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ANTI-DEPRESSANTS AND SUICIDE

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ANTI-DEPRESSANTS AND SUICIDE

ABSTRACT

Suicide takes the lives of around a million people each year. Between 30 and 90 percent of those who complete suicide are thought to suffer from depression. Anti-depressant drug medication is an important tool to help distraught people make it through difficult periods in their lives, but in recent years there has been great and growing controversy about whether one of the best-selling drug classes in the world – selective serotonin reuptake inhibitors (SSRIs), an anti-depressant drug introduced in the 1980s – increases or decreases the risk of completed suicide. Economic and medical theory is ambiguous, and there is currently no scientifically credible empirical estimate available on this question. Randomized clinical trials are not informative in this application, in part because sample sizes are too small to detect impacts on relatively rare outcomes like suicide mortality, and most observational studies have used weak research designs. In this paper we present the first estimates for the effects of SSRI on suicide that has both a plausibly exogenous source of identifying variation and adequate statistical power to detect impacts on suicide mortality. We use data from 26 countries for up to 25 years to estimate the effect of SSRI sales on suicide mortality using just the variation in SSRI sales that can be explained by variation in the sales growth of new drugs more generally. We find an increase in SSRI sales of 1 pill per capita (12% of 2000 sales levels) reduces suicide by 5%.

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I. INTRODUCTION

Suicide claims the lives of about a million people around the world each year (Goldsmith et al., 2002), and is common in developed as well as developing countries. For example 32,439 people took their own lives in the U.S. in 2004, about twice the number of deaths that occurred from homicide, ranking suicide 11th among leading causes of death (National Vital Statistics Reports, 2007). Yet economists have devoted surprisingly little attention to the topic of suicide. There is a small but growing theoretical literature that seeks to understand the nature of suicidal behavior (e.g., Hamermesh and Soss, 1974, Cutler, Glaeser and Norberg, 2001, Becker and Posner, 2004). Even less attention has been devoted to applying the tools of economics to the problem of suicide prevention.[1]

The value of suicide prevention is suggested by research indicating that in many cases, social welfare can be enhanced by helping prevent suicidal people from acting on their desires or changing their desire for self-harm. As Becker and Posner (2004) note, some people in bad circumstances – particularly the young – may overly discount the prospect that their fortunes will improve in the future. Many people are at elevated risk for suicide because of major depressive disorder, which afflicts between 30 and 90 percent of those who complete suicide (Goldsmith et al., 2002, p. 70) and around 17 percent of all American adults at some point over their lifetimes (Kessler, Berglund et al., 2005). Acute episodes of mental illness may cause people to have what Becker and Posner aptly describe as "inefficient utility machines … this inability to get pleasure out of circumstances that most people would not find oppressive may define a mental disorder" (p. 3). The value of suicide prevention is most ambiguous for those with chronic health problems, a major risk factor for suicide and one reason why suicide rates are highest among the elderly (Goldsmith et al., 2002).[2] But even here, treatment of depression and chronic pain can increase the desire to live.[3]

[1] Some exceptions include Ludwig and Cook (2000), Duggan (2003) and Stevenson and Wolfers (2006).
[2] Chronic physical health problems appear to be quite prevalent even among prime-age suicide victims. Cook and Ludwig (2000, p. 26) use data from the 1993 National Mortality Followback Survey to show that around one-quarter of suicide decedents between the

This paper examines the effects on suicide from one of the most important, but increasingly controversial, tools for preventing suicide – modern anti-depressant drug treatment. We provide what we believe to be the first scientifically credible estimates for the causal effects on suicide mortality from selective serotonin reuptake inhibitors (SSRIs). The SSRIs were first introduced in the 1980s, and by 2000 was the most commonly prescribed drug class in the U.S. and the third best-selling drug class in the world (IMS Health, 2006). Yet SSRIs have been the subject of recent government safety warnings in the U.S. and U.K., which have led to large, widespread reductions in their use (Gibbons et al., 2007) and substantial divergence in professional opinions about the safety of these drugs. As one researcher involved in the FDA's reviews of SSRIs told the *New York Times*, "Sitting up there and having the public yell that you're killing their children is no fun." A medical historian told the *Times* "It's like a religious war," with a level of argument not seen since "the 1960s and 1970s, when scientists were challenging psychoanalysis" (Carey, 2006).

The net effect of the introduction and growing use of SSRIs on suicide mortality is theoretically ambiguous. On the one hand, antidepressants may help people persevere through difficult but transitory periods of their lives or improve the efficiency of their "utility machines." SSRIs generally seem to be about equally effective in treating depression as the older class of tri-cyclic antidepressants (TCAs) that were first introduced in the 1950s, but the SSRIs have fewer physical side effects and are less toxic in overdose. Since major depression is a leading risk factor for suicide and SSRIs have contributed to a substantial increase in the share of people receiving treatment for depression, it might be expected that the SSRIs would help reduce overall suicide mortality rates. On the other hand most antidepressants appear to improve patient energy levels before they improve mood, which may contribute to an increase in the risk of suicide during the early

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ages of 15 to 55 had some marker of poor physical health in the year before their death (such as Alzheimer's or cancer), about twice the prevalence rate compared to people 15-55 who died as a result of motor vehicle crashes.

[3] One study found that among a sample of suicidal elderly people who had requested euthanasia, two-thirds changed their minds within two weeks (Hendin, 1999). This may or may not indicate that the desire to attempt suicide is fleeting, since even those with chronic or terminal health problems may postpone a suicide attempt for the option value of possible improvements in their quality of life in the future, as suggested by Becker and Posner (2004).

stages of treatment (FDA, 2006). The lagged impact on mood could also discourage some patients who had put off attempting suicide for what Becker and Posner (2004) term the "option value" of a possibly better quality of life from treatment. Adverse effects could also arise from the possible behavioral responses of patients and medical practitioners to the improved safety and reduced side effects of SSRIs relative to the older TCAs, a version of what Viscusi (1984, 1985) terms the "lulling effect."

Acute concern about the safety of SSRIs has been motivated by the results of several meta-analyses of randomized clinical trials (RCTs) suggesting that SSRI treatment elevates the risk for suicidal thoughts and non-lethal self-injurious behavior among pediatric patients (Hammad et al., 2006; FDA, 2006) and perhaps adults as well (Fergusson et al., 2005; Gunnell et al., 2005; FDA 2006). Yet randomized trials, normally the "gold standard" for assessing drug effects, are ultimately not very informative about how SSRI treatment impacts the outcome that is arguably of ultimate policy importance – suicide mortality. The main problem is that RCTs employ sample sizes that are too small to detect effects on important but rare health outcomes like suicide mortality. For example even in the FDA's recent meta-analysis of multiple pediatric SSRI trials, there was not a single completed suicide in the entire pooled sample of RCTs (Hammad et al., 2006). Gunnell et al. (2006) note that in order to have adequate statistical power to detect an effect of 20 percent on suicide mortality, a randomized trial would need 1.9 million subjects. But suicide impacts much smaller than 20 percent would still be of great importance for both drug regulators and clinical practitioners, and so even a sample of 1.9 million would be inadequate. To detect an impact of, say, 5 percent, a randomized trial would need to enroll around 30 million patients – which is about twice the number of people in the U.S. who suffer from major depressive disorder in any given year.

Because no clinical trial – or even pooled study of clinical trials – has had anything like a sample size of 1.9 million, much less 30 million, researchers have focused on measures of non-lethal "suicidality." But only a small fraction of patients with suicidal thoughts attempt suicide, few attempts are fatal, and, crucially,

the risk factors for suicide attempts versus completions differ markedly (Cutler, Glaeser and Norberg, 2001; Baldessarini et al., 2006). These measures are also retrospectively derived from what is written down in patient records, and so are susceptible to "ascertainment bias" – compared to placebo, treatment with any active drug (including SSRIs) will entail more side effects, and so will generate more doctor visits and thus more expansive medical records (Gibbons et al., 2007). Classification of these non-fatal suicide reports is something less than straightforward.[4] And RCTs suffer problems of external validity as well, because for ethical and practical reasons they exclude those people who are at highest risk for suicide (Pearson et al., 2001),[5] and the type of treatment in RCTs may be unrepresentative of usual community levels of care.[6]

Given the intrinsic limitations of RCTs for studying the effects of SSRIs on suicide mortality, progress on this question is instead likely to require careful analysis of non-experimental data. Unfortunately most of the non-experimental studies that have been conducted to date employ weak research designs, typically before-after comparisons using data from one or a few countries. More recently a few studies have drawn on county- or country-level panel data to at least control for shared period effects and jurisdiction-level fixed effects (Dahlberg and Lundin, 2005; Gibbons et al., 2005; Ludwig and Marcotte, 2005). Yet causal inference from these studies remains difficult, since even the sign of any omitted variable bias is hard to predict. SSRI sales might increase because the prevalence of depression has increased, or SSRI sales could increase as part

[4] Posner et al. (2007) describe the new classification system adopted by a team of Columbia University researchers commissioned by the FDA to review drug company data. The drug companies classified 427 adverse events across 25 pediatric trials, while the Columbia team identified 26 possibly suicidal events not classified by the drug company and eliminated 12 events that the drug companies had classified as suicidal. There was much less agreement between the Columbia team and the drug companies as to what adverse events should be classified as an actual "suicide attempt," with the Columbia classification system identifying only half as many attempts compared to the system employed by the drug companies.

[5] See for example Goldsmith et al. (2002), Zimmerman et al (2002), Baldessarini (2005), Ferguson et al. (2005), Baldessarini et al. (2006), and Khan et al. (2000, 2001). Some evidence of these external validity limitations can be had from the RCT included in the FDAs meta-analysis, for which the collective suicide rate for patients receiving SSRIs was 4.17 per 100,000. This is substantially lower than the approximately 11 per 100,000 in the general population during the period these trials were conducted, despite the fact that a key inclusion criterion for these trials was a mental health condition that is a substantial risk factor for suicide.

[6] For example, they may take place in academic medical centers and outpatient settings, with structured protocols and better staffing than may be available in non-academic mental health settings.

of a larger effort to improve mental health services. Despite the massive amount of research and public concern, there is to date no scientifically credible estimate available for how SSRIs impact suicide mortality.

In this paper we present what we believe to be the first estimates for the effects of SSRI on suicide that has both a plausibly exogenous source of identifying variation and adequate statistical power to detect impacts on mortality outcomes, rather than on measures of non-fatal suicidality. We construct a panel dataset with suicide rates and SSRI sales per capita for 26 countries for up to 25 years, which enables us to detect impacts on suicide mortality that are much smaller than anything that could be detected from randomized trials. Since SSRI sales may be endogenous, we exploit just the variation in SSRI sales across countries over time that can be explained by differences across countries in sales growth of new drugs in general. As discussed below, countries differ with respect to how they regulate, price and distribute prescription drugs. These institutional features of each country's prescription drug system have some common effect on how the use of new drugs diffuses, which Berndt et al. (2007) show are relevant for anti-depressants as well as other drugs. As shown below, differences across countries in the rate of sales growth for SSRIs is strongly related to the rate of sales growth of the other major new drugs that were introduced in the 1980s for treatment of *non-psychiatric* health conditions. This source of variation in SSRI sales helps overcome the problem of reverse causation and many of the most obvious omitted-variables concerns with past studies.

Our instrumental variables (IV) estimates suggest that an increase in SSRI sales of 1 pill per capita (around a 12 percent increase over 2000 sales levels) would reduce suicide mortality rates by around 5 percent. This relationship holds up even after conditioning on country and year fixed effects, country-specific linear trends, and many of the risk factors for suicide identified in a recent IOM report on suicide (Goldsmith et al., 2002) including a country's population age structure or divorce rate. These estimates imply that around

1 suicide is averted for every 200,000 pills sold.[7] Our IV estimates are about twice as large as those from OLS, which is important because the magnitudes of impacts – not just their signs – will obviously matter for benefit-cost or cost-effectiveness analyses of any medical intervention. Commonly used SSRIs can be obtained in the U.S. for around $0.13 per pill,[8] which suggests a cost per statistical life saved from increasing SSRI use of around $26,000 – far below most other government regulations or policies.

One drawback of country-level data is that SSRI sales information is not available at the country-year level broken out by different population sub-groups. This limits our ability to identify heterogeneity in treatment effects by age, which could in principle be valuable for helping health policymakers target SSRI use within the population. However the degree to which regulators can in fact influence SSRI use in an age-targeted way remains unclear. After the FDA issued a warning in 2004 about SSRI use in pediatric patients, SSRI use declined among all adult age groups as well, with the only exception being for those 60 and older (Gibbons et al., 2007). Given this broad-based patient response to even narrowly age-targeted warnings, the question that our paper seeks to address seems relevant to a broad range of policy decisions about how to regulate SSRI use.

The most important concern with our estimates comes from the fact that our instruments are of course not randomly assigned across countries, and so there is necessarily the question of whether they are plausibly orthogonal to other determinants of suicide such as overall economic affluence, the quality of health care, or other factors. We provide a number of tests that together provide some support for the validity of our design.

One concern is that prescription drugs, like many other medical technologies, may diffuse more rapidly in higher-income countries (Slade and Anderson, 2001), which could in principle pose a problem to our IV design since economic hardship is a risk factor for suicide (Goldsmith et al., 2002). However we show

[7] In Table 1 below we show that the mean suicide rate for our sample over the study period is about 10 per 100,000. Our point estimate thus implies that an increase in SSRI sales of 1 pill per capita reduces suicide mortality by 5%*(10 / 100,000) = .000005 deaths per capita. So an increase in SSRI sales of 200,000 pills would reduce mortality by 1 statistical life.

[8] The on-line retailer www.drugstore.com lists prices of generic Prozac and Paxil at around $0.25 to $0.30 per pill. Walmart's prices are even lower, offering 30 pills of generic SSRIs for $4, or about $0.13 per pill.

that our results are not much affected when we control for unemployment rates or GDP, or when we restrict our analytic sample to just member countries of the OECD, which may be less dissimilar to one another compared to our broader sample of countries with respect to potential confounding socio-economic factors.

We may be worried that new drugs may diffuse more quickly in countries that are more intensive users of medical care overall. In this case our IV design may partly pick up any effects that more or better health care may have in reducing the sorts of chronic health problems that lead some people to contemplate suicide. But even countries that have made generally similar policy decisions about how to operate their general health care systems have made different choices about how to regulate, price or distribute prescription drugs. For example Berndt et al. (2007) show that the way a country finances its health care system does not seem to be related to the rate at which new drugs diffuse. Below we also demonstrate that the rate at which new drugs diffuse is related to the *level* of health care expenditures in a country but not to the *trend* in health spending, which is the more relevant challenge to valid estimation in a panel data setup. When we directly control in our regressions for total health spending per capita our results barely change. The country with the highest rate of predicted SSRI growth in our sample – the U.S. – experienced a decline in most major health outcomes, such as overall life expectancy, relative to other OECD countries during our study period (Anderson and Hussey, 2001). And we show that there is no estimated SSRI "effect" on accidents, a major cause of death that should not be causally affected by treatment with antidepressant drugs.

Perhaps in countries where new drugs diffuse more rapidly, physical health outcomes or perhaps pain treatment could be of higher quality, which could lead our instruments to have a separate direct effect on suicide mortality aside from their relationship with SSRI sales growth. This counter-explanation for our findings would predict that in countries where new drugs diffuse more rapidly we should see the largest declines in suicide mortality among older people, for whom physical health problems and chronic pain are most prevalent. We can test this hypothesis by re-estimating our preferred IV model, but now replacing the

main dependent variable (overall suicide mortality) with suicide rates to specific age groups. This is not a good test of age heterogeneity in treatment response to SSRIs, since we do not know the rate at which SSRI sales change over time by age group. But this does provide one check on the possibility that our drug-sale instruments are operating through the channel of influencing physical health outcomes directly. In contrast to the prediction of this counter-explanation for our results, we find that in countries where our IV design predicts SSRI sales to increase most rapidly, suicide declines mostly among teenagers and young adults.

A different falsification test comes from examining whether countries that our IV design predicts to have high rates of SSRI growth have similar trends in suicide rates to other countries during the time period *before* SSRI sales become common. We provide evidence for quite similar "pre-treatment" trends in suicide mortality going back to 1980 for our entire analytic sample, and for the sub-set of our sample for which a longer time series of data is available, we can show this is true going all the way back to 1960. These countries have divergent suicide rates only in the 1990s, when SSRI sales started to take off. One might still worry that other forms of mental health treatment may have increased over the 1990s as well, but there were no increases in use of psychotherapy or older TCA anti-depressant drugs during the 1990s, at least in the handful of countries for which longitudinal data on these other mental health services are available.

The remainder of the paper is organized as follows. The next section provides some additional discussion of the pathways through which anti-depressant drug treatment could affect suicide, while section 3 reviews the available empirical evidence on this question. We discuss our data in section 4 and empirical methods in section 5. The main findings are in section 6, while implications are discussed in section 7.

II. BACKGROUND

A recent Institute of Medicine report emphasizes that suicide is a complex outcome influenced by biological, psychological, social and cultural factors (Goldsmith et al., 2002, p. 2). While biological and psychological factors do not fully determine the risk of suicide, they are important.

Since major depression is a leading risk factor for suicide, and because antidepressant drugs are generally effective in treating depression (Goldsmith et al., 2002), it might be expected that increasing use of antidepressants would reduce suicide. However the magnitude of any beneficial impact on suicide is ambiguous. As Becker and Posner (2004) note, economic models of suicidal behavior imply that "potential suicides require an unusually successful intervention before they no longer want to commit suicide" (p. 9, emphasis in original).

The concern that antidepressant drugs could increase, rather than decrease, the risk of suicide dates back to the introduction of the first tri-cyclic antidepressants (TCAs) in the 1950's. Long before the FDA's recent "black box" warning for SSRIs, the agency required that antidepressant drugs include some standard warning language for patients. There are both clinical and behavioral arguments for why TCAs might increase the risk of suicide. One clinical mechanism has to do with the slow therapeutic effects of these drugs. Most antidepressants (including both SSRIs and TCAs) take at least four or more weeks to result in a clinically significant improvement in depressed mood. However, other psychopharmacological effects may occur within the first few days of treatment. As early as the 1960's, psychiatry textbooks warned that the risk of suicide may increase during early phases of treatment because the medications may give depressed patients the energy to follow through on a suicidal motive, long before they lead to an improvement in mood.

A second clinical concern stems from the possibility of heterogeneity in drug effects across patients, including by age. As psychopharmacological treatments become more accepted in clinical pediatric practice, there has been ongoing concern that medications developed and tested in adults might have different effects in children, and that exposure of children and adolescents to psychoactive drugs might result in subtle but significant effects on neural development.

One behavioral mechanism through which antidepressant drugs might increase suicide risk stems from the potential of TCAs to be highly toxic in overdose, so that a prescription might provide easy access to an

effective method of self harm. This type of "instrumentality effect" rests on the assumptions that suicide methods are not perfectly substitutable and that people at high risk for suicide are at least somewhat responsive to the availability of different methods, or in the terminology of economic models of suicide, that instrument availability influences the "costs of death" (Hamermesh and Soss, 1974, Becker and Posner, 2004).[9] Another behavioral mechanism through which anti-depressant drug treatment could increase the risk of suicide is suggested by the possibility that forward-looking suicidal people who have some uncertainty about their future outcomes may choose to wait to attempt suicide to see if their life conditions improve (Becker and Posner, 2004). People who are hoping that drug therapy may improve their lives could interpret the lack of mood improvement during the early stages of anti-depressant drug treatment as indicating that they will never respond to treatment, and so give up hope that their lives will ever improve.

A major technological innovation in the treatment of depression (and the focus of the present study) occurred in 1984 with the introduction of the selective serotonin reuptake inhibitors (SSRIs). SSRIs are described as "selective" because they affect only the reuptake pumps responsible for serotonin, a small molecule that serves as a neurotransmitter, or "chemical messenger," in the brain. In contrast to SSRIs, the TCAs affect multiple neurotransmitters. While the SSRIs seem to be similar to the older TCAs in their ability to reduce depression,[10] they are more selective in their operation and therefore have fewer physical side effects (such as dry mouth, drowsiness, or cardiac arrhythmia) and are less toxic in overdose.

The introduction of SSRIs may have reduced suicide in two ways. First, the greater safety in overdose probably led SSRIs to be prescribed for a much wider range of patients by a wider range of practitioners

[9] 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), tall buildings or bridges are more common in some places than others, and some people are more likely to receive prescription medications than others. Research provides at least qualified support for the idea that changing access to suicide methods – such as reduced access to guns, or reducing the carbon monoxide content of domestic gas – may achieve at least temporary reductions in suicide (Krietman, 1976; Ludwig and Cook, 2000; Goldsmith et al., 2002; Duggan, 2003).

[10] See for example Trindade et al. (1998), Goldsmith et al. (2002), Mallick et al. (2003), Ryan (2003), Green (2003), and Vaswani et al. (2003).

(Guze, 1996; Lawrenson et al., 2000). Some of the increase in SSRI use could have been substitution from talk therapy, and current research is ambiguous about the relative effectiveness of the two forms of treatment (e.g., Klein, 2000). But overall SSRIs have probably played a role to increase in the number of people being treated for depression in the U.S. (Kessler, Demler et al., 2005; Thorpe et al., 2004). A second mechanism through which SSRIs might reduce suicide comes from the fact that SSRIs might substitute for the older TCAs. The lower toxicity of SSRIs relative to TCAs could therefore reduce the risk of suicide through an instrumentality effect.[11]

However there are also clinical and behavioral mechanisms through which SSRIs could increase the risk of suicide to patients using antidepressant drugs and overall suicide rates. The clinical concern stems from possible heterogeneity in psychopharmacological effects, and in particular the possibility that the risk of an adverse effect of antidepressant drug treatment on mood may be more pronounced with SSRIs than TCAs. Even if SSRIs and TCAs had the same effects on suicidal states, the increased prevalence of drug treatment after SSRIs are introduced could lead to an increased number of persons at risk for an adverse drug reaction.

It is also possible that SSRIs could increase suicide risk through a "lulling effect" (Viscusi, 1984, 1985). Economists have long been concerned about the possibility that consumers will reduce safety precautions in response to the introduction of new, safer consumer products (see for example Peltzman, 1975). Viscusi's (1984, 1985) elaboration of this idea raises the possibility that improved product safety could increase product injury rates if consumers misperceive risks. In the case of SSRIs, the increased safety of these drugs relative to TCAs may have led a broader (and perhaps less experienced or qualified) set of health practitioners to be willing to provide drug treatment for depression,[12] and may also have led payers,

[11] The improved ratio of a therapeutic dose to a toxic dose of SSRIs means that an act of intentional self harm by swallowing, say, a one-month supply of SSRIs is probably less lethal than swallowing a one-month supply of TCAs. Little is known about the case fatality rates for overdoses with SSRIs versus TCAs, and it is an open question whether persons attempting self harm via overdose are aware of the relative toxicity of one medication over another.

[12] In many countries there have been dramatic changes in the locations of psychiatric service provision over the past 40 years, with state psychiatric hospitalization being replaced by treatment in community settings. The development of safer and more effective drug treatments is thought to have contributed to this shift in the location of care. But there is a long history of concern that the

clinicians, and patients to accept a shortening of in-patient hospital stays and reduction of intensity of outpatient treatment[13] with a consequent drop in the vigilance of patient monitoring.

Another "lulling effect" might stem from the fact that some self-injury attempts may be motivated by reasons other than the desire to end life, including to signal for help, punish family or friends, or secure resources more generally (Rosenthal, 1993; Cutler, Glaeser and Norberg, 2001; Marcotte, 2003). The introduction of a safer overdose alternative – SSRIs – could paradoxically lead to an increase in the number of suicide attempts, thus increasing the number of unintentional deaths resulting from self-injury attempts without lethal intent.

III. PREVIOUS EVIDENCE ON SSRI'S AND SUICIDE RISK

The question of whether antidepressant drugs might increase suicide risk first came to national attention in 1990, with the publication of a case study describing six adults who apparently became suicidal as a result of being treated with fluoxetine, i.e. Prozac (Teicher et al., 1990). While case studies have obvious limitations for drawing causal inferences, the ensuing debate led the FDA to review the issue and hold hearings in 1991. Since then most of the public attention has been focused on evidence from randomized clinical trials (RCTs), despite the well-known limitations (discussed above) of using RCTs to estimate drug effects on suicide. Because the FDA has commissioned several lengthy reviews of the available literature and RCT evidence, we focus here on providing just a selective review of the most recent major meta-analyses.

The FDA's 2003 review of pediatric trials found that among a pooled sample of 4400 patients age 18 or younger, SSRI use was estimated to double the risk of suicide-related behaviors or ideation versus placebo (4% vs. 2%). However the pooled set of trials examined in this meta-analysis did not include any completed

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deinstitutionalization process may have led to a higher suicide rate (e.g. Hansen et al., 2001; Flechner, Wolf and Priebe, 1995; Salzer et al., 2006) for much the same reasons that improved product safety could increase the risk of product injury rates if consumers (or clinicians or policy makers) have misperceived the actual risks.

[13] Many studies find that a combination of drug treatment and psychotherapy is more effective than either treatment alone (eg, March et al., 2004), so SSRIs might increase the risk of suicide among those patients who would formerly have been referred for more intensive treatment and supervision.

suicides (Hammad et al., 2006). A more recent meta-analysis that draws on an updated set of pediatric trials also finds an elevated risk for suicide behavior (ideation or attempts) for SSRI versus placebo for pediatric patients with major depressive disorder (3% vs. 2%; N=2910, p=.08), with smaller risk differentials for pediatric patients who have obsessive-compulsive or other anxiety disorders (Bridge et al., 2007).

Recent meta-analyses of RCT data also suggest that SSRIs may increase the risk of suicide for *adults* as well. Fergusson et al. (2005) find a positive and statistically significant increase in suicide attempts for those treated with SSRIs compared to placebo (odds ratio=2.28, 95% CI 1.14 to 4.55, N=36,445), with odds ratios above 1 for all adult age groups except for those over age 60 – that is to say, for the vast majority of adults. The meta-analysis of Gunnell et al. (2005) yields similar findings for the most serious non-fatal indicator of suicidality that they examine, non-fatal self-harm attempts, although this estimated effect is not quite statistically significant (odds ratio = 1.57, 95% CI 0.99 to 2.55), even with N=45,704 patients. The FDA's own 2006 review of RCTs that enrolled a total of 99,839 adult patients yields qualitatively similar findings: Compared to placebo, SSRIs may reduce the risk of less serious indicators of suicidality, such as suicide ideation (odds ratio=0.86, 95% CI 0.69 to 1.06), but may increase the risk for the more serious indicator of suicide preparation or worse (odds ratio = 1.23, 95% CI 0.82 to 1.85). For suicide preparation the FDA estimates separate odds ratios by age that are greater than 1 for all adult age groups below 65, but these results do not seem to distinguish the effects of SSRIs from other antidepressants.

Given the limitations of RCTs in answering this question, numerous investigators have used non-experimental research designs to examine the association between SSRIs and suicide mortality. However, most previous population-based studies of SSRIs and suicide have used research designs with limited power to rule out the influence of competing explanations. Specifically, most of these studies have simply compared suicide rates before and after SSRIs become available in a particular jurisdiction. Studies of Sweden, Finland, Norway, Hungary and Australia using this type of interrupted time series design have found that suicide rates

declined as SSRI use increased (Isacsson, 2000; Rihmer et al., 2001; Ohberg et al., 1998; Hall et.al., 2003), although studies in Iceland and Italy found no effect (Helgason et al., 2004, Barbui et al., 1999). Yet 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 other factors such as deinstitutionalization that might be changing over the same time period.

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 in a standard fixed-effects setup with panel data.[14] Two studies have used this approach to examine variation in SSRI sales across jurisdictions over time within a single country. Using data for the U.S. for the years 1996 to 1998, Gibbons et al. (2005, 2006) find that increases in prescriptions for SSRIs and other newer anti-depressants are associated with lower suicide rates both within and between counties, including for children and adolescents. 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.

[14] A different approach adopted by Jurrlink et al. (2006) is to use individual-level data from medical records and compare suicide rates for those who receive SSRI treatment versus others, using propensity-score matching methods to control for selection into SSRI treatment on the basis of observable background characteristics. Gibbons et al. (2007) employ a difference-in-difference design with individual-level patient data from the VA, comparing trends in suicide attempt rates for those diagnosed with depression who do versus do not receive drug treatment.

The obvious concern is that even standard "fixed effects" estimates that compare trends across countries over time may be susceptible to bias from other unmeasured factors that affect both changes in SSRI use and suicide mortality. For example, if countries try to improve access to psychiatric medications in tandem with other improvements to their mental health systems, a standard panel-data analysis may overstate any socially beneficial effect of SSRIs on suicide mortality. Alternatively, the movement towards deinstitutionalization, or other forces leading to increases in the prevalence of mental health problems in the non-institutionalized population, may have driven increased anti-depressant drug sales, or caused government regulators to bring SSRIs to market sooner.[15] In this case, any beneficial effect of SSRI sales on suicide risk might be masked by the positive correlation between suicide rates and market demand for drug treatment of depression. For these reasons, the direction of bias we should expect with OLS is not obvious.

Our paper tries to overcome this source of bias by using just the variation in SSRI sales that can be predicted from the rate of growth in sales of the major *non-psychiatric* medications that were introduced over the same time period (the 1980s) in which SSRIs were introduced. The next section describes our data while subsequent sections discuss our methods and findings.

IV. DATA

Our study uses country-level data to take advantage of both the statistical power for studying suicide mortality and the variation across countries in both the levels and trends of sales of SSRI and other drugs. Annual data on suicide mortality is widely available for a large sample of countries from the World Health Organization (WHO), which in turn obtains these data from national vital statistics reporting systems. Data for each country include 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

[15] 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).

extend the panel through at least 2000 for about half of our countries.[16] There may be some differences across countries in the ability or willingness of medical officials to determine and report mortality events as suicides, and vital statistics systems in developing countries are in particular through to be problematic (Goldsmith et al., 2002, p. 212-3). Improvements in suicide recording practices that are shared across all countries will be captured by the time effects included in our model, stable country-specific differences in recording practices for suicides should be accounted for by our country fixed effects, while the inclusion of country-specific linear trends in our models should also help account for gradual country-specific changes in data quality. Unless any remaining measurement error in these suicide data is systematically related to our instruments, then problems with the suicide data should simply reduce the precision of our estimates. We also present estimates for just the OECD countries in our dataset, which should have more similar data practices.

The main constraint on the construction of our country-level sample is the availability of data on SSRI sales. Our core analytic sample consists of the 26 countries for which we have been able to obtain annual SSRI sales data from IMS Health, Inc., a commercial firm that provides data on international pharmaceutical sales to manufacturers and health care providers. The diverse set of countries in our main analytic sample (with their year of first SSRI sale in parentheses) are: Argentina (1989); Australia (1990); Austria (1985); Belgium (1985); Brazil (1989); Canada (1989); Chile (1989); Colombia (1990); Ecuador (1991); Finland (1989); France (1986); Greece (1990); Ireland (1989); Israel (1989); Italy (1988); Japan (1999); Luxembourg (1985); Mexico (1989); Netherlands (1985); New Zealand (1988); Norway (1996); Portugal (1986); Spain (1987); United Kingdom (1987); United States (1988); and Venezuela (1990). One possible concern is that

[16] Most of these suicide reports were recorded by local medical or public health officials using the International Classification of Diseases, 9th Revision (ICD-9) system for coding cause of death, although by the end of the panel some countries use the newer ICD-10. 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 described below also account for the possibility of variation in how suicides are reported or officially recorded by controlling in all models for year and country fixed effects, as well as country-specific linear trends.

our sample of countries is *too* diverse, although we demonstrate below that our results are similar when we restrict attention to just member nations of the OECD.[17,18]

For each of these countries we have information about drug approval dates back to 1980 for all SSRIs, which includes fluvoxamine, paroxetine, fluoxetine, sertraline, citalopram and venlafaxine. We have also been able to obtain data on actual SSRI sales for these countries for each year back to 1990. The fact that we do not have SSRI sales data before 1990 could in principle complicate our analysis, although it is important to note that most countries began to sell SSRIs starting only in the late 1980s and in almost all countries SSRI sales growth was a phenomenon of the 1990s (see Table 1). For countries that approved SSRIs before 1990 we do know what sales were in the years before approval – zero. We use linear interpolation to impute sales in years between the date of SSRI approval and 1990.[19] More complicated imputation procedures are possible, but we show below that our results are not sensitive to how we address this problem since we obtain nearly identical results when we set to missing those country-year observations in the 1980s that come after SSRIs had been approved in a country.

In our analyses we also controlled for a number of factors identified by a recent IOM report as risk factors for suicide (Goldsmith et al., 2002). For example there is a powerful age structure to suicide mortality (Table 1), and so we control for the annual distribution of each country's population across different age groups. We also have data on unemployment rates from the OECD, data on real per capita gross domestic

[17] This restriction drops Argentina, Brazil, Chile, Colombia, Ecuador, Israel, and Venezuela.

[18] We exclude countries that transitioned from communist to other forms of government during our sample period (including Germany) in part because of limited availability of data on drug sales and in some cases for suicides during the pre-transition period. We also wish to avoid confounding the introduction of SSRIs with the profound social changes that accompanied these transitions. For example in the Ukraine suicide mortality rates per 100,000 declined steadily from 1981 to 1991 from 23.7 to 20.5, but following 1991, when Ukraine became an independent country, suicide rates increased steadily and by 2000 equaled 29.3, perhaps related to increases in heavy drinking (Webb et al., 2005). For Germany the challenge is that we cannot obtain annual suicide mortality data for East Germany prior to 1989; in that year suicide rates per 100,000 are more 1.5 times as high in East versus West Germany (25.8 versus 16.5). Using data just on West Germany over our study period is problematic in part because of increased migration of East Germans into the West following reunification.

[19] Specifically for each country we know sales in the year before approval (zero) and from our data sales levels in 1990, and then just linearly interpolate SSRI sales data in the intervening years.

product adjusted for changes over time in exchange rates (World Bank, 2006), health care expenditures per capita for a subset of OECD countries, and divorce rates.

V. EMPIRICAL STRATEGY

In this section we discuss the empirical strategy that we use to estimate the effect of SSRIs on suicide mortality. We begin by outlining a basic OLS approach that provides a benchmark for estimates that come from our preferred IV design, which is discussed in detail in the second sub-section below.

A. Least Squares Setup

We begin by estimating equation (1) using least squares, where Y_{it} is equal to the natural log of country *i*'s suicide rate per 100,000 people in year *t*, and $SSRI_{it}$ is the number of SSRI pills sold per capita in country *i* in year *t*. We control for the share of the population in different age groups (15-24, 25-34, 35-44, 45-54, 55-64 and 65 and up), an indicator for whether the country records deaths in that year using the ICD-10 versus -9 system, country and year fixed effects d_i and d_t and country-specific time trends, $Time_t \times d_i$.[20]

$$(1)\ Y_{it} = a_0 + a_1\, SSRI_{it} + a_2\, X_{it} + d_i + d_t + (Time_t \times d_i) + v_{1it}$$

Equation (1) is estimated using population-weighted least squares, since our suicide mortality rates are essentially grouped data and the ratio of signal to noise seems to be much higher for more populous countries. A Breusch-Pagan test confirms that OLS residuals from estimating equation (1) vary substantially by country size. As we show in the next section, the point estimates from our unweighted regressions are similar to the population-weighted results but less precisely estimated – as we would expect from an estimate that gives the same weight to noisy suicide data from small countries like Luxembourg that is given to observations from

[20] The raw data suggested that these country-specific linear terms may be important given differences in trends 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 18.1 by 2001. In contrast, the suicide rate in Mexico increased steadily from 1.4 per 100,000 in 1980 to 3.8 by 2001. The rise in suicide rates over the panel for Mexico may reflect a change in reporting, rather than real patterns of mortality, due to a declining stigma associated with suicide. Other predominantly Catholic countries (Ireland, Spain, Italy) saw similar patterns.

larger countries like the U.S.[21] To account for serial correlation we cluster standard errors at the country level (Bertrand et al., 2004).[22]

Most of the variation in suicide mortality rates in our panel is across countries rather than over time: country fixed effects account for around four-fifths of the total variation in log suicide rates. For example the suicide rate in 1990 per 100,000 people was 3.4 in Greece, 12.4 in the U.S. and 23.3 in Austria. These persistent differences in suicide rates across countries are thought to be due to in part to climate, culture, urbanicity, and perhaps differences in data recording practices (Smith et al., 1995; Goldsmith et al., 2002, Chapter 6). In any case, the substantial cross-sectional variation in suicide mortality suggests that a proportional response model is more appropriate than one focused on impacts measured in levels. Our preferred model takes a log-linear form, although as we show below the results are generally not very sensitive to functional form decisions. Country and year fixed effects plus country-specific linear trends account for 90 percent of the variation in log suicide rates in our panel.

B. Instrumental Variables Design

The main concern with OLS estimates of equation (1) is that SSRI sales may be endogenous to the conditions that influence suicide. For example, increases in major depressive disorder could drive up SSRI sales. Since reliable longitudinal, population-level estimates for the prevalence of severe depressive disorder are not available even in our sample of developed countries, OLS estimates may understate in absolute value any beneficial effect of SSRIs on suicide. On the other hand, countries might expedite approval of SSRIs or implement policies designed to improve access to SSRIs as part of a larger portfolio of efforts designed to improve mental health, in which case OLS would overstate the protective effects of SSRI on suicide.

[21] The suicide rate per 100,000 in the U.S. changes modestly year to year (from 1980 to 1985 the annual rate was equal to 11.9, 12.0, 12.2, 12.1, 12.4, 12.4). The year-to-year variability is much larger in Luxembourg (12.8, 16.7, 21.3, 21.9, 18.6, and 14.8).
[22] Hansen (2006) shows that standard errors calculated in this way may be overly conservative compared to more efficient generalized least squares estimates. Since our main IV estimates below are statistically significant with the more conservative approach, we present clustered standard errors throughout the paper for simplicity.

Our preferred research design seeks to identify the effect of SSRIs on overall suicide mortality using just the variation in SSRI sales across countries over time that can be explained by differences across countries in how quickly new drugs are generally approved,[23] and the general rate at which sales of new drugs usually increase once they are approved for sale on the market. This second source of variation turns out to be more important for our IV design, since as discussed below most countries in our panel turn out to be fairly rapid adopters of new drugs in general. Our IV estimates are thus driven mostly by variation across countries in the rate at which new drugs diffuse over time, and the validity of our estimates depends on whether rates of diffusion of new drug technologies in general are indeed orthogonal to other determinants of suicide mortality across countries. We argue below that this assumption seems plausible, and present some empirical results to support this view. It is also worth noting that unknown to us when we started this research, one other study has used an identification strategy that relies on differential rates of drug diffusion across areas to examine the effects of a very different class of drugs (antipsychotics) from the one examined here. In that case the non-experimental findings were later validated by evidence from a subsequent RCT.[24]

Conceptually, our IV design takes advantage of the fact that there are institutional differences across countries in the way that new drugs are regulated, priced and distributed that are common to both SSRIs and to other drugs. Data on the sales trajectories of other drugs that are not used to treat psychiatric conditions can tell us something about the combined impact of these institutional differences in drug systems across

[23] 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 vary 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.

[24] Duggan (2005) uses variation across areas of California in drug diffusion to show that second-generation antipsychotic drugs do not on net reduce health care spending. A similar finding was produced by a subsequent randomized clinical trial involving 1,493 patients (Rosenheck et al., 2006).

countries on drug diffusion rates. These general drug diffusion tendencies for countries should not be affected by the level or trend in mental health conditions, which is perhaps the main threat to validity with OLS.

Importantly, the institutional features that influence drug diffusion within countries seem to be in large part independent of other aspects of the country's health care system. Countries that have made generally similar policy decisions about how to structure their overall health care systems differ in how they choose to regulate, subsidize or distribute drugs. Berndt et al. (2007) examine data from 15 countries, most of which are included in our own analytic sample, and find that the rate of sales growth for new drugs is unrelated to the country's type of health care system – that is, whether health care costs are supported by a tax-funded system, by a social insurance-based system, or by a mixed system. Below we show that predicted rates of SSRI sales growth are unrelated to trends in health care expenditures across our sample of countries.

Consider for example the cases of Australia, Canada, and the UK, which all provide universal health care coverage funded in large part by general tax revenues, rely mostly on public hospitals, and use physicians as gatekeepers for the system who are then reimbursed on a fee-for-service basis (at least in Australia and Canada; physician reimbursement is more complex in Britain; see Commonwealth Fund, 2005). Yet these three countries have different systems for handling prescription drugs. The Australian government subsidizes most drug purchases in the country and accounts for the majority of all expenditures on drugs, but these subsidies are limited to drugs that are listed in a "positive formulary" (Morgan et al., 2006). Drugs not included on this list receive very little use. The Australian government negotiates the prices for drugs on this list with pharmaceutical companies. In the UK drugs are provided through the National Health System, with a "negative formulary" (a list of drugs excluded from the NHS subsidy) and a fixed charge to patients per prescription. During our study period the UK had some regional variation in drug coverage (Morgan et al., 2006). In the UK, unlike Australia, the government does not negotiate drug prices, but instead regulates profits for drug companies for on-patent drugs and allows free pricing for off-patent drugs (Kanavos, 2006).

This relatively greater pricing flexibility for companies in the UK leads generics to be relatively more common in that country, which incidentally they also are in the US (Konigbauer, 2006). The Canadian government funds only around half of all drug purchases, subsidies that are provided through a mixture of federal and local drug plans that all have their own positive formularies. But supplemental private insurance to help cover outpatient drug costs is widespread (Watson Wyatt Insider, 2007). And as our results below demonstrate, there are indeed important differences across these three countries in sales growth of new drugs.

While systematic research on the role of specific drug sector characteristics in explaining drug diffusion rates is limited, existing studies provide at least a few clues. Berndt et al. (2007) show that there is important variation across countries in how new drugs are priced, and this variation in new drug prices influences the rate at which new drugs diffuse. Also relevant is the degree to which pharmaceutical companies promote new drugs. Berndt et al. (2007) find a positive relationship between new drug diffusion and the number of contacts between drug representatives and doctors ("details"). Chintagunta and Desiraju (2005) study a sample of five countries, four of which are in our analytic sample. Among these four countries they find that the frequency of detailing for SSRIs is highest in the US, followed by France, then the UK, then Italy. As shown below, this is also exactly the ranking of these countries in the rate at which our instrument predicts SSRI sales to grow over time. Another factor that may influence drug diffusion rates across countries comes from the I/O decisions made by pharmaceutical companies in different countries. For example Chintagunta and Desiraju find some evidence that there is a "home bias" in the behavior of pharmaceutical companies, which behave more aggressively towards competitors in the drug markets within the country where the company is based. In the US we have seen that a change to the way pharmaceuticals are financed for the elderly in the US, in the form of a new 2006 Medicare drug benefit, increased retail spending on prescription drugs by 8.5 percent in its first year (Pear, 2008).

Since data on the specific institutional features of each country's pharmaceutical regulation and distribution are not available for many countries, we try to instead capture these differences across countries by looking at variation in how *other* new drugs generally diffuse across countries. This approach raises the question of which new drugs we should use to construct our instruments. We obtained data from IMS Health about drug introduction dates and sales for those drug classes that satisfied three criteria: (1) Like SSRIs, they must have been introduced in the 1980s so that the set of institutions that generally affect the drug adoption process are similar across drug types; (2) Unlike SSRIs, these drugs should not be used in the treatment of psychiatric illnesses, to avoid the potential endogeneity problems described above; (3) Like SSRIs, they must have been among the top-ten selling drug classes at the end of our study period (1998-2000), in the event that there is some general "major drug" effect on regulatory approval or sales trends.

The drug classes that satisfy these criteria 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; and two drug classes used to treat hypertension, calcium channel blockers (CCBs) and angiotensin-converting enzyme (ACE) inhibitors.[25] Together with SSRIs, the drugs included in our instrument set accounted for 83 percent of the sales of the top 10 drugs sold in the U.S. in 1998 (Kreling et al., 2000) and account for 4 of the 5 top selling drug classes (BarentsGroup, 1999).[26]

Mechanically, our IV design works as follows. We begin with a just-identified IV setup given by:

$$Y_{it} = b_0 + b_1 SSRI_{it} + b_2 X_{it} + d_i + d_t + Time_t * d_i + v_{2it} \quad (2)$$

$$SSRI_{it} = c_0 + c_1 PSALES_{it} + c_2 X_{it} + d_i + d_t + Time_t * d_i + v_{3it} \quad (3)$$

Our instrument, $PSALES_{it}$, equals the SSRI sales level that we predict for country *i* in year *t* if the country had approved SSRIs as quickly as the country approved the four major non-psychiatric drug classes

[25] We were only able to obtain sales data for these drugs back to 1994, and so linearly interpolate annual sales data for countries for the years between when the country first approved the drug for sale and 1994 (in cases where countries approved before 1994).
[26] The fifth class is antihistamines.

that were introduced in the 1980s (Statins, PPIs, CCBs, and ACE inhibitors), and then if SSRI sales grew each year they are on the market at the same rate as these other drugs. Put differently, our instruments represent the counterfactual SSRI sales pattern we would have expected in these countries if SSRI sales followed the same introduction and sales patterns observed for other major new drugs. We argue that this variation in SSRI sales is driven by institutional factors that are largely specific to each country's pharmaceutical system. To construct this instrument we first calculate the predicted SSRI adoption lag for each country (P_Lag_i), defined as the average adoption lag for each country for the four instrument drugs (Statins, PPIs, CCBs, ACE inhibitors) which are indexed by d. In equation (4) $launch_d$ equals the year in which drug d was first sold (or "launched") anywhere in the world, and $launch_{di}$ is the year drug d was launched in country i specifically.

$$(4)\quad P\_Lag_i = \text{int}\left(\sum_d \frac{launch_{di} - launch_d}{4}\right)$$

Then for each country and calendar year we calculate the number of years we predict SSRIs *would have been* on the market if the SSRI adoption lag for that country was the same as the average adoption lag observed for the four instrument drugs. That is, $Predicted\_Year_{it}$ equals the year in which SSRIs were first sold anywhere in the world ($launch_{SSRI}$) plus the country's average adoption lag for the four instrument drugs (P_Lag_i). For example, the U.S. approved Statins, PPIs, CCBs and ACE inhibitors on average one year after they were introduced anywhere on the world market. Since SSRIs were first launched on the world market in 1984, for the U.S. $Predicted\_Year_{it}$=1 in 1985 (a bit earlier than when SSRIs were actually first sold in America, 1988), $Predicted\_Year_{it}$ =2 in 1986, and so on for each of the k years SSRIs would have been for sale in each country.[27] Then for the k^{th} year we predict SSRIs to have been on the market in a given country, our instrument, $PSALES_{it}$, equal the average sales of Statins, PPIs, CCBs, and ACE inhibitors in the k^{th} year that *these* drugs were on the market in country i. So for the U.S. when $Predicted\_Year_{it}$=1 in 1985, $PSALES_{it}$

[27] Mechanically, we calculate the predicted year as $Predicted\_Year_{it} = \max\{0, 1 + t - (launch_{SSRI} + P\_Lag_i)\}$

equals the average sales of Statins, PPIs, CCBs and ACE inhibitors in their first years on the U.S. market. In 1986, $Predicted\_Year_{it}$=2 and the value of $PSALES_{it}$ is the average sales of our four instrument drugs the second year they were on the U.S. market. So, beginning in the first predicted year, we predict SSRI sales as:

$$(5) \qquad PSALES_{it} = \frac{1}{4}\sum_{k}\sum_{d} Sales_{dk} \times 1(Predicted\_Year_{it} = k)$$

One limitation of our just-identified IV setup is that the first-stage model imposes the assumption that each 1-unit increase in sales of our other instrument drugs (i.e., all other top-selling drugs also introduced in the 1980s not used to treat psychological problems) always has the same effect on SSRI sales, regardless of how long these drugs have been on the market. But from Table 1 it is clear that SSRI sales growth was initially quite slow, which was not typical of the other major drugs introduced in the 1980s that we use to construct our instrument. For this reason we also estimate a version of our IV model that allows the relationship between sales of other drugs and sales of SSRIs to vary with time these drugs are on the market, by creating a separate instrument equal to general drug sales the k^{th} year these drugs are on the market and allowing the coefficients to vary. In this more flexible first-stage specification we predict SSRI sales in the kth year for each country as:

$$(6) \qquad PSALES(k)_{it} = \frac{1}{4}\sum_{d} Sales_{dk} \times 1(Predicted\_Year_{it} = k)$$

We then estimate the following system, exploiting k separate instruments to identify the effects of SSRI growth within countries on changes in suicide rates:

$$(7) \qquad Y_{it} = b_0 + b_1 SSRI_{it} + b_2 X_{it} + d_i + d_t + Time_t * d_i + v_{2it}$$

$$(8) \qquad SSRI_{it} = c_0 + \sum_{k} \delta_k PSALES(k)_{it} + c_2 X_{it} + d_i + d_t + Time_t * d_i + v_{3it}$$

VI. FINDINGS

As a point of departure, consider the time series of log suicide rates and SSRI sales per capita for the OECD countries in our sample from 1980 to 2000 (Figure 1). Consistent with the hypothesis that SSRIs may reduce suicide we find a decline in suicide mortality in this sample of countries starting in the mid-1990s, about when SSRI sales increase dramatically. However this is less than definitive proof given the data also show some changes in suicide mortality early in the period before SSRIs were on the market.[28]

Our preferred IV estimates, which use just the variation in SSRI sales across countries over time that can be explained by variation in the rate of growth in sales of other drugs, suggest that an increase in SSRI sales of 1 pill per capita reduces suicide mortality by around 5 percent – about twice as large as what is suggested by OLS estimates. This relationship is largest in absolute value among relatively younger people.

A. OLS Results

Table 3 shows countries that experienced relatively larger increases in SSRI sales over our study period also experienced relatively larger declines in suicide. When we regress log suicide rates against SSRI sales and country and year fixed effects (column 1), an increase in sales of 1 pill per capita (about 12 percent of the mean 2000 sales levels in our sample) is associated with a reduction in suicide of around 3.5 percent. As best we can tell, the increase in SSRI sales in our data comes from about equally large changes along the extensive margin (number of patients treated) and intensive margin (pills per patient, which could be due in part to increased patient treatment fidelity because of fewer physical side effects of SSRIs vs. TCAs).[29]

[28] The increase in the early 1980s observed in Figure 1 is probably driven by changes in suicide in several countries during a period of economic recession. Another contributing factor is the increase in suicide rates in Mexico from extremely low initial levels up closer to international norms, which might reflect some declining stigma of suicide in that predominantly Catholic country.

[29] Ludwig and Marcotte (2005, Figure 4) show that in the U.S., the number of TCA prescriptions held steady from the late 1980s through the late 1990s at around 30 million prescriptions per year. Paulose-Ram et al. (2007) suggest that the proportion of people 17 and older receiving psychotropic treatment for depression increased from 2.5 percent in 1988-94 to 8.1 percent in 1999-2002, which would suggest an increase from 4.9 to 17.9 million people receiving treatment. Our IMS data suggest the number of SSRI sales in the mid-points of the two periods studied by Paulose-Ram et al. went from around 215 million doses to 4.2 billion doses. If we assume around 20 doses per prescription for TCAs (about the number implied by our data on SSRI doses and SSRI prescriptions from Ludwig and Marcotte's Figure 4), then there were around 815 million doses of anti-depressant drugs sold to around 4.9 million people in the 1988-94 period, or about 166 doses per patient per year, while in 1999-2002 there were (assuming TCA dose sales held constant) 4.8 billion doses sold to 17.9 million people, or about 268 doses per patient. These calculations imply that roughly half of the increase in SSRI doses sold of 4 billion from 1988-94 to 1999-2002 came from an increase in the number of people receiving treatment, the other half from an increase in the number of doses per patient.

Figure 2 provides some additional intuition about this estimate by plotting for each country the change in log suicide rates from 1980-95 against the change in SSRI sales.[30] Figure 2 helps illustrate the substantial variation in the growth of SSRI sales across countries. For example SSRI sales increased about twice as much in the US as in the UK, while by 1995 Japan had not even introduced SSRIs for sale yet. Of course countries may experience different trajectories in suicide rates for a variety of reasons other than SSRI sales. The second column of Table 3 shows that controlling for population age structure reduces the magnitude of the point estimate by around one-third. Adding country-specific linear trends (column 3) has only a modest impact on the magnitude of our point estimate. This estimate (2% suicide reduction per pill per capita) is of about the same magnitude as in Ludwig and Marcotte (2005), though the sample of countries is different.

The main concern with these OLS estimates is that SSRI sales may be endogenous to the conditions that influence suicide. For example there is much more variation across countries in how quickly they approve SSRIs for public sale compared to how quickly these countries approve other drugs: Of the 26 countries in our panel, 23 approved the four major non-psychiatric drugs that we use as instruments (from Table 2, Statins, PPIs, CCBs, and ACE inhibitors) within the first 3 years that these drugs came on the world market. In contrast, only 6 of our 26 countries approved SSRIs for sale within the first 3 years that these drugs first came on the market in 1984.[31] The extra variability in the timing of SSRI approval compared to other drugs suggests regulators in some countries may have had special concerns about the SSRIs, or that demand for mental health services are more variable across countries than demand for other medical services.

In fact we find some evidence suggesting that countries with increasing suicide rates may have been quicker to approve SSRIs for public use, as shown in the fourth column of Table 3. We re-estimate our basic

[30] Even though we have suicide and SSRI sales data through at least 1999 for all of the countries in our sample, with our IV design described below we lose some country-years' of data after 1995, and so for consistency in these figures we focus here on the 1980-95 period. Re-doing Figure 2 using data through 1999 yields a similar picture.

[31] SSRIs were first sold anywhere in the world in West Germany in 1984, which is dropped from our sample as described in Section III because of the effects of reunification on suicide in Germany plus the difficulty of obtaining reliable data on suicides for East Germany prior to this period.

panel-data setup as in equation (1) but now add a set of indicator variables for each of the five years *before* SSRIs were first sold in each country. We find these pre-SSRI year indicators are jointly significant ($p<.01$) and become less negative (smaller in absolute value) as we get closer to the time SSRIs were approved.[32]

It is more difficult to generate a similarly transparent test for the endogeneity of SSRI sales growth once these drugs are on the market, though there is ample reason to be worried about simultaneity with trends in SSRI sales and mental health conditions. These conceptual concerns together with the empirical findings above motivate the IV analysis that follows.

B. Main IV Results

The first column of Table 4 shows the first-stage results from estimating our just-identified IV model. Each one-pill increase in predicted sales for our four other instrument drug set is associated with higher levels of SSRI sales equal to around two-fifths of a pill per capita. The F-statistic on our instrument is equal to 21.2 ($p=.0001$). The second column shows our second-stage estimate: Each one-pill increase in predicted SSRI sales is associated with a decline in suicide rates of around 8.5 percent ($p<.05$).

As noted above, a limitation of our just-identified setup is that it assumes that a given unit change in sales of our instrument drugs has the same effect on SSRI sales regardless of where we are in the lifecyle of the drug. But SSRI sales were slower during the first few years they were on the market compared to the more rapid increase in sales that we see for our instrument drugs. The IV design with interacted instruments allows the coefficient on our predicted SSRI sales level to vary by the number of years SSRIs are predicted to have been on the market in a country. The third column of Table 4 shows our first-stage results with this set of interacted instruments, which compared to the just-identified first-stage in column (1) increases our first-

[32] One possible concern with this specification check comes from Wolfers's (2006) observation that jurisdiction-specific linear trends could pick up un-modeled dynamic policy responses in addition to picking up differences across areas in pre-existing trends, which could bias our coefficient estimates for the indicators for pre-SSRI years. Some protection against this concern comes from the fact that our key explanatory variable of interest in these OLS models is actual SSRI sales, rather than a simple indicator for SSRIs being on the market. In any case we obtain similar results when we re-run our specification test without country-specific linear trends, or replace the SSRI variable with a series of indicator variables for the number of years SSRIs were on the market.

stage F-test statistic by more than one-third (29.2 versus 21.2). Given that we have a relatively large number of instruments (15) the concentration parameter may be a better indicator for first-stage explanatory power (Hansen, Hausman and Newey, 2005), which in our case is equal to 15×(F-1)=422.9.[33] Hansen's J test of the over-identifying restrictions in this model yields a p-value of .495.

The final column of Table 4 shows that the estimates from our multiple-instrument second-stage equation suggest that an increase of 1 SSRI pill per capita reduces suicide rates by around 5 percent ($p<.05$). This estimate is smaller than our just-identified result, but from here forward we use this interacted-instrument setup as our preferred model given the relatively greater first-stage power and (as shown below) general robustness to a wide range of sample restrictions and other sensitivity tests.

Our preferred IV estimate in column (4) of Table 4 is about twice as large as the OLS estimates in Table 3, consistent with the idea that variation in actual SSRI sales may be driven in part by worrisome trends within these countries with respect to suicide mortality or negative mental health conditions generally, although a standard Hausman test (1978) shown in the last row of the table does not quite allow us to reject the null hypothesis that our OLS and IV estimates are equal ($p=.11$).[34] For purposes of interpretation, a one pill per capita increase in SSRI sales represents about a 12 percent increase over the average 2000 sales level across our sample of countries. An increase of one pill per capita also represents a 41 percent increase in average sales over our *entire* sample period, so that the estimated elasticity of suicide with respect to SSRI sales implied by the results in Table 4 is equal to around -.12. Our IV estimates also seem generally consistent with the sort of effect on suicide mortality we would predict based on the RCT evidence for how

[33] Hahn and Hausman (2002) suggest an alternative test for weak instruments that is essentially based on a comparison of IV estimates run "forward" versus "backward" (i.e. switching the dependent variable and endogenous explanatory variable, then rescaling the latter). If the two sets of estimates are significantly different then 2SLS may be inappropriate and LIML or other estimation strategies might be preferred. However in our application we cannot reject the null hypothesis that the forward and backward estimates are the same and so present 2SLS estimates.

[34] When we replicate our IV estimates and include indicator variables for each of the five years before we *predict* SSRIs to first be sold in each country, we find these indicators are not statistically significant. However this is not a very powerful test because there is so little variation across our countries in the predicted timing of when SSRIs would first be sold if each country's adoption lag for SSRIs was similar to the average adoption lag for Statins, PPIs, CCBs and ACE inhibitors.

SSRIs impact depression together with the epidemiological literature on how depressive disorder elevates the risk for suicide completion, although we note these calculations themselves are subject to some uncertainty.[35]

C. Robustness Checks

Our results seem generally robust to alternative model specifications and changes in our analytic sample. For example our findings are not driven by the experiences of just a few outlier countries. This is easiest to see from a visual inspection of the difference-in-difference analog to our preferred IV estimates (Figure 3). The horizontal axis shows the change in the *predicted* value of SSRI sales from 1980 to 1995 for each country from equation (4) above, while the vertical axis shows the simple change in log suicide rates over the same period. The simple bi-variate relationship between change in log suicide rates and change in predicted SSRI sales is negative, consistent with the results of our preferred IV analysis; visual inspection suggests the estimate does not appear to be driven by the experiences of outlier countries.

More formally in Table 5 we re-estimate our preferred IV model excluding different countries. First, we drop countries that Figure 3 suggests might exert special leverage over the regression line (the U.S.,

[35] Note that not all of the relevant data we would want for calculating the suicide mortality impact we would expect from the effect of SSRIs on depression and the link between depression and suicide are available, and so this calculation requires a number of assumptions. As noted in an earlier footnote, we estimate that in the 1999-2002 period, the typical patient receiving psychotropic drug treatment for depression received around 268 doses per year, so that an additional 1 pill per capita increase in SSRI sales in the US multiplied by a population of 270 million implies around 270 million additional doses, or roughly 1 million more people receiving anti-depressant drug treatment. The recent IOM report on suicide suggests that between 30 and 90 percent of suicide decedents suffered from depression; we assume a mid-point figure, of 60 percent, or around 18,000 of the 30,000 suicide decedents in the US each year. These figures imply a suicide mortality rate of 128 per 100,000 for those with depression versus around 6 per 100,000 for those without depression, using Kessler et al.'s (2002) estimate of 14 million American adults suffering from major depressive disorder in a given year (and so 195 million Americans without depression). Bech et al.'s meta analysis (2000) finds that SSRI treatment reduces the probability of depressive symptoms by 55 percent. But, placebo reduces the probability by fully 35 percent. The placebo effect in treatment of major depressive disorder is large and its interpretation remains contentious (Stolk et al., 2003; Miller, 2003; and Walsh et al, 2002). It is not clear whether the placebo effect is part of the therapeutic package associated with SSRI treatment, such as visits with doctors and follow up care, or simply measuring the abatement of symptoms. If it is the former, this type of indirect effect of SSRI on suicide through doctor visits and follow up care would be captured by our estimate. If we take only the direct effect (over and above placebo) as a lower bound, then 20 percent of the additional 1 million receiving anti-depressants would respond. If these patients now have suicide mortality rates about equal to the general population, then the number of suicides averted in the US in 2002 due to SSRI treatment is around 200,000 (additional people no longer suffering from depressive disorder) times a change in mortality risk per 100,000 of (128 - 6), implies a reduction of about 244 suicides, or just under 1% of all suicide deaths in the US. If we include the indirect (placebo) effect, this would imply an effect of around 2%. If the fraction of suicide decedents suffering from depression is 90%, which some studies suggest, rather than 60%, the effect we would expect from a 1 pill per capita increase in SSRI sales would be around 3.5%. Note that this 1 to 3.5 percent range of expected effects comes from clinical evidence derived from the US; since our IV estimates suggest a relatively small impact in the US (our point estimates increase in absolute value when we drop the US, as seen in Table 5), this range of expected effects for the US seems fairly consistent with the 5 percent effect we estimate for the full sample of countries.

Mexico, and Japan) and obtain similar results. The second column of Table 5 shows that qualitatively similar results hold when we restrict the analytic sample just to member nations of the OECD in our sample. We also obtain comparable results when we drop countries with populations smaller than 5 million (Ireland, Israel, Luxembourg, New Zealand, and Norway).

The remainder of Table 5 shows the results are qualitatively similar under a variety of other changes in our estimation approach, including dropping country-year observations in the late 1980s when SSRI sales were imputed, or excluding our controls for population age structure and ICD-10 coding. We also obtain similar results when we add controls for a variety of risk factors that have been shown to be associated with suicide (Goldsmith et al., 2002), including each country's divorce rate and measures of economic conditions or hardship such as unemployment rate and real GDP per capita.

Our panel is a bit unbalanced because the amount of data available on our instrument drugs varies a bit across years,[36] but replicating our analysis on a balanced panel using data just through 1997 yields similar results. While our main estimates weight by country population, the un-weighted point estimate is similar although somewhat less precisely estimated. Re-calculating the estimates using actual rather than logged suicide rates yields a point estimate of -.24, which given an average suicide rate of 10.2 in our panel (Table 1) implies that an increase in SSRI sales of 1 pill per capita reduces suicide by around -2.5%, about half the size of the log specification and now no longer statistically significant. However given the substantial differences in suicide levels across countries described above a log-linear model that estimates SSRI impacts in proportional rather than absolute terms seems preferable.

Implicit in our IV design is the notion that there is some "usual" way that new drugs are approved and sold within a country. Consistent with this assumption we find that the adoption lags across the OECD

[36] We have sales data through at least 1999 for all countries, and for a few additional years for a sub-set of our sample. In addition because there is a bit of variation across countries in when they approved our four instrument drugs for sale the number of years-on-the-market for which we can calculate our instruments will vary slightly across countries. As a result our standard IV estimates drop some country-year observations in the late 1990s.

countries in our sample for our four instrument drugs are all highly correlated (between +.8 and +.9). If we regress actual sales values for our instrument drugs against one another using our panel of country-level data the R-squared values are usually on the order of .5 to .6.[37]

D. Additional Specification Tests

The main threat to our study is the possibility that the our instruments – the rate at which new drugs generally diffuse within each country – may not be orthogonal to other determinants of suicide, such as the quality or quantity of health care, or that drug diffusion itself may directly influence suicide mortality by affecting physical health conditions or the amount of pain treatment for chronically ill people, or other hard-to-measure variables such as the prevalence of psychotherapy use. In this section we provide several empirical tests that try to rule out these alternative explanations.

One obvious concern is the possibility that new drugs diffuse more rapidly in countries that spend more on health care. In this case, we may attribute reductions in suicide to SSRI use rather than to underlying changes in the sorts of chronic physical health problems that may lead people to contemplate suicide. We address this concern by utilizing data on health care expenditures per capita that we can obtain for a sub-set of our analytic sample, most of which are OECD member nations. It turns out that countries where drug sales increase more rapidly (and so are predicted to have higher rates of SSRI growth) do not seem so atypical with respect to growth in overall health spending. Figure 4 shows that when we divide the countries for which we have health spending data into three categories – those that are predicted to have high levels of SSRI growth on the basis of our instruments (<7 SSRI doses per capita), medium levels of growth (4-7 doses), and low levels of growth (<4 doses) – we see similar trends in health expenditures over the period 1980-2000. When

[37] Another way to see this is by constructing new versions of our instruments that use separately each of the four instrument drugs (Statins, CCBs, ACE inhibitors and PPIs). In our full sample the estimates using Statins, ACE inhibitors, and PPIs range from -.03 to -.045, close to our preferred IV estimate of -.05. The outlier comes from using CCBs alone to construct our instruments, which seems to be driven in part by the fact that CCBs were a smash success in Japan, with CCB sales levels that are much higher than in any other country (and also much higher than those of our other drugs in Japan for that matter). CCB sales will thus have more limited power to explain growth in SSRI sales because Japan has unusually high CCB sales but unusually low SSRI sales (given its late adopter status). When we restrict our sample to just OECD countries, the Japan effect in distorting the first stage with the CCB instruments is even more pronounced.

we re-estimate our IV model using just the sub-set of countries for which we have health spending data, adding the health expenditure variable as a control has hardly any impact on our IV estimate for the effect of SSRI sales on suicide (-.071 with vs. -.075 without, statistically significant in both cases).

A different test for whether our instruments may simply be picking up the effectiveness of the overall health care system comes from re-estimating our IV model for a different cause of death that should not be causally affected by SSRI treatment. This sort of falsification test would be most informative if we focus on causes of death that should also not be substantially affected by drug treatments of any type, since our basic IV design comes from comparing countries with relatively high and low rates of growth in new drugs more generally. One natural candidate is accidents. The estimated coefficient for the "effect" of SSRI sales on the log of accident mortality rates is equal to -.0108 (se=.0269), which is not statistically significant and about one-fifth as large as the estimated effect of SSRIs on suicide.

Even if our instruments are not systematically related to the structure or resources of a country's overall health care system, it is logically possible that our instruments could potentially have a direct effect on suicide mortality by affecting physical health. That is, in countries where new drugs diffuse more rapidly, it could be that drug therapy does more to reduce the sorts of chronic health problems that lead some people to consider suicide, or that pain treatment for such cases is more intensive. This hypothesis would predict that in countries where we predict more rapid SSRI sales growth – that is, where new drugs generally diffuse more rapidly – suicide mortality reductions should be concentrated among older people, since the prevalence of most of the serious physical health problems increase with age.[38]

To test this prediction we can re-estimate our preferred IV specification, but now replacing the dependent variable measure of overall suicide mortality with age-specific suicide mortality rates. This is not a very good test for age heterogeneity in treatment response to SSRIs, since we do not have data from IMS

[38] For example, results of the National Health and Nutrition Examination Survey in the U.S. indicate that prevalence of hypertension and high levels of serum cholesterol – conditions treated by three of our four instrument drugs -- rise substantially with age (http://www.cdc.gov/nchs/about/major/nhanes/datatblelink.htm, tables 67 and 68, accessed Dec. 7, 2007.)

Health on SSRI sales for separate age groups. Data from countries where data on SSRI sales by age are available – the U.S., Australia, and Canada – suggest that over the course of the 1990s SSRI use increased the most in proportional terms among younger people, although we would not make too much of this fact since these three countries represent just a small sub-set of our total analytic sample.[39] But in any case examining how changes in overall SSRI sales affect suicide mortality to different age groups does provide some power to rule out the specific counter-explanation that our results may be due to the instruments' effects on physical health or pain control. Yet as Table 6 shows, we find that the estimated relationship between SSRI sales and suicide mortality is largest in both proportional and absolute terms for people ages 15-24. The only other group for which we find a significant relationship is for those between the ages 25-34.[40] This pattern is not consistent with a "physical health" channel, but is consistent with the idea that relatively younger people are the ones who are most likely to become depressed and consider suicide in response to adverse, but temporary, changes in their life conditions (Goldsmith et al., 2002), and so may benefit the most from depression treatment that helps them weather these difficult spells. Survey data from the U.S. show the lifetime prevalence of major depression disorder is much higher than the 12-month prevalence, 17.9 versus 7.6 percent (Kessler, Berglund et al., 2003); depression for some people is a temporary rather than permanent condition.

Of course, absent random assignment, a reader with enough time can always come up with alternative stories that challenge the validity of any instrumental variables design. Perhaps countries where new drugs

[39] For example, in the U.S., between 1988 and 2002 the proportion of adults in the U.S. prescribed antidepressants increased from 2.5% to 8.1% (Paulose-Ram et al., 2007). Between 1987 and 1996 the increase in the rate of prescriptions to children and adolescents ranged from four to ten fold in different Medicaid and HMO claims files (Zito et al., 2003). By 1996, Zito et al. estimate that about 2% of children and adolescents were being treated with antidepressants. In Australia, between 1990 and 2001 the use of antidepressants among 15-24 year olds increased by ten-fold, from 1.2 defined daily doses (DDD) per 1,000 people per day to 14.3 for males, and from 3.2 to 30.7 for females. This compares to an increase of four-fold for 45-54 year olds, from 10.9 to 43.4 for males and 24.2 to 86.7 for females (Hall et al., 2003). In Canada, the percent of persons with major depression treated with antidepressants increased between 1994 and 2001 from 6.8 to 30.6 for 15-34 year olds, compared to 21.0 to 31.3 for 35-54 year olds (Patten and Beck, 2004).

[40] We also find that the IV point estimates are larger in proportional terms for females than males, although since the baseline suicide mortality rate in our data is about three times as high for males as for females (Table 1) the estimated association between SSRIs and suicide in absolute terms (deaths per 100,000) will be somewhat larger for males than females.

diffuse more rapidly also have more pronounced preferences for psychotherapy, etc. Because good measures for use of psychotherapy and many other variables are not readily available over long periods of time for our set of countries, it is difficult to directly regression-adjust to account for other omitted variables stories.

One final and quite general test of our identification strategy comes from examining whether the countries that our research design predicts should have more rapid versus less rapid growth in SSRI sales over time have similar trends in suicide mortality rates *before* SSRIs come on the market. The top panel of Figure 5 shows there is almost no relationship between the predicted growth in SSRI sales for our countries during the period 1990-95, when SSRI use became common, with the rate of change in log suicide rates during the *previous* period from 1980-90 (the slope of the regression line is equal to -.005). In contrast, there is a pronounced negative relationship between the change in log suicide rates from 1990-95 with the predicted change in SSRI sales over this period (the slope is -.04, quite close to our formal IV estimate).[41]

For a subset of our countries we can obtain suicide mortality data going back to 1960, and here again we see evidence of quite similar "pre-treatment" trends in suicide. We divide these countries into three groups based on the predicted growth rate of SSRI sales from our IV design. Figure 6 shows that suicide rates showed a similar upward trend from about the mid-1960s through the late 1980s in countries with high, medium, and low predicted growth rates in SSRI sales. This steady upward trend in suicide mortality persists through the year 2000 in countries with low or medium predicted rates of SSRI sales, but shows a clear break in trend for the high-SSRI-growth group starting in the very late 1980s – just as SSRI sales start to take off.

We have established that countries with different predicted growth rates in SSRI sales have similar suicide trends before SSRI use became prevalent, that trends in suicide mortality only differ across these countries in the period when SSRI sales increased substantially, that there is not relationship between predicted SSRI sales growth and either trends in health care spending or other causes of death such as

[41] If we regress change in log suicide rates 1980-85 against change predicted SSRI sales 1990-95 the coefficient is equal to -.012, while using as the dependent variable the 1985-90 change in log suicide rates the coefficient is +.009.

accidents that should not be causally related to SSRI treatment, and that the estimated effect of SSRI sales on suicide is concentrated among relatively younger people, rather than among older people for whom chronic physical health conditions that could potentially be influenced by drug treatment will be more prevalent and more important contributing factors to suicide risk.

The one final threat to our design comes from the possibility that other forms of mental health treatment also increased during the 1990s in those countries where SSRI use increased more rapidly. While the available data are quite limited, the evidence that we can assemble does not seem consistent with this counter-explanation. Figure 7 shows that while SSRI sales were increasing worldwide into the twenty-first century, trends in sales of other anti-depressants were relatively flat through the end of our study period. Second, there is little evidence of any increase over the course of the 1990s in the use of TCAs in any of the countries for which data are available – U.S., Canada, Australia, Italy, Netherlands, and Norway. Many of these countries are predicted by our instrument to have unusually rapid growth in SSRI sales, and also show larger-than-average declines in suicide mortality (see for example Figure 3 above).[42] Third, there is no evidence of systematic increases in psychotherapy during the period in which SSRI growth took off in the countries for which data on this form of mental health treatment are available (U.S., U.K., and Australia).[43]

[42] Ludwig and Marcotte (2005, p. 264) show sales of TCA anti-depressant drugs were flat over the 1990s in the U.S. Similarly, there is little evidence of an increase in TCA or other older antidepressants such as monoamine oxidase inhibitors (MAOIs) in other countries, regardless of their predicted level of SSRI growth. In Canada, market share of TCAs and MAOIs remained constant between 1981 and 2000 (Hemels, et al. , 2002). In Australia, there was a decline of the use of TCAs and MAOIs from about 1,000,000 defined daily doses per day in 1975 to about 700,000 in 2002 (Mant et al., 2004) and a decline of around 25% in TCA prescriptions from 1990 to 1998 (McManus et al., 2000). In Italy, the use of TCAs remained unchanged between 1983 and 2000 (Guaiana et al., 2005; Barbui et al., 1999). In the Netherlands, TCA use remained stable while SSRI use increased in the 1990s (Meijer et al, 2004). In Norway, sales of all other antidepressants remained static as SSRIs came onto the market and grew rapidly (Reseland et al., 2006), although they grouped all non-SSRI antidepressants together, including TCAs with SNRIs.

[43] In the U.S. the share of the population that received outpatient psychotherapy remained unchanged following the introduction of SSRs, equal to 3.2 percent in 1987 and 3.6 percent in 1997 (Olfson et al., 2002). Wang et al. (2006) examine changes in sources of mental health care among Americans and report a large increase in care from general practitioners and psychiatrists, and a 73% decline in care from therapists other than medical doctors. In the UK, trends in use of psychotherapy were relatively flat from 1993 to 2000. Specifically Brugha et al. (2004) show that among adults with neurotic disorders, the share receiving psychotherapy declines for females from 1993 to 2000 (2.9 percent to 1.8 percent), with a slight increase for males (6.2 percent to 9.8 percent). Averaging the results across genders together suggests a relatively flat trend in use of psychotherapy. Finally, a survey of Australian psychiatrists reported a substantial decline in the provision of psychotherapy there between 1997 and 2002, contemporaneous to a large increase in use of medication (Rey et al., 2004).

Our estimates also do not appear to be influenced by the introduction in the mid to late 1990s of another class of anti-depressants, the serotonin-norepinephrine reuptake inhibitors (SNRIs). As their name suggests, the SNRIs act on two neurotransmitters (serotonin and norepinephrine) rather than just one as with SSRIs. SNRI sales did not really begin to increase until the late 1990s. Changes in SNRI sales are unlikely to be driving our IV estimates for the effects of SSRIs in part because they do not represent a major technological change in the treatment of depression compared to SSRIs. But more importantly Figure 7 shows that SNRI sales did not begin to substantially increase until the late 1990s, while Table 5 shows that our IV estimates for the effects of SSRIs on suicide are not much affected by using data only through 1997. Another way to see this comes from re-estimating our model dropping country-year observations in which SSRIs accounted for less than 90 percent of total anti-depressant sales. The point estimate and standard error (-.0514, 0.190) are similar to our baseline model.

VI. CONCLUSIONS

Understanding the effects of SSRI antidepressants on suicide is important for government regulators as well as for doctors, patients, and the family and friends of those suffering from severe depression. It is unlikely that randomized clinical trials (RCTs) will ever be able to identify the effects of SSRIs on suicide mortality, both because of small samples and because these samples exclude those at highest risk for suicide. Previous clinical trials instead focus on measures of non-lethal "suicidal behavior," but the association between these indicators and actual suicide mortality remains unclear. Moreover the conditions under which subjects in RCTs use SSRI drugs (for example level of physician monitoring) may differ from the usual community standard of care.

In light of these practical and ethical constraints, we must turn to population-based observational studies to adequately identify the effects of SSRIs on suicide completion rates. We believe our study represents a substantial improvement over previous research by using population-level data together with a

plausibly exogenous source of identifying variation in SSRI use. Specifically we use just the variation in SSRI sales across countries over time that can be explained by how quickly these countries adopt new drugs in general, and the rate at which sales increase for these new drugs once they are on the market.

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. We find that increase in SSRI sales of 1 pill per capita per year (about a 12% increase over 2000 sales levels) is associated with a decline in suicide mortality of around 5%. This IV estimate is about twice as large in absolute value as OLS estimates, consistent with our general concern that both the timing of SSRI approval and the rate at which SSRI sales increase over time may be endogenous to what is happening with mental health and suicide within countries. We also find no relationship between SSRI sales and accidental deaths, a type of mortality that should not be affected by SSRI use, and we find little relationship between trends in log suicide rates over the course of the 1980s and predicted SSRI sales growth in the 1990s.

Note that the impact we estimate here is the average effect from expanding SSRI sales in our sample of countries during the years after these drugs were first introduced to the public. If SSRI treatment went first to those who would benefit the most, or if markets are now becoming saturated, additional expansions of SSRI sales may have somewhat smaller impacts on suicide mortality than our IV estimates would suggest. However it is possible the difference between the average effect implied by our estimates and the effects arising from further expansions in SSRI use might be modest, given the relatively low rates of current mental health treatment even in wealthy countries like the U.S. For example data from the National Co-morbidity Survey – Replication conducted in 2001-3 suggest that only around 40 percent of Americans with severe mental health disorders were receiving any treatment (Kessler, Demler et al., 2005).

Our estimates suggest that at least on average SSRIs may be a very cost-effective means for saving lives. Commonly used SSRIs can currently be obtained in the United States for around $0.13 per pill.[44] Our estimates thus imply that each additional $26,000 spent on SSRIs will avert one suicide completion, far below the cost per life saved from most other public health, regulatory, or other forms of government intervention. But using this estimate in a more formal benefit-cost analysis raises difficult conceptual and normative questions about the appropriate way to value the life of someone who subjectively prefers death (at least at the time of the intervention). Viscusi's (2005) review of the literature on the statistical value of life puts the median estimate at $7 million for working age adults. We might expect SSRI use to be concentrated among cases where the patient (or their family and friends) believe they would benefit from treatment. Since anyone outside of a mental institution always has the option of stopping SSRI treatment, it seems reasonable to assume that the lower bound for the social welfare impact of each suicide prevented from SSRI use is zero. In this case given the very low cost per life saved it is difficult to believe that expanding SSRI treatment does not easily pass a benefit-cost test, particularly when we also consider the effects of depression on other outcomes such as parental functioning, educational attainment and other human capital accumulation, employment, productivity, crime, child abuse, homelessness, and divorce (Frank and McGuire, 2000; Marcotte and Wilcox-Gök, 2001; Currie and Stabile, 2004).

[44] For example, Walmart fills prescriptions for three of the drugs in the SSRI class for $4 (citalopram, fluoxetine, and paroxetine, http://i.walmart.com/i/if/hmp/fusion/four_dollar_drug_list.pdf)

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Figure 1

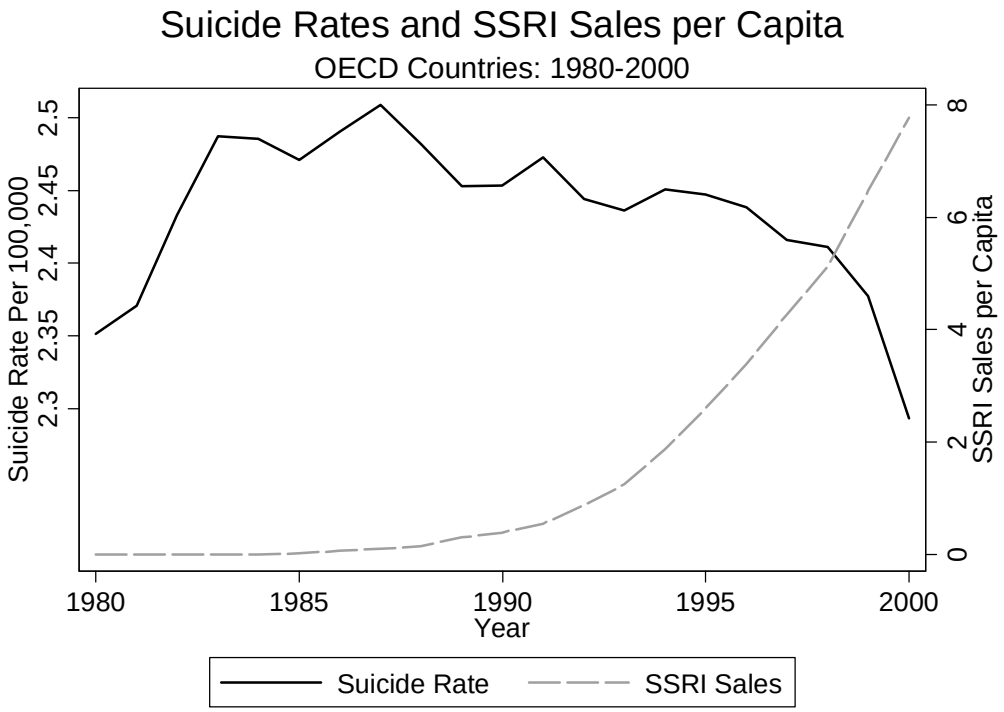

Suicide Rates and SSRI Sales per Capita
OECD Countries: 1980-2000
Suicide Rate Per 100,000
2.3
2.35
2.4
2.45
2.5
SSRI Sales per Capita
0
2
4
6
8
1980
1985
1990
1995
2000
Year
Suicide Rate
SSRI Sales

Figure 2: OLS Model – Changes in log suicide rates, 1980-95, vs. changes in SSRI sales

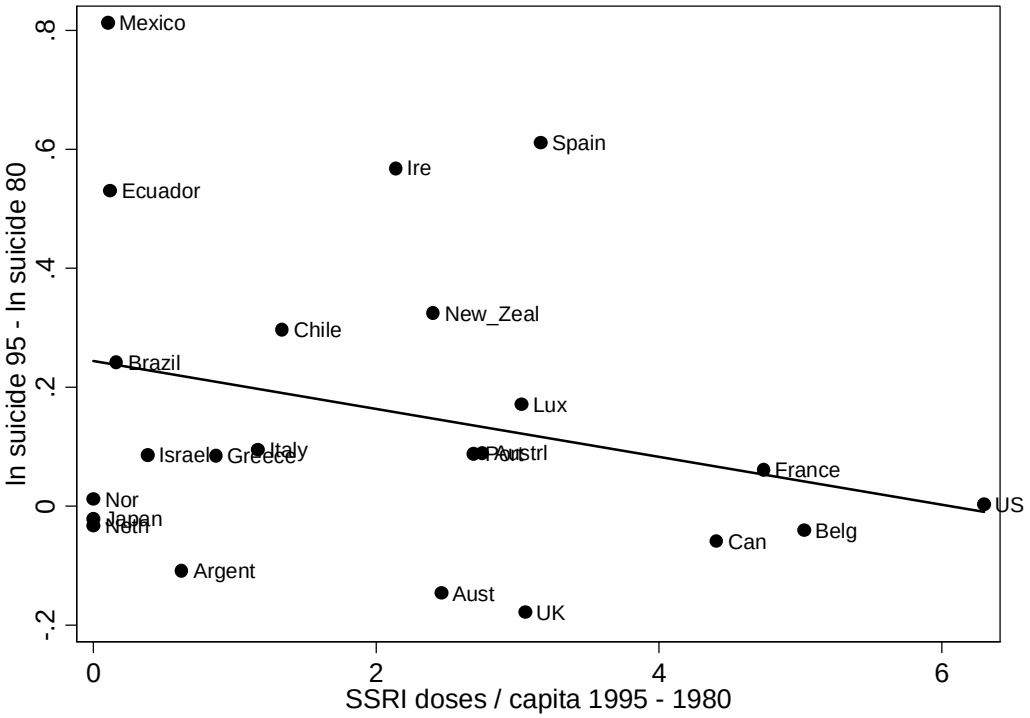


Figure 3: IV Model – Change Log Suicide Rates, 1980-95 vs. Predicted Change SSRI Sales

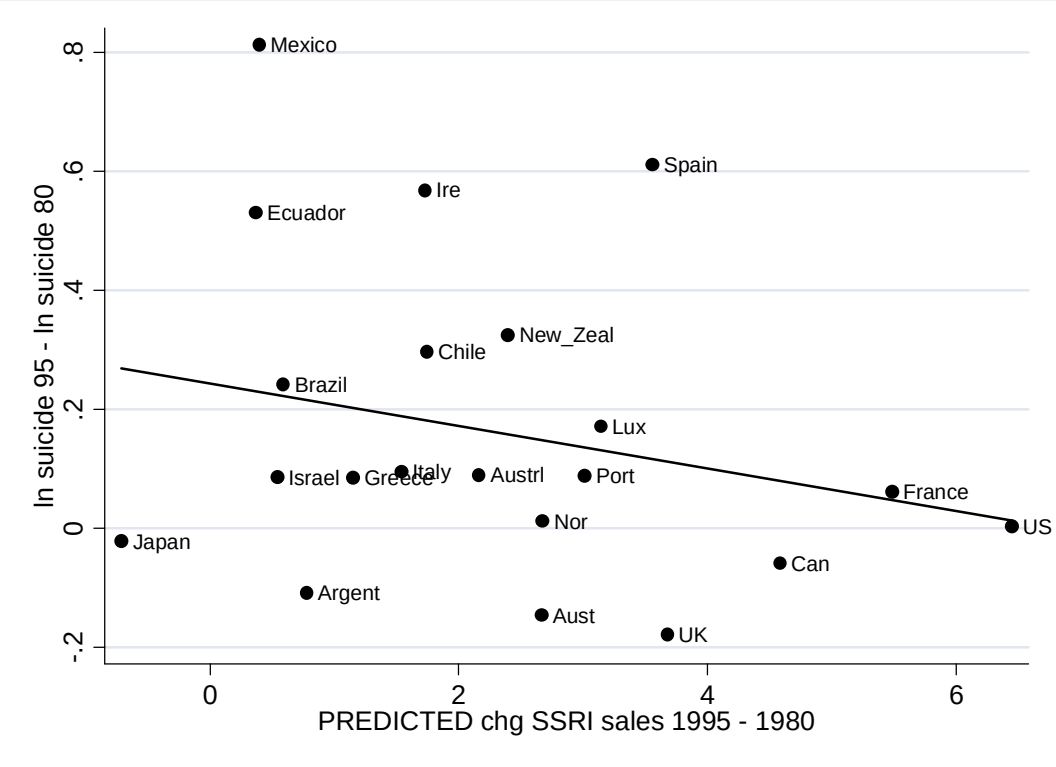
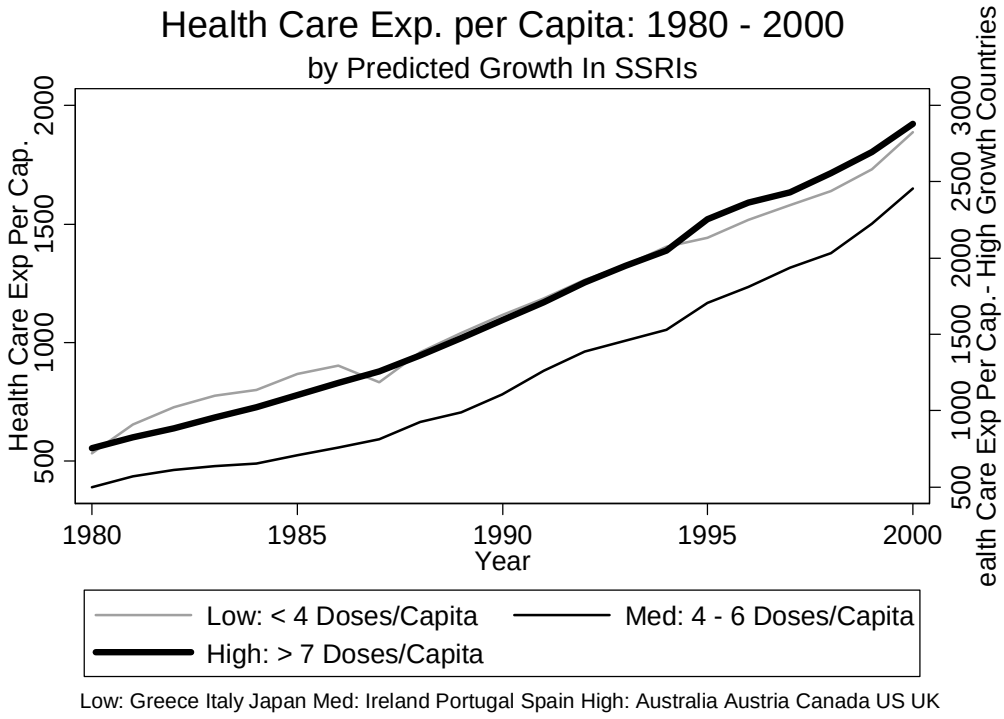


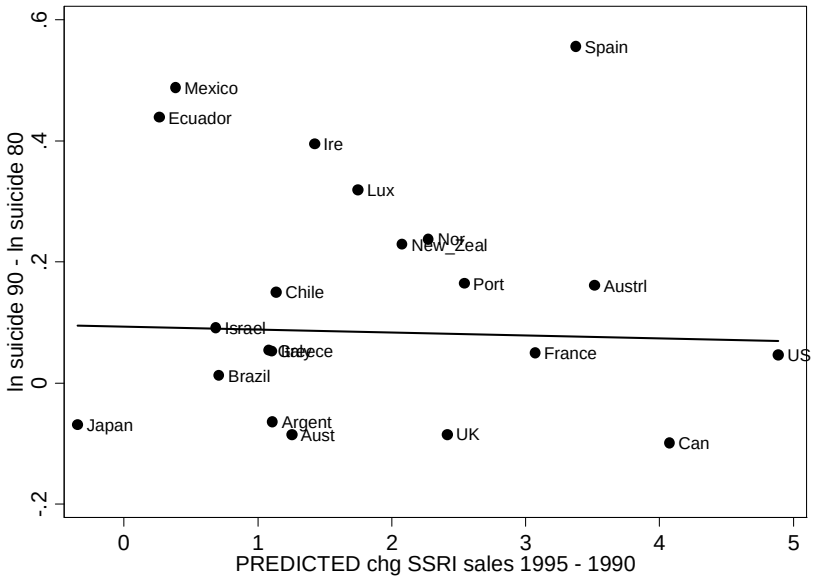
Figure 4
Trends in Total Health Expenditures Per Capita by Predicted SSRI Growth



Low: Greece Italy Japan Med: Ireland Portugal Spain High: Australia Austria Canada US UK

Figure 5:
Falsification Check, Changes in Suicides Pre and Post SSRI Changes

Panel A: Change suicides 1980-90 vs predicted change SSRIs 1990-95



Panel B: Change suicides 1990-95 vs predicted change SSRIs 1990-95

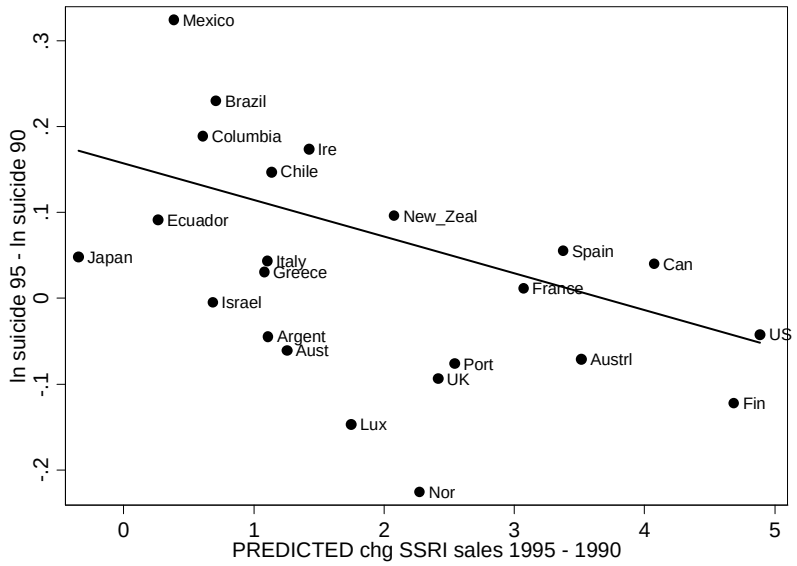
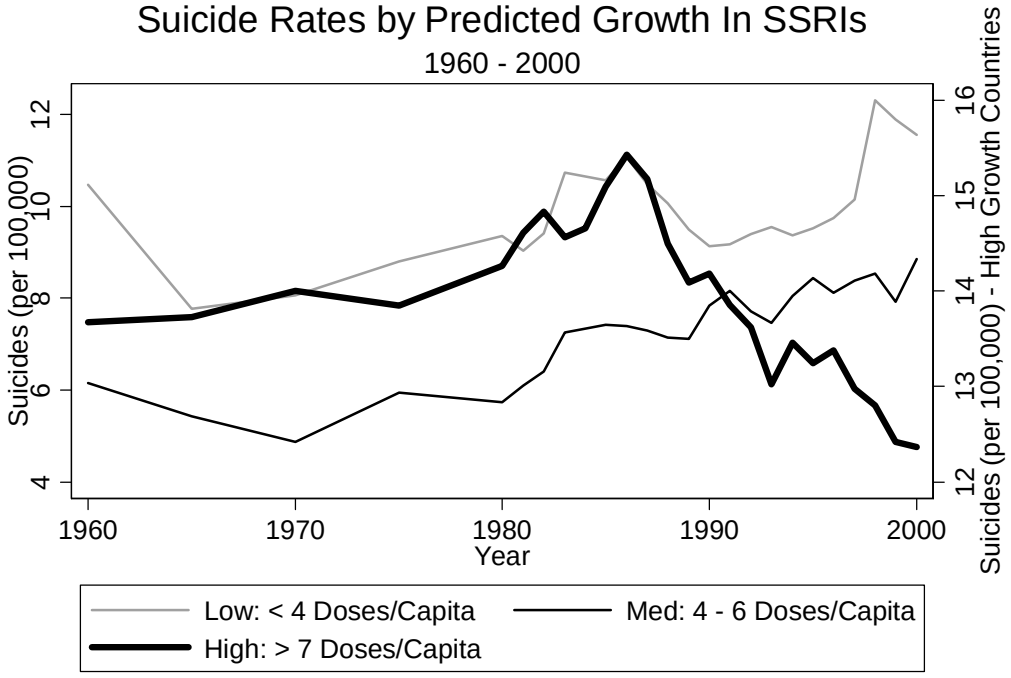


Figure 6



Low: Greece Italy Japan Med: Chile Ireland Portugal Spain High: Australia Austria Canada US UK

Figure 7:

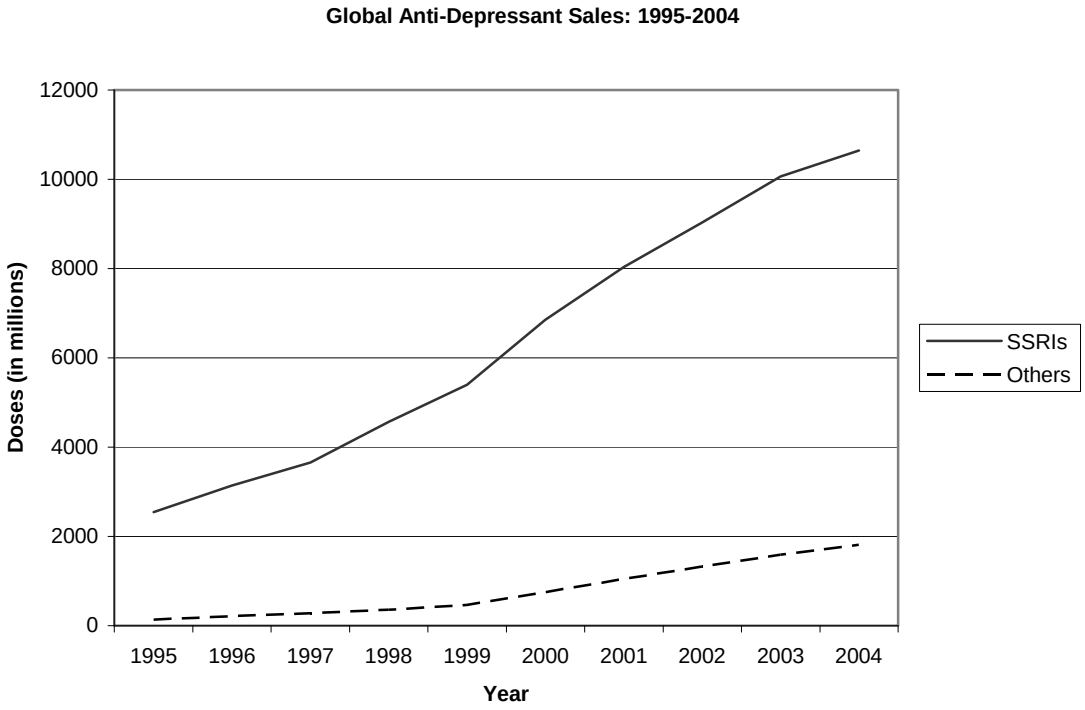

Global Anti-Depressant Sales: 1995-2004
Doses (in millions)
12000
10000
8000
6000
4000
2000
0
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
Year
SSRIs
Others

Table 1: Descriptive Statistics for Full Sample of Country-Level Panel Dataset

Variable	Mean	Standard Deviation
Full sample (1980-2000)		
SSRI doses per capita	2.1290	4.0924
Suicide rates per 100,000		
Total	10.1419	5.9929
Male	15.4149	8.5891
Female	5.1935	5.1935
Age 15-24	8.2268	4.0046
Age 25-34	11.1920	5.5708
Age 35-44	12.2534	6.8066
Age 45-54	14.1380	8.7442
Age 55-64	14.5407	8.9454
Age 65 and over	18.5482	11.9183
% population in age group:		
15-24	16.4555	2.7964
25-34	15.4560	1.3395
35-44	13.2939	1.9874
45-54	10.5985	2.4970
55-64	8.4401	2.5647
65 and over	10.5681	4.3550
Real GDP per capita[a]	16,747	8,118
Unemployment rate	7.1428	3.8937
Suicide data coded using ICD10	.1993	.3999
1980		
Suicides per 100,000	9.3718	5.9366
SSRI doses capita	0	0
1985		
Suicides per 100,000	10.3165	6.5327
SSRI doses per capita	.0015	.0126
1990		
Suicides per 100,000	9.7190	5.7663
SSRI doses per capita	.3675	.4292
1995		
Suicides per 100,000	9.9122	5.5527
SSRI doses per capita	2.5327	2.6395
2000		
Suicides per 100,000	9.617	6.4063
SSRI doses per capita	5.6454	5.4700

NOTES: Authors' calculations from WHO mortality and SSRI sales data for sample countries (see text). Calculations are weighted by country population. a = GDP per capita adjusted for changes over time across countries in currency exchange rates.

Table 2: Information on SSRIs and other Top Selling Pharmaceutical Classes

Drug class	Drug purpose	Year first sold	Country first sold
Selective serotonin reuptake inhibitors	Anti-depressant	1984	Germany
Statins	Cholesterol regulation	1987	US
Proton pump inhibitors	Ulcers	1988	Netherlands
Calcium channel blockers	Hypertension	1982	US, Spain, Italy, Finland, Australia, Canada and Ireland
ACE inhibitors	Hypertension	1982	Canada, Portugal, Australia and France

Table 3
OLS Regression Estimates with Country-Level Panel Data 1980 to 2000

	Outcome measure = log(suicides/100,000)	Outcome measure = log(suicides/100,000)	Outcome measure = log(suicides/100,000)	Outcome measure = log(suicides/100,000)
SSRI doses sold per capita	-.0350 (.0074)**	-.0258 (.0011)**	-.0198 (.0102)*	-.0204 (.0094)**
Population age distribution				
% pop 15-24		.0305 (.0254)	.0007 (.0221)	.0006 (.0203)
% pop 25-34		.0297 (.0187)	.0275 (.0224)	.0218 (.0201)
% pop 35-44		.0287 (.0143)**	.0087 (.0212)	-.0061 (.0184)
% pop 45-54		.0025 (.0291)	-.0298 (.0251)	-.0159 (.0218)
% pop 55-64		.0072 (.0231)	.0535 (.0242)**	.0556 (.0217)**
% pop 65 and over		.0059 (.0214)	.0130 (.0259)	.0268 (.0254)
ICD-10 system used to classify mortality codes		-.0079 (.0422)	-.0417 (.0252)	-.0279 (.0238)
Indicators for Years Before SSRIs on the market:				
1 year before				-.0309 (.0194)
2 years before				-.0625 (.0416)
3 years before				-.0846 (.0443)*
4 years before				-.0994 (.0410)**
5 years before				-.0867 (.0353)**
Model specification				
Year indicators?	Yes	Yes	Yes	Yes
Country indicators?	Yes	Yes	Yes	Yes
Country-specific linear trends?	No	No	Yes	Yes
N	541	531	531	531
R-squared	.977	.981	.991	.992

NOTES: Table reports least squares regression coefficients. Standard errors in parentheses. Regression models also include a constant intercept term and in the last three columns 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 4
First and Second Stage Instrumental Variables Estimates

	Outcome measure = SSRI sales per capita	Outcome measure = log (suicides/100,000)	Outcome measure = SSRI sales per capita	Outcome measure = log (suicides/100,000)
SSRI doses sold per capita		-.0854 (.0341)**		-.0542 (.0190)**
Instrument: Predicted Drug Sales	.3879 (.0842)**			
Instruments: Predicted Drug Sales by Year Since Predicted Approval Date				
Year 1			.4815 (.15627)**	
Year 2			.3613 (.1283)**	
Year 3			.3566 (.1769)**	
Year 4			.3034 (.1534)*	
Year 5			.2866 (.1293)**	
Year 6			.2757 (.1278)**	
Year 7			.2523 (.1285)*	
Year 8			.2845 (.1246)**	
Year 9			.2765 (.1224)**	
Year 10			.3461 (.1094)**	
Year 11			.3942 (.1112)**	
Year 12			.4013 (.1062)**	
Year 13			.3799 (.0985)**	
Year 14			.3985 (.1131)**	
Year 15			.5312 (.1181)**	
% Pop 15-24	.2506 (.1148)**	.0069 (.088)	.1867 (.1233)	-.0010 (.0196)
% Pop 25-34	-.6177 (.1834)**	-.0334 (.0366)	-.5009 (.1693)**	-.0111 (.0280)
% Pop 35-44	-.2863 (.2774)	-.0017 (.0327)	-.2821 (.2909)	.0199(.0347)
% Pop 45-54	.4277 (.3063)	.0330 (.0343)	.4729 (.2487)*	.0264 (.0282)
% Pop 55-64	-.1596 (.2867)	.0547 (.0347)	-.1292 (.2786)	.0524 (.0361)
% Pop 65 +	-.2122 (.3999)	-.0338 (.0479)	-.2096 (.3346)	-.0307 (.0391)
ICD-10 system to code mortality causes	-.2763 (.2954)	.0250 (.0473)	-1.5687 (.7415)**	.0412 (.0549)
Model specification				
Year indicators?	Yes	Yes	Yes	Yes
Country indicators?	Yes	Yes	Yes	Yes
Country-specific linear trends?	Yes	Yes	Yes	Yes
F test on joint significance of instruments in first stage	21.24 (p=.0001)		29.19 (p<.0001)	
N	428	421	421	421
R-squared	.985		.988	.996
Hausman test of endogeneity of SSRI sales (t-statistic)	1.96 (p =.05)		1.64 (p =0.11)	

NOTES: Table reports least squares regression coefficients. Standard errors in parentheses. Regression models 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: Sensitivity Analyses

Model Specification	*Full sample*	*OECD countries only*
Baseline specification	-.0542 (.0190)**	-.0499 (.0178)**
Drop US	-.0975 (.0383)**	-.0665 (.0252)**
Drop Mexico	-.0745 (.0238)**	-.0770 (.0227)**
Drop US and Mexico	-.1475 (.0473)**	-.0917 (.0580)
Drop Japan and Mexico	-.0601 (.0190)**	.0191 (.0184)
Drop small countries[a]	-.0467 (.0194)**	-.0368 (.0226)
Drop obs with imputed sales	-.0503 (.0168)**	-.0496 (.0176)**
No time-varying covariates	-.0408 (.0161)**	-.0319 (.0112)**
Control for divorce rate	-.0470 (.0144)**	-.0435 (.0145)**
Control for unemployment rate	-.0509 (.0191)**	-.0521 (.0182)**
Control for real per capita GDP[b]	-.0513 (.0173)**	-.0318 (.0171)**
Control for unemployment and real per capita GDP[a]	-.0515 (.0167)**	-.0353 (.0177)**
Restrict sample to ≤ 1997	-.0464 (.0173)**	-.0353 (.0210)*
Unweighted	-.0442 (.0269)	-.0307 (.0273)
Not logged	-.2404 (.2070)	-.2973 (.3001)

NOTES: a = Small countries are those with average population under 5 million. These are Ireland, Israel, Luxembourg, Norway and New Zealand.
b = Figures for real per capita GDP adjusted for exchange rate variation over time.
Each cell includes the coefficient for predicted SSRI sales values by applying the basic IV estimation approach as in Table 4 to the analytic sample described at the top of the column, with deviations from the basic model setup described at left for each row.
Robust standard errors are in parentheses, clustered at the country level to account for serial correlation. * = p<.1, ** = p<.05

Table 6: IV Results for the Estimated Effect of SSRI Sales on Suicide Mortality for Population Sub-Groups

Dependent variable	*Full sample*	*OECD countries only*
Log suicide, age 15-24	-.0978 (.0275)**	-.0849 (.0556)
Log suicide, age 25-34	-.0525 (.0226)**	-.0326 (.0341)
Log suicide, age 35-44	.0000 (.0303)	.0223 (.0306)
Log suicide, age 45-54	-.0171 (.0305)	-.0249 (.0251)
Log suicide, age 55-64	-.0398 (.0318)	-.0228 (.0317)
Log suicide, age 65 +	-.0253 (.0394)	-.0145 (.0335)
Log suicide, females	-.0775 (.0174)**	-.0937 (.0184)**
Log suicide, males	-.0539 (.0215)**	-.0483 (.0214)*

NOTES: Each cell includes the coefficient for predicted SSRI sales values by applying the basic IV estimation approach as in Table 4 to the analytic sample described at the top of the column, with the dependent variable of interest described at left for each row. Robust standard errors are in parentheses, clustered at the country level to account for serial correlation. * = p<.1, ** = p<.05