI sales equals -.05. The second column also shows that after controlling for country and year fixed effects as well as country-specific linear trends (coefficients not shown in Table 4 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 baseline findings do not appear to be very sensitive to our choice of functional form. 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), we find that an increase of 1 pill per capita in SSRI sales is associated with a change in the suicide rate of -0.497 ($p<.05$), 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 population 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. In what follows we focus on applying 2SLS to estimate equations (3) and (4) using the basic log-linear specification described in column 2 of Table 4.

B. "Throwing Out" Variation in SSRI Sales Growth

Table 5 present the results of estimating the relationship between SSRI sales and suicide mortality rates using just the variation in SSRI sales across countries over time that can be explained by the timing of when SSRI sales are *actually* first sold in each country. This IV estimate basically "throws out" the variation in SSRI sales across countries over time that is due to differences across countries in the rate at which SSRI sales grow once these drugs are on the market, which will obviously be endogenous to mental health conditions in the country. This is

not our preferred IV estimator, because we believe (and demonstrate below) that the timing of SSRI approval is also endogenous, but we discuss these estimates briefly to help develop the intuition of our preferred IV estimates shown next and to demonstrate that variation in rate of growth in SSRI sales may in fact be problematic for our present purposes.

The first column of Table 5 presents the results of regressing SSRI doses sold per capita for each country and year against a series of indicators for the Kth year that SSRIs were sold in a given country in a given year (for K=1 to 17). The estimates shown in the first column initially do not regression-adjust for anything else, to help fix ideas. The coefficients shown in column 1 represent the average SSRI sales levels for the countries in our sample during the 1st year SSRIs were on the market (0.46 doses per capita), the 2nd year SSRIs were on the market (0.59 doses per capita), and so on. Note first that the general pattern is for SSRI sales to increase steadily over time up through about the 12th year SSRIs are on the market; the pattern of coefficients changes at this point, but this is due in large part to changes in the composition of countries that contribute to estimating the coefficients for the 12th through 17th year SSRIs are on the market. (As Table 3 suggests, we observe up to 17 years of post-SSRI sales data for only a subset of the countries in our analytic sample).

The second column of Table 5 shows the first-stage coefficients for our instruments but now conditioning on the same set of covariates as included in our baseline panel-data model in the second column of Table 4 – namely, country and year fixed effects, country-specific linear trends, and covariates such as GDP per capita, divorce rates and indicators for whether the country uses the ICD-10 versus ICD-9 coding system to record mortality. The basic pattern is the same as shown in the first (no controls) column, although conditioning on country and year fixed effects and the other covariates helps smooth out the pattern of coefficients in the later

years to adjust for compositional changes in the analytic sample. Note also that the instruments have strong explanatory power in the first stage even conditioning on the other covariates – the first-stage F statistic for the joint significance of the instruments is 26.6, with a p-value of less than .001.

The third column presents the results of our second-stage equation, which replaces the actual SSRI sales figure with the predicted value based on the instruments from column 2 in a regression against the log suicide rate per 100,000 residents. The point estimate is equal to -.058 (standard error .016). The fact that this IV estimate is about twice as large as the baseline panel-data estimate (column 2, Table 4) provides at least suggestive evidence that the variation in SSRI sales across countries once SSRIs are on the market is driven in part by worsening in country mental health conditions.

Of course for IV estimates to be valid the selected instruments must be unrelated to the outcome of interest, except through the channel of interest. If the dates of adoption of SSRI's, after controlling for country and year fixed effects and our other covariates, have no further association with suicide rates except through their influence on SSRI sales, then the predicted value of SSRI sales will be orthogonal to the unmeasured but varying country-year determinants of suicide reflected in the error term of the second stage equation (e_{it}), and the procedure would generate an unbiased estimate for the causal effects of SSRI sales on suicide. We can formally test this hypothesis by estimating a reduced-form regression of each country's annual log suicide rate against the initial instrument set, consisting of indicator variables for the Kth year SSRIs are on the market in country *i* and calendar year *t*, and a set of indicator variables for the first

through fifth years *before* a country introduces SSRIs for sale.[6] If the date of first sale is unrelated to the year-by-year variations in suicide rates, then we should fail to reject the null hypothesis that these pre-SSRI-sales indicators are jointly zero. Yet the F-statistic for this specification test is equal to 8.3, statistically significant at the .001 level. It appears that suicide rates before entry to market *do* predict the date of first sale and that the timing of adoption of SSRIs seems to be related to the country's trends in depression or suicide.

C. Preferred IV Estimates

Our preferred IV estimation approach is illustrated by the results shown in Table 6. The first column highlights the intuition behind our preferred first-stage equation: We regress SSRI sales (doses per capita) against indicators the number of years SSRIs would have been on the market in a given country-year observation if that country had brought SSRIs to market with the same lag (compared to the first seller in the world market) as for Statins, the cholesterol drug. These indicators basically capture year of first sale for SSRIs ignoring the speed-up or delay in approval for SSRIs compared to Statins.

These instruments have significant explanatory power even after conditioning on country and year fixed effects, country-specific linear trends and other covariates, as shown in the second column of Table 6. The F-statistic on the instruments is equal to 238.1, with a p-value <.001. Our IV estimates would not appear to be susceptible to concerns about weak instruments.[7]

The third column shows the results of our second-stage equation, regressing the predicted value of SSRI sales for each country-year observation against log suicide rates, which yields a

[6] These regressions also include our standard set of socio-demographic covariates, country and year fixed effects and country-specific linear trends, weight by country population in each year, and adjust standard errors for serial correlation using the approach suggested by Bertrand et al. (2004).

[7] Staiger and Stock (1997) suggest that a joint F-test for the null hypothesis that the instruments are jointly zero in the first stage equation should be equal to at least 10.0 to avoid bias.

coefficient of -0.041 (se=.017). This result is about two-thirds larger than the basic panel-data baseline specification shown in column 2 of Table 5.

These instruments appear to be successful in overcoming the endogeneity of the timing of when SSRIs are first sold across countries, as suggested by the results shown in the final column of Table 6: Indicators for years before SSRIs were predicted to be sold based on each country's lag in introducing Statins for sale (compared to the world's first seller) are jointly insignificant, with a F-test statistic equal to 1.15 (p=.36).

How sensitive are these estimates to how we predict first sales of SSRIs using first-sale lags for other drugs? To help develop the intuition behind our estimation approach we have focused on using first-sales lags for Statins, which as noted above is like the SSRIs in that it is one of the top-selling drug classes and was introduced in the early- to mid-1980s, but is unlike SSRIs in that Statins are not used to treat mental health conditions, and so the rate at which Statins are adopted should be unrelated to unmeasured determinants of mental health outcomes across countries over time. We also replicate this analysis using a broader class of drugs to predict SSRI sales timing. For each of the four top selling drug classes that were introduced during the 1980s and do not treat mental health conditions (Statins, calcium channel blockers, proton pump inhibitors, and angiotensin-converting enzyme inhibitors), for each country we calculate the lag from first sale of that drug anywhere in the world to when that drug was sold in that particular country. Then for each country we calculate the average first-sale lag across these four drug classes.

When we use the average first-sale lag across these four drugs to construct an instrument for when countries would have first sold SSRIs, we obtain results that are qualitatively similar to those from using Statin sales lags alone. As shown in the first row of Table 7, the second-stage

point estimate is equal to -.031, with a standard error of .014. As with our estimates using just the Statins instruments, the drug-bundle instruments have substantial explanatory power in the first stage (F-test statistic of 54.1, p<.001). And as with the Statins estimates, a reduced-form regression of log suicide rates against our instruments (indicators for years since SSRIs were predicted to have been on the market) together with indicators for years *before* SSRIs were predicted to have been sold suggest the latter are not jointly significant (F=1.3, p=.29). The next three rows show the results are qualitatively similar when we use each element of this drug bundle alone to predict first SSRI sales, although the statistical significance varies somewhat across specifications owing in part to variation in standard errors across models.

The final rows of Table 7 show the results of using the other best-seller drug classes to construct our instrument. These other drugs do not perform as well, for two reasons. First, some of these drug classes were introduced to the world market much later than were SSRIs (for example Cox-2 anti-inflammatory drugs were first sold in 1999, and alternative anti-convulsant agents to treat seizures were first sold in 1993). Our instruments intend to capture the counter-factual of what the pattern of first SSRI sales across countries would have looked like following introduction of SSRIs anywhere in the world in 1984 if the rate at which countries approved SSRIs for sale were not influenced at all by the country's mental health conditions. Because drug approval times vary substantially over time within countries, using drug approval times from the 1990s will be a poor predictor of SSRI sales lags.[8]

The second reason is that the drugs in the final three rows are all used to treat mental illnesses: Anti-convulsant drugs are used to treat mood-disorders; Anti-psychotics are used in treatment of schizophrenia, and; ADHD drugs in the treatment of attention deficit hyperactivity

[8] For example Berndt et al. (2005) report that the mean approval teams in the U.S. for new molecular entities was equal to 33.6 months in 1979-86, 28.2 months in 1986-92, 18.6 months in 1992-97, and 16.1 months for 1997-2002.

disorder. It is likely that approval of these drugs is endogenous to local trends in mental health problems as with SSRI approval times.

D. Sensitivity Analysis

One potential concern with our estimates has to do with measurement problems associated with recording suicide across countries over time. Our suicide variable is that most values are recorded by countries using the ICD-9 coding system, although during our panel some countries shift to the ICD-10. In principle this coding change could affect recorded suicide rates in some countries. To determine whether this is a problem we re-calculate our estimates using the Statin and drug-bundle estimates shown above, dropping all country-year observations where countries classify suicides using the ICD-10 system. The estimated coefficients equal -.039 and -.032, respectively, quite close to those shown in Tables 6 and 7.

Many other common concerns about measuring suicide rates across countries [see Douglas, 1967] should be addressed by our model. 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.

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 Statin and drug-bundle IV estimates setting SSRI sales figures before 1990 to

missing values. This 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.

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 20mg and 40mg 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 others. However, like our measure of SSRI pills, this 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.

When we use our SSRI variable measured in kilograms sold per capita we obtain estimates using our Statin and drug-bundle instruments that are negative but with smaller t-statistics compared to those shown in Tables 6 and 7 (t=-1.46 for the Statin instrument and t=-1.66 for the drug-bundle instrument). In our view the dose per capita measure is the more appropriate indicator for the prevalence of SSRI use within the population, since it is 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 towards zero, consistent with the pattern that we find in our data.

One additional 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 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 are similar to those shown above. 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. When 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) we get an estimate almost identical to our preferred IV models.

VII. Discussion and Conclusions

Our results are consistent with the hypothesis that the net effect of the introduction and subsequent sales of SSRIs is to reduce death by suicide. Using the predicted date of SSRI adoption as our instrument, we find that an increase in SSRI sales of 1 pill per capita per year (about a 13% increase over 1999 sales levels) is associated with a decline in suicide mortality of around 3-4%. This IV estimate is larger in absolute value than the association estimated from the standard panel-data analysis of Ludwig and Marcotte (2005), a difference that is consistent with our concern about the presence of bias with other estimation approaches.

Understanding the effects of SSRI antidepressants on suicide is important for government regulators as well as doctors, patients with severe depression, and family and friends of those suffering from this condition. Previous randomized clinical trials (RCTs) are not able to identify the effects of SSRIs on suicide mortality in part because of small samples that exclude those at highest risk for suicide. Many studies instead focus on measures of non-lethal "suicidal behavior," but the association between these indicators and actual suicide mortality is not at all clear. Another problem with existing clinical research is that the conditions under which participants in RCTs use SSRIs (for example the level of monitoring by physicians) may differ from the usual community standard of care for patients using these drugs outside of the RCT

context. In light of these practical and ethical constraints, it remains an open question of whether any RCT could ever adequately identify the effects of SSRIs on suicide completion rates.

Previous epidemiological studies try to address this problem by using population-level data to gain sufficient statistical power to detect impacts on rare outcomes like suicide mortality. However must non-experimental studies in this literature use research designs that provide limited power in ruling out alternative explanations for observed associations between aggregate measures of SSRI use (such as sales volume) and suicide mortality. The best studies in this literature to date use standard panel-data techniques to control for area- and period-fixed effects and in some cases a handful of observable covariates. But changes within areas over time in SSRI use are likely to be related to other hard-to-measure factors that influence trends in both SSRI use and suicide mortality, such as mental health or other government policies focused on treating mental health conditions.

In the absence of useful evidence from randomized experiments about the effects of SSRIs on suicide mortality, for the foreseeable future clinical and policy decisions will necessarily be guided in large part by non-experimental findings. We believe our study represent a substantial improvement on what has been reported in previous research by developing the first estimates that have adequate power to detect impacts on suicide mortality and at the same time employ a plausibly exogenous source of identifying variation in SSRI use. Our design seeks to combine the statistical power of the epidemiological approach with the ability to derive causal inferences from the "natural experiment" approach to empirical research.

The key to our research design is the variation across countries in the rate at which they approve for public sale new drugs in general. We demonstrate that this instrument has very good first stage power in explaining variation in actual SSRI sales levels across countries over time in

our panel dataset. But the lag in SSRI adoption predicted by the rate at which countries adopt other drugs that are not used to treat mental health disorders will be plausibly orthogonal to other determinants of suicide mortality. Empirical support for this point comes from our evidence that suicide rates are not systematically different in countries during the years right before we predict SSRIs to go on the market using our instrument for average lag to first sale of other drugs. In contrast we find that suicide rates are systematically different in countries during the years right before they *actually* first bring SSRIs to market, which supports our concern about the endogeneity of SSRI sales in standard panel-data models.

Our estimates suggest that SSRIs may be an unusually cost-effective means for saving lives on balance, although understanding more about heterogeneity in SSRI effects on different types of patients remains what is arguably the top priority for future research in this area. In any case commonly used SSRIs can currently be obtained in the United States for around $0.33 per pill. Our estimates suggest as a result that each additional $66,000 spent on SSRIs will on balance save one statistical life, a cost per life saved that is far below most other public health interventions. The finding is particularly important given what appear to be very low current rates of mental health treatment, even in affluent developed countries like the U.S.

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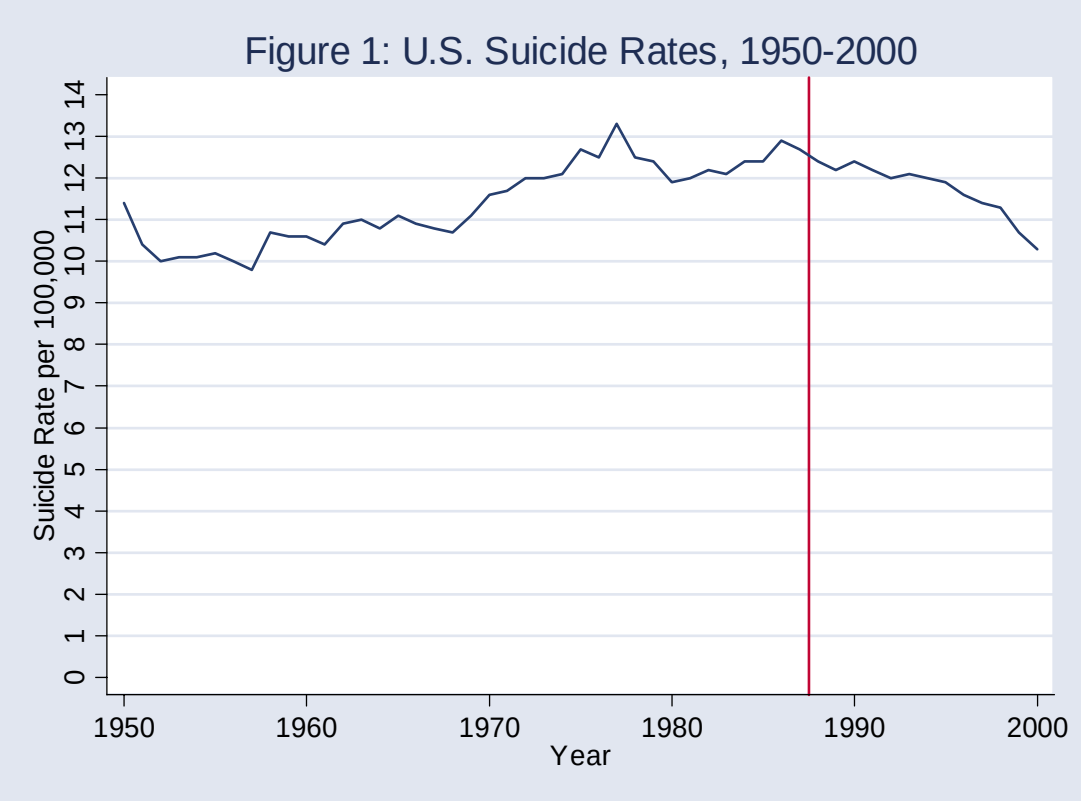

Figure 1: U.S. Suicide Rates, 1950-2000
Suicide Rate per 100,000
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1950
1960
1970
1980
1990
2000
Year

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
(% GDP missing)	.152	.360
Divorce rate	36.778	14.556
(% divorce missing)	.190	.393
Unemployment rate	8.564	3.821
(% unemployment missing)	.095	.294
% 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 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

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

Table 2: Top Selling Pharmaceutical Classes, 1998-2002

Drug class	Drug purpose	Year first sold	Country first sold
Selective serotonin reuptake inhibitors	Anti-depressant	1984	Germany
Statins	cholesterol	1987	US
Proton pump inhibitors	ulcers	1988	Netherlands
Cox-2	anti-inflammatory (pain)	1999	US and others
Alternative anti-convulsant agents	seizures	1993	US and UK
Calcium channel blockers	hypertension	1982	US, Spain, Italy, Finland, Australia, Canada and Ireland
Atypical anti-psychotics	schizophrenia	1988	Netherlands
ACE inhibitors	hypertension	1982	Canada, Portugal, Australia and France

Table 3: Lag in Drug Introduction Dates

Country	Lag in SSRI sales	Lag in Statin sales
Australia	-6	-3
Austria	-1	-1
Belgium	-1	-2
Bulgaria	-10	-15
Canada	-5	-1
Czech Republic	-6	-7
Finland	-5	-1
France	-2	-2
Germany	0	-7
Greece	-6	-2
Hungary	-6	-7
Ireland	-5	-2
Italy	-4	-2
Latvia	-11	-8
Luxembourg	-1	-11
Netherlands	-1	-2
Norway	-12	-9
Poland	-9	-8
Portugal	-2	-2
Slovak Republic	-6	-7
Slovenia	-8	-7
Spain	-3	-4
United Kingdom	-3	-2
United States	-4	0

Table 4
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)
<u>% population in age group:</u>				
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)**
<u>Model specification</u>				
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

NOTES: 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

Table 5: Illustrative IV Estimates for International Panel Data Years 1980 to 2000

	Outcome = SSRI doses sold per capita	Outcome = SSRI doses sold per capita	Outcome = log (suicides / 100,000)	Outcome measure = log (suicides / 100,000)
SSRI doses sold per capita (Predicted value)			-0.058 (0.016)**	
Indicators for Years Before SSRIs on Market:				
-5				-0.061 (0.017)**
-4				-0.097 (0.037)**
-3				-0.119 (0.046)**
-2				-0.167 (0.059)**
-1				-0.253 (0.071)**
Indicators for Years Since SSRIs on Market:				
1	0.46 (0.18)**	0.49 (0.15)**		-0.378 (0.094)**
2	0.59 (0.19)**	0.77 (0.19)**		-0.499 (0.110)**
3	0.72 (0.22)**	1.03 (0.31)**		-0.665 (0.141)**
4	0.89 (0.24)**	1.39 (0.46)**		-0.839 (0.164)**
5	1.36 (0.38)**	1.92 (0.68)**		-1.036 (0.191)
6	2.05 (0.56)**	2.71 (0.89)**		-1.241 (0.224)**
7	2.84 (1.04)**	3.74 (1.17)**		-1.451 (0.260)**
8	3.75 (1.33)**	4.74 (1.41)**		-1.677 (0.299)**
9	4.84 (1.58)**	5.81 (1.63)**		-1.939 (0.334)
10	5.67 (1.67)**	6.64 (1.84)**		-2.205 (0.376)**
11	6.92 (2.39)**	8.07 (2.09)**		-2.509 (0.426)**
12	8.19 (2.71)**	8.83 (2.36)**		-2.802 (0.474)**
13	5.03 (1.76)**	9.93 (2.73)**		-3.139 (0.527)**
14	4.13 (2.49)	11.09 (3.00)**		-3.470 (0.593)**
15	2.37 (1.15)**	12.28 (3.58)**		-3.878 (0.654)**
16	1.87 (0.72)**	12.62 (3.93)**		-4.243 (0.726)**
17	8.24 (0.05)**	12.93 (3.82)**		-4.567 (0.757)**
Model specification Year indicators, country indicators, country-specific linear trends, and socio-demographic controls?	No	Yes	Yes	Yes
F statistic (p-value) for indicators for years before SSRIs on market				8.30 (p<.001)
F statistic (p-value) for indicators for years since SSRIs on market		26.62 (p<.001)		
Sample (N)	515	515	492	492
R-squared	0.58	0.99	0.98	0.99

NOTES: 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

Table 6: Preferred IV Estimate – Identifying SSRI Sales Using Date of 1st Statins Sales

	Outcome = SSRI doses sold per capita	Outcome = SSRI doses sold per capita	Outcome = log (suicides / 100,000)	Outcome measure = log (suicides / 100,000)
SSRI doses sold per capita (Predicted value)			-0.041 (0.017)**	
Indicators for **Predicted** Years Before SSRIs on Market (based on lag for Statins):				
-5				-0.039 (0.027)
-4				-0.055 (0.053)
-3				-0.081 (0.075)
-2				-0.138 (0.095)
-1				-0.190 (0.121)
Indicators for **Predicted** Years Since SSRIs on Market (based on lag for Statins):				
1	0.029 (0.088)	0.059 (0.128)		-0.250 (0.151)
2	0.062 (0.099)	0.042 (0.248)		-0.315 (0.188)
3	0.121 (0.115)	-0.155 (0.353)		-0.376 (0.223)
4	0.187 (0.137)	-0.258 (0.504)		-0.451 (0.264)
5	0.632 (0.156)**	0.018 (0.643)		-0.515 (0.304)
6	0.824 (0.169)**	0.074 (0.797)		-0.602 (0.351)*
7	1.104 (0.180)**	0.128 (0.936)		-0.674 (0.396)
8	1.390 (0.191)**	0.152 (1.124)		-0.776 (0.446)*
9	1.980 (0.250)**	0.156 (1.272)		-0.893 (0.498)*
10	3.097 (0.305)**	0.600 (1.466)		-0.999 (0.557)*
11	4.566 (0.543)**	1.440 (1.578)		-1.129 (0.618)*
12	5.760 (0.762)**	2.159 (1.715)		-1.269 (0.680)*
13	6.891 (0.927)**	2.780 (1.890)		-1.442 (0.746)*
14	7.903 (1.015)**	3.029 (2.115)		-1.604 (0.817)*
15	11.479 (0.406)**	4.865 (2.450)*		-1.837 (0.891)*
16	13.257 (0.345)**	4.372 (2.822)		-2.040 (0.944)**
17	8.135 (0.063)**	4.244 (2.681)		-2.181 (1.045)**
Model specification Year indicators, country indicators, country-specific linear trends, and socio-demographic controls?	No	Yes	Yes	Yes
F statistic (p-value) for indicators for years before SSRIs on market				1.15 (p=.36)
F statistic (p-value) for indicators for years since SSRIs on market		238.1 (p<.001)		
Sample (N) Adj. R-squared	492 0.898	492 0.99	450 0.99	450 0.99

NOTES: 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

Table 7: Additional IV Specifications and Results

Drugs Used to Predict Date of First SSRI Sales	Second-stage estimate for effect of SSRI sales on suicide	F-test for explanatory power of instruments, first stage	Specification check: F-test for indicators on years before SSRI sales predicted on market
Avg lag for Statins, PPIs, ACE, CCB	-0.032 (0.014)**	54.1 (p<.001)	1.31 (p=.29)
Proton Pump Inhibitors	-0.036 (0.015)**	10.3 (p<.001)	1.10 (p=.40)
ACE	-0.027 (0.020)	126.8 (p<.001)	1.18 (p=.35)
CCB	-.029 (0.015)**	44.0 (p<.001)	0.76 (p=.59)
Cox2	-0.033 (0.014)**	19.4 (p<.001)	3.22 (p=.02)
Alternative anti-convulsants	-0.016 (0.009)*	13.8 (p<.001)	5.24 (p<.01)
Atypical anti-psychotics	-0.012 (0.013)	8.4 (p<.001)	5.69 (p<.01)
ADHD	-0.021 (0.020)	67.6 (p<.001)	2.5 (p=.07)

Table 8: Estimates for Association between SSRI Sales and Suicide Rates to Different Age Sub-groups, Panel-Data Weighted Least Squares versus Instrumental Variables

Age group	Weighted Least Squares*	Instrumental Variables (predicted SSRI sales date from Statin first-sale lag for each country)
15-24	-.033 (.029)	-.029 (.023)
25-34	-.049 ** (.011)	-.054** (.027)
35-44	-.019 (.013)	-.033* (.018)
45-54	-.008 (.009)	-.016 (.019)
55-64	-.019** (.009)	-.053** (.020)
65 and older	-.017**(.008)	-.044**(.015)

Notes: * Panel-data weighted least squares estimates in second column from Ludwig and Marcotte (2005). Model controls for country and year fixed effects, country-specific linear trends and other covariates as described in column 2 of Table 1 above.