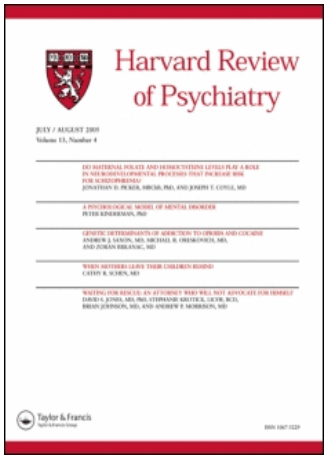

Harvard Review of Psychiatry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713723043

Ecological Studies of Antidepressant Treatment and Suicidal Risks

Online Publication Date: 01 July 2007
To cite this Article: Baldessarini, Ross J., Tondo, Leonardo, Strombom, Indiana M., Dominguez, Svetlana, Fawcett, Jan, Licinio, Julio, Oquendo, Maria A., Tollefson, Gary D., Valuck, Robert J. and Tohen, Mauricio (2007) 'Ecological Studies of Antidepressant Treatment and Suicidal Risks', Harvard Review of Psychiatry, 15:4, 133 - 145
To link to this article: DOI: 10.1080/10673220701551102
URL: http://dx.doi.org/10.1080/10673220701551102

REVIEW

Ecological Studies of Antidepressant Treatment and Suicidal Risks

Ross J. Baldessarini, MD, Leonardo Tondo, MD, Indiana M. Strombom, PhD, Svetlana Dominguez, Jan Fawcett, MD, Julio Licinio, MD, Maria A. Oquendo, MD, Gary D. Tollefson, MD, PhD, Robert J. Valuck, PhD, and Mauricio Tohen, MD, Dr PH

Ongoing discussion of potential benefits and risks of antidepressant treatment with respect to suicidal behaviors includes many ecological, or population-based, correlational studies of temporal or regional trends in suicide rates and rates of usage of modern antidepressants including serotonin-reuptake inhibitors (SRIs). Since this body of research has not been compiled and evaluated, we used computerized literature searching to identify 19 relevant published studies. They yielded heterogeneous findings: only 8/19 found significant inverse correlations between rising sales of modern antidepressants in the 1990s and falling suicide rates not anticipated in the 1980s. Average reductions in suicide rates in the 1990s (10.7%) and 1980s (10.0%) differed little in 11 studies with data from both eras. Reduction of suicide rates in the 1990s was unrelated to geographic region, population size, units of analysis, publication year, or growth in antidepressant usage, but was greater with higher initial suicide rates, in men, and in older persons. In the same decade, suicides rates decreased in only half of 79 large countries. Overall, these findings yield limited and inconsistent support for the hypothesis that increased use of modern antidepressants might limit suicide risk, and no evidence that the risk increased. Suicidal risk is determined by complex factors, including access to clinical services, in general, and more comprehensive treatment of depression, in particular. Overall, as with findings from randomized trials and cohort or case-control studies, evidence of specific antisuicidal effects of antidepressant treatment from ecological analyses remains elusive. (HARV REV PSYCHIATRY 2007;15:133–145.)

Keywords: **antidepressants, ecological studies, international, national, serotonin reuptake inhibitors, suicide rates**

From the Department of Psychiatry and Neuroscience Program, Harvard Medical School, and International Psychopharmacology Program, McLean Hospital, Belmont, MA (Drs. Baldessarini, Tondo, and Tohen); Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN (Drs. Strombom and Tohen, and Ms. Dominguez); Department of Psychiatry, University of New Mexico (Dr. Fawcett); Department of Psychiatry & Behavioral Sciences, University of Miami (Dr. Licinio); Department of Psychiatry, Columbia University (Dr. Oquendo); Orexigen Therapeutics (Dr. Tollefson); and School of Pharmacy, University of Colorado (Dr. Valuck).

Supported by Eli Lilly and Company (IMS, SD, GDT, MT), by a grant from the Bruce J. Anderson Foundation (RJB), and by the McLean Private Donors Psychopharmacology Research Fund (RJB).

The non–Lilly employee coauthors were uncompensated for their consultative efforts in assembling this review. IMS Health Corporation provided recent international data concerning antidepressant sales.

Original article received 9 October 2006; revised manuscript received 29 March 2007, accepted for publication 15 June 2007

Correspondence: Ross J. Baldessarini, MD, Mailman Research Center, McLean Hospital, 115 Mill St., Belmont, MA 02478. Email: rjb@mclean.org

DOI: 10.1080/10673220701551102

Urgently renewed efforts are under way to clarify relationships of antidepressant treatment to suicidal behaviors in persons with increased suicidal risk due to major mood disorders. In 1990, Teicher and colleagues[1] reported six cases involving increased suicidal thoughts or behaviors during treatment with the then-new serotonin reuptake inhibitor (SRI) R,S-fluoxetine hydrochloride in adults with depressive disorders. Subsequent reports provided evidence both challenging and supporting this adverse association of treatment with SRIs or other types of antidepressants.[2–8] New evidence of a possible adverse association of SRI treatment with suicidal risk has emerged since 2004 in meta-analyses of data reported to regulatory agencies in the United Kingdom and United States and from randomized, controlled trials (RCTs) involving children or adolescents with various depressive, anxiety, or behavioral disorders.[9–13] Similar concerns have been raised concerning depressed young adults under age 25 years.[14]

Assessment of associations of antidepressant treatment and altered suicidal risk—either adverse or favorable—is especially challenging. Suicidal acts are uncommon in both experimental treatment trials and clinical practice, and rare in children. Moreover, most therapeutic trials involving acutely depressed patients attempt to exclude those at high risk of suicidal behavior, and in most such studies, suicidal thoughts or acts are not explicit outcome measures but, instead, are encountered as incidental adverse events and reported with uncertain reliability and accuracy.

Several recent reports relevant to this topic have concentrated on information pooled from placebo-controlled RCTs by use of meta-analysis. Such pooled analyses have found only minor and inconsistent differences in rates of attempts or suicides among persons treated with SRIs, other antidepressants, or placebo.[2,12–20] In contrast, studies of clozapine in schizophrenia[21,22] and of lithium in recurrent major mood disorders[23,24] have found major reductions of risk of suicidal behaviors with these treatments. However, since placebo-controlled antidepressant RCTs have found selective, antidepressant-associated reductions of ratings of suicidal *ideation*,[2,7,15,20,25] it may well be that effects of specific treatments on suicidal ideation and behavior differ.

Other types of research pertinent to suicide and antidepressant treatment include case series and large cohort-outcome and case-control studies. Among these are at least nine major studies using case-control designs based either on UK[26–28] or New Zealand general practice databases,[29] or cohort designs in large U.S.,[30–32] Danish,[33,34] or Finnish[35] databases. Overall, these studies found no convincing evidence that use of SRIs or other modern antidepressants increased risk of suicides or attempts, and some findings suggested decreased risk of suicide with more antidepressant treatment.[33,34] Of note, there was evidence that more severe depressive illness history, higher antidepressant doses, and use of multiple psychotropic agents were associated with suicide or attempts.[26,27] These observations suggest potential confounding by indication.[29] That is, greater illness-severity is likely to be associated with suicidal risk and to encourage treatment, and so may misleadingly associate antidepressant use with suicidal behavior. The type of antidepressant used (usually SRIs vs. tricyclic antidepressants [TCAs] or others) usually bore little relationship to suicidal risk.[26–29] Moreover, increased risk of suicide attempts was found shortly before antidepressant treatment started[32] or early in treatment,[27] and risk did not increase as treatment progressed.[32] In a U.S. study, there was a weak association of suicidal acts with antidepressant treatment in previously hospitalized, depressed, Medicaid patients of all ages, uncorrected for illness severity, especially of suicide attempts in male juveniles treated with TCAs more than SRIs.[31] Finally, to the contrary, a greater number of prescription refills for SRIs or other modern antidepressants was associated with lower suicide risk.[33]

Another popular study design assesses correlations of suicide rates and the rates of antidepressant use within selected geographical areas over time or between regions at one time. Such *ecological* analyses compare aggregate-level exposures for groups or subpopulations with aggregate suicide rates as the outcome measure. These studies can serve as useful hypothesis-generating analyses and may also have some value in testing already identified hypotheses.[36–38] However, the major limitation of such studies (the "ecological fallacy") is that they do not identify *individuals* who are or are not exposed to a factor of interest, such as antidepressant treatment. Therefore, they cannot exclude relevant and possibly more important intervening or modifying individual or aggregate variables,[36–38] such as illness severity influencing the treatment offered. Given the growing number of such studies now available and their potential to clarify relationships between antidepressant treatment and suicidal behaviors, we reviewed ecological studies of antidepressant usage rates and suicide rates.

METHODS

We evaluated peer-reviewed research literature reported between 1970 and July 2007 through MedLine, considering citations in identified reports and recent reviews, and focusing on reports pertaining to suicidal risks in association with the availability of antidepressant drugs of various types, including SRIs and other modern agents. We extracted and compared the available data concerning changes in antidepressant prescription or sales rates (as a surrogate for usage rates) and suicide rates in men and women (separately, if possible) in the decades preceding and following the

introduction of the first successful modern antidepressant agent fluoxetine in late 1987, which was soon followed by a series of SRIs and other modern antidepressants in the 1990s. Some studies also considered trends in suicide rates before the 1990s, prior to introduction of modern antidepressant drugs. Antidepressant availability in most studies was based on national or regional sales data or per capita rates of prescriptions from commercial pharmacies gathered by organizations that contract with the pharmaceutical industry. In some studies antidepressant usage was standardized by dosing equivalents (mg/day), based on *defined daily doses* (DDDs), as provided by the World Health Organization.[39]

We scored study outcomes, by consensus, into several global categories: (1) evidence that suicide rates were inversely related to antidepressant usage rates by region or years was considered as a "positive" finding; (2) inverse correlations during the 1990s, but preceded by decreasing suicide rates in the 1980s, were scored as "positive but present earlier"; (3) inverse correlations only for particular subgroups by age or sex were considered "inconsistent"; and (4) outcomes lacking such inverse correlations, or involving rising suicide rates in the 1990s, were rated as "negative."

We summarized and compared particular findings of interest, using standard statistical procedures to determine means and variances (as standard deviation or 95% confidence interval [CI], as noted), and linear (r) or nonparametric (r_s) correlations, based on commercial software (Stata-8®, Stata Corp., College Station, TX; Statview-5®, SAS Corp., Cary, NC).

RESULTS

We identified 19 published ecological studies that correlated annual SRI or other antidepressant sales or prescription rates with annual suicide rates in countries or regions (usually counties), sometimes adjusted for age and reported for men and women separately (Table 1).[40–58] Of the 19 included studies, 11 yielded largely positive findings (inverse correlation of rising antidepressant availability in the 1990s with falling suicide rates, including 3 in which declining suicide rates were also found in the 1980s); 5 were inconsistent in finding such inverse correlations only in subgroups defined by age or sex, and 3 failed to find correlations between antidepressant availability and suicide rates (2 found increasing suicide rates in the 1990s).

Overall, antidepressant availability during the 1990s increased by an average of nearly 4-fold (395%; 95% CI, 217%–571%) as annual suicide rates declined by −14.3% (95% CI, −22.1% to −6.6%). However, across 17 of the studies with relevant data, these two measures were not statistically correlated ($r_s = -0.082$; $p = 0.75$). Several studies found reductions of suicide risk in the 1990s mainly in older persons, especially above age 45 years (Table 2).[44,48,50,52,54] To facilitate comparisons, we also consolidated available findings for antidepressant usage rates and suicide rates for both the 1980s and 1990s, as well as for changes in suicide rates overall and for men and women separately (Table 2). The compiled data indicate that antidepressant availability increased 10.6-fold more rapidly in the 1990s than in the 1980s (395% vs. 37.2%). Annual suicide rates decreased in both decades but did so less than half as much in the 1980s (by −6.46%; 95% CI, −14.3% to +1.4%) as in the 1990s (by −14.3%; 95% CI, −22.1% to −6.6%; Table 2). However, the overlapping 95% CIs indicate statistical nonsuperiority for the 1990s versus 1980s. Moreover, when 11 studies[41–44,46,47,49–51,53,58] reporting changes in total annual suicide rates for *both* decades were compared directly (Table 2), the average decrease in suicide rates in the 1980s was by −9.98% (95% CI, −15.7% to −4.3%) compared to −10.7% (95% CI, −18.0% to −3.4%) in the 1990s—again, not statistically different. Decreases in suicide rates were found in both men and women in the 1990s, but were 4.4-times greater than in the 1980s among men (−14.4% vs. −3.31%), but only slightly greater among women (−19.7% vs. −16.9%) in the more recent decade.

The preceding findings indicate that decreases in suicide rates in the 1990s were at least partly evident earlier,[40,41,43,44,51,53] possibly with an acceleration of the process with rapid and wide application of modern antidepressants in the 1990s. It is of interest to consider trends in Sweden[41] and the United States[59,60] specifically, where significant inverse correlations between rising antidepressant usage and falling suicide rates in the 1990s were found in several studies (Table 1).[41,43,47,55–58] Such downward trends in suicide rates were ongoing in both countries since the late 1970s, though they appear to have accelerated in Sweden in the modern antidepressant era (Figure 1).

Internationally, among 79 large countries reporting to the World Health Organization,[59] with non-zero suicide rates between 1990 and 2003, there was a similar prevalence of unchanged or higher (37/79 = 46.8%) versus decreased annual suicide rates (42/79 = 53.2%%; Figure 2). Countries with substantial decreases included several northern European nations (Denmark, Germany, Iceland, United Kingdom) as well as central or eastern European (Armenia, Austria, France, Georgia, Hungary), southern European (Greece), and some Asian (Sri Lanka, Thailand) and South American countries (El Salvador, Paraguay, Puerto Rico) (Figure 2). Other countries from the same world regions experienced increases in reported suicide rates over the same decade (e.g., Albania, Malta, Mexico, Nicaragua, Poland, Portugal, Romania, Russia, Spain, Suriname; Figure 2). These observations indicate a high degree of variation among countries, even within world regions, including the Nordic countries.[58]

TABLE 1. Ecological Studies of Association of Suicide Rates Versus Increased Use of SRIs and Other Modern Antidepressants

Study	Country (population in millions)	Years	Methods	Findings	Outcomes
Barbui et al. (1999)[40]	Italy (57.0)	1988–96	SRI sales/10k vs. national suicide rate vs. yrs	SRI (392%) and other AD prescriptions increased; suicide rate decreased in women (19.7%/year, though had been falling since 1970) but increased in men (4.8%/year)	Inconsistent; present earlier
Isacsson (2000)[41]	Scandinavia (24.0)	1978–96	AD DDDs vs. national suicide rate vs. yrs	AD use increased (268%); suicide rate fell in men and women of all ages (19%) and in most Swedish counties, plus Denmark, Finland, and Norway, in the 1990s; trend had started earlier in Sweden (17% in the 1980s)	Positive but present earlier
Rihmer et al. (2000)[42]	Hungary (10.0)	1984–97	AD DDDs/1k vs. national suicide rate vs. yrs	Suicide decreased 38% faster in the 1990s (2.6%/yr) vs. 1980s (1.9%/year) as AD use increased (224%) and other clinical care measures increased (unspecified for sex and age)	Positive
Carlsten et al. (2001)[43]	Sweden (8.6)	1977–97	AD DDDs vs. national suicide (+UC) rate vs. yrs.	With increased AD use in the 1990s (254%), suicide rates decreased more rapidly in the 1990s in men (2.6%/year) and women (2.9%/year) at all ages, but had also declined in the 1980s (1.2% & 1.0%/year, respectively)	Positive but present earlier
Hall et al. (2003)[44]	Australia (19.0)	1986–2000	AD DDD/1k vs. national suicide rate vs. yrs vs. age	AD use increased (209%) in the 1990s, as suicide rates decreased in women aged >45 years (13.9%) and men >55 years (5.2%), following decreases in the 1980s; AD use rose with age	Positive but present earlier
Kelly et al. (2003)[45]	No. Ireland (1.7)	1989–99	AD DDD/1k vs. national suicide (+UC) rate vs. yrs	Increased AD use (464%) was associated with 8.0% increased national suicide rate, especially at ages <30 years (unspecified for sex)	Negative
Oravecz et al. (2003)[46]	Slovenia (2.0)	1985–97	AD RXs/1k vs. national suicide rate vs. yrs	Increased AD use (58%) was associated with 7.1% increased national suicide rate (unspecified for sex and age)	Negative
Grunebaum et al. (2004)[47]	United States (281)	1985–99	AD RXs/1k vs. national suicide rate vs. yrs	Increased AD use (247%) was associated with 13.7% decreased national suicide rate (unspecified for sex and age)	Positive

TABLE 1. Ecological Studies of Association of Suicide Rates Versus Increased Use of SRIs and Other Modern Antidepressants (Continued)

Study	Country (Population in millions)	Years	Methods	Findings	Outcomes
Gunnell & Ashby 2004[48]	United Kingdom (59.0 M)	1976–98	SRI RXs/1k vs. national suicide rate vs. yrs	Increased AD use (129%) in the 1990s was associated with a decreased national suicide rate in women ≥30 years (14.0%) and men ≥55 yrs (9.7%); similar trends occurred in the 1980s	Inconsistent
Helgason et al. 2004[49]	Iceland (0.3)	1950–2000	AD DDD/1k vs. national suicide rate vs. yrs	Increased AD use (388%) in the 1990s was associated with unchanged suicide rates (or other health measures), which were also stable in the 1980s	Negative
Dahlberg & Lundin (2005)[50]	Sweden (8.6)	1990–2000	AD DDD/1k vs. county ($n = 21$) suicide rate vs. years	Increased AD use (60%) in the 1990s associated with decreased suicide rates in men (27.0%) and women (26.7%), but not after adjusting for socioeconomic factors, except at ages 10–24 years; rates declined before the 1990s, though somewhat less	Inconsistent
Gibbons et al. (2005)[51]	United States (281)	1996–98	AD RXs/capita/year vs. county ($n = 3142$) suicide rate	AD exposure varied by 152%, county suicide rate by 134%; suicide rate correlated inversely with relative SRI/TCA usage (and population density), but not total AD use; adjusted for age, sex, race, income	Positive
Guaiana et al. (2005)[52]	Italy (57.0)	1955–2000	AD DDD/1k vs. national suicide rate vs. years	Increased AD use (219%) in 1990s associated with slight decreases in suicide rate in men and women, but only >45 years, among whom rates had risen from 1975–85 and decreased after 1985	Inconsistent
Ludwig & Marcotte (2005)[53]	20 nations (849)	1980–2000	SRI RXs/capita/year vs. country suicide rate vs. years	Increased SRI use (1094% in 1990s) correlated with decreased suicide rate (5.4% in the 1990s), even after adjusting for covariates (age, sex, divorce, GDP, unemployment); suicide rate had increased in the 1980s; benefit/cost ratio = 7.1 ($6.4 million/$0.9 million), and greater for men	Positive

(Continued on next page)

TABLE 1. Ecological Studies of Association of Suicide Rates Versus Increased Use of SRIs and Other Modern Antidepressants (Continued)

Study	Country (Population in millions)	Years	Methods	Findings	Outcomes
Barak & Aizenberg (2006)[54]	Israel (6.3)	1998–2002	AD RXs/capita vs. suicide rate vs. yrs	As AD use increased (160%), suicide rate declined (17.6%), but statistically significantly only among men aged 55–74 years	Inconsistent
Fazel et al. (2006)[55]	Sweden (8.6)	1989–2000	SRI DDD/1k vs. suicide rate vs. yrs	As SRI use increased (1042%), the suicide rate decreased in the general population (19.1%) and among post-hospitalized mood and anxiety disorder patients (16.1%), in both sexes and at all ages	Positive
Gibbons et al. (2006)[56]	United States (39)	1996–98	SRI RXs/capita/yr vs. suicide rate vs. county	County suicide rate (0.7–1.7/100k/yr) correlated inversely with SRI usage at ages 5–14 years; adjusted for sex, race, income, access to care (specialists per county), and county variance	Positive
Milane et al. (2006)[57]	United States (281 M)	1988–2002	FLX RXs/1k vs. suicide rate vs. yrs	As FLX use increased (1248%), national suicide rate declined (14.4%) in men and women at all ages; before 1990, suicide rate had fallen in women but increased in men	Positive
Reseland et al. (2006)[58]	Scandinavia (24.0)	1961–2003	AD DDD/1k vs. suicide rate vs. yrs	As SRI use increased in the 1990s (410%), suicide rates (Denmark, Finland, Norway, Sweden) decreased (33.6%) after increasing (7.1%) in the 1980s in Norway and Finland	Mostly positive

AD, antidepressant; DDD, defined daily doses (WHO-based typical mg/day); FLX, fluoxetine; GDP, gross domestic product; SRI, serotonin reuptake inhibitor; TCA, tricyclic antidepressant; UC, undetermined cause of death. Of the 19 studies, 11 yielded largely favorable findings (decreasing suicide rate as drug availability increased; in 3 studies as a continuation of previous trends), 5 were inconsistent among subgroups, and 3 were negative, including 2 with rising suicide rates in the 1990s.

Overall, the 19 studies under review yielded strikingly heterogeneous outcomes, ranging from strong to very weak associations of rising availability of modern antidepressants and falling rates of suicide, and even some increases in suicide rates in the 1990s.[40,45,46,58] We considered possible explanations for this variability by use of regression modeling (not presented here). Changes neither in antidepressant availability nor in suicide rates in the 1990s were correlated with the year of publication, population of the country involved, or number or types of units of measurement (years, countries, or counties). Moreover, since changes in suicide rates and in antidepressant usage were uncorrelated, as noted ($r_s = -0.082$), countries with greater reductions in suicide rates did not necessarily have greater increases in antidepressant usage. For example, Iceland experienced a somewhat greater increase in antidepressant availability during the 1990s (by 388%) than other Scandinavian countries (331%) but had no decrease in suicide rates (Table 2). Moreover, use of antidepressants in the 1990s increased similarly in Northern Ireland (464%) and Sweden (482%), but the suicide rate in Northern Ireland increased by 8%, whereas that in Sweden declined by 24% (Table 2).

TABLE 2. Percentage Change in Antidepressant Use and Annual Suicide Rate in the 1980s to 1990s, by Country, Estimated from Data in the Articles Reviewed

Study	Country (population in millions)	Era	Percentage change			
			Antidepressant use	Suicide rate		
				Men	Women	Total
Barbui et al. (1999)[40]	Italy (57.0)	1990s	391.7	+4.08	−17.9	−2.19
Isacsson (2000)[41]	Scandinavia (24.0)	1980s	46.2	—	—	−16.8
		1990s	268.4	—	—	−19.3
Rihmer et al. (2000)[42]	Hungary (10.0)	1980s		—	—	−13.1
		1990s	224.3	—	—	−20.6
Carlsten et al. (2000)[43]	Sweden (8.6)	1980s	31.9	−18.4	−22.7	−19.7
		1990s	253.8	−22.5	−29.4	−24.6
Hall et al. (2003)[44]	Australia (19.0)	1980s	—	−5.08	−9.59	−5.98
		1990s	209.5	−0.36	−4.54	−1.16
Kelly et al. (2003)[45]	No. Ireland (1.7)	1990s	464.0	—	—	+7.95
Oravecz et al. (2003)[46]	Slovenia (2.0)	1980s	27.3	—	—	−17.6
		1990s	57.6	—	—	+7.14
Grunebaum et al. (2004)[47]	United States (281)	1980s	57.9	—	—	0.00
		1990s	246.7	—	—	−10.8
Gunnell & Ashby (2004)[48]	United Kingdom (59.0)	1980s	2.8	+14.2	−31.1	−2.46
		1990s	129.5	−9.19	−12.3	−10.0
Helgason et al. (2004)[49]	Iceland (0.3)	1980s	35.5	—	—	0.00
		1990s	387.9	—	—	0.00
Dahlberg & Lundin (2005)[50]	Sweden (8.6)	1990s	150.0	−27.0	−26.7	−26.9
Gibbons et al. (2005)[51,a]	United States (281)	1990s	151.8	—	—	−57.1
Guaiana et al. (2005)[52]	Italy (57.0)	1980s	6.1	−15.9	−25.5	−18.5
		1990s	219.2	−9.84	−12.4	−10.5
Ludwig & Marcotte (2005)[53]	International[b] (849)	1980s	—	—	—	+15.7
		1990s	1100.0	—	—	−5.71
Barak & Aizenberg (2006)[54]	Israel (6.3)	1990s	163.6	—	—	−17.6
Fazel et al. (2006)[55]	Sweden (8.6)	1990s	1043.3	−18.6	−21.0	−19.3
Milane et al. (2006)[57]	United States (281)	1990s	1249.3	−13.2	−17.6	−14.1
Reseland et al. (2006)[58]	Scandinavia (24.0)	1980s	90.2	+8.55	+4.35	+7.40
		1990s	93	−32.7	−35.4	−33.4
All studies ($n = 19$) [Averages with 95% CI]		1980s	37.2% [13.6 to 60.9]	−3.31% [−21.2 to +14.6]	−16.9% [−24.6 to +0.8]	−6.46% [−14.3 to +1.4]
		1990s	395% [217 to 571]	−14.4% [−23.6 to −5.1]	−19.7% [−27.1 to −12.3]	−14.3% [−22.1 to −6.6]

[a] For this study, "change" is the range of values across all U.S. counties ($n = 3141$) in the years 1996–98; a later, similar report[55] did not provide changes in U.S. county suicide rates.

[b] The countries ($n = 27$) were Australia, Austria, Belgium, Belorussia, Bulgaria, Canada, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Ukraine, United Kingdom, and United States. Suicide rates declined in both the 1980s (−9.98%; 95% CI, −15.7% to −4.3%) and 1990s (−10.7%; 95 CI, −18.0% to −3.4%).

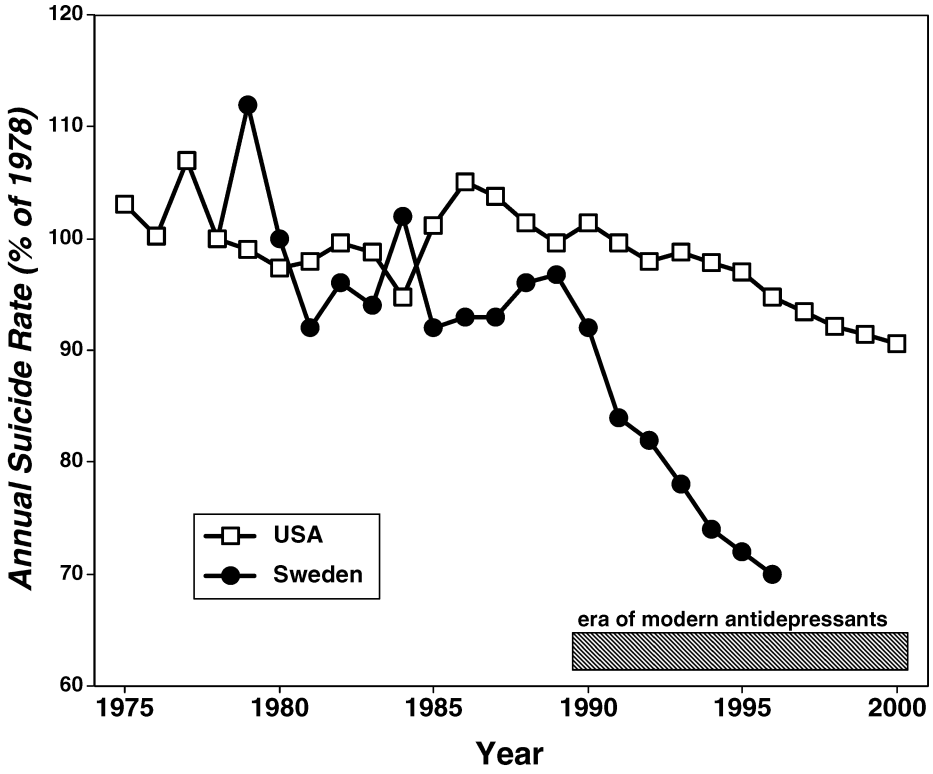

FIGURE 1. Trends in annual suicide rates in recent decades in the United States and Sweden, with annual suicide rates (per 100,000 population) expressed as a percentage of the 1978 rate for each country to support comparisons between countries and years. Data are from Isacsson[41] for Sweden and from the U.S. Centers for Disease Control for the United States.[59] In both countries, suicide rates decreased between 1975 and the advent of SRIs and other modern antidepressants in the early 1990s. In Sweden, the rate of decrease may have increased in the 1990s.

Nevertheless, there was a plausible tendency for larger decrements in suicide rates to associate with higher initial rates at the start of the modern antidepressant era. That is, suicide rates at the start of the 1990s were moderately correlated with the decreases in these rates across the decade ($r_s = 0.488$; $p = 0.04$). A possibly related observation was that the relative difference in the reduction of suicide risk in the 1990s versus 1980s (2.2-fold overall) was greater among men (4.4-fold improvement) than women (1.2-fold; Table 2), and the initial suicide rate (per 100,000/year) at the start of the decade also was much higher for men (24.3 ± 11.0) than women (8.76 ± 5.05; not shown). Finally, as already noted, decreases in suicide rates were more likely above age 45, when suicide rates tend to increase, especially among men.[61] Not surprisingly, these findings suggest that higher initial suicide rates are more likely to show greater numerical improvements.

DISCUSSION

The 19 ecological studies of relationships of suicide rates and rapidly rising usage rates for modern antidepressants reviewed here yield a range of outcomes. Only 8/19 studies[42,47,51,53,55–58] found significant inverse correlations between lower suicide rates and greatly increased use of modern antidepressants in the 1990s that were not preceded by falling suicide rates in the 1980s or earlier (Tables 1 and 2; Figure 1). In addition to these published reports, another very recent U.S. study found only a weak and nonsignificant relationship between rising antidepressant sales and slightly lower suicide rates (by state and by times between 1997 and 2003) in adolescents aged 15–19 years, and no relationship (and no decline in suicide rates over time) among younger subjects aged 10–14.[62] Moreover, in unpublished findings (Baldessarini RJ, 2007), total annual antidepressant sales data provided by IMS Corporation for 29 leading national antidepressant markets showed a nonsignificant correlation with 2000 suicide rates obtained from the World Health Organization.[60] Overall, these 20 analyses, as well as similar new Finnish[63] and Norwegian[64] studies appearing after the present analyses, have yielded highly heterogeneous outcomes that do not indicate a consistent inverse relationship between the increase of antidepressant usage in the 1990s and falling national suicide rates. Furthermore,

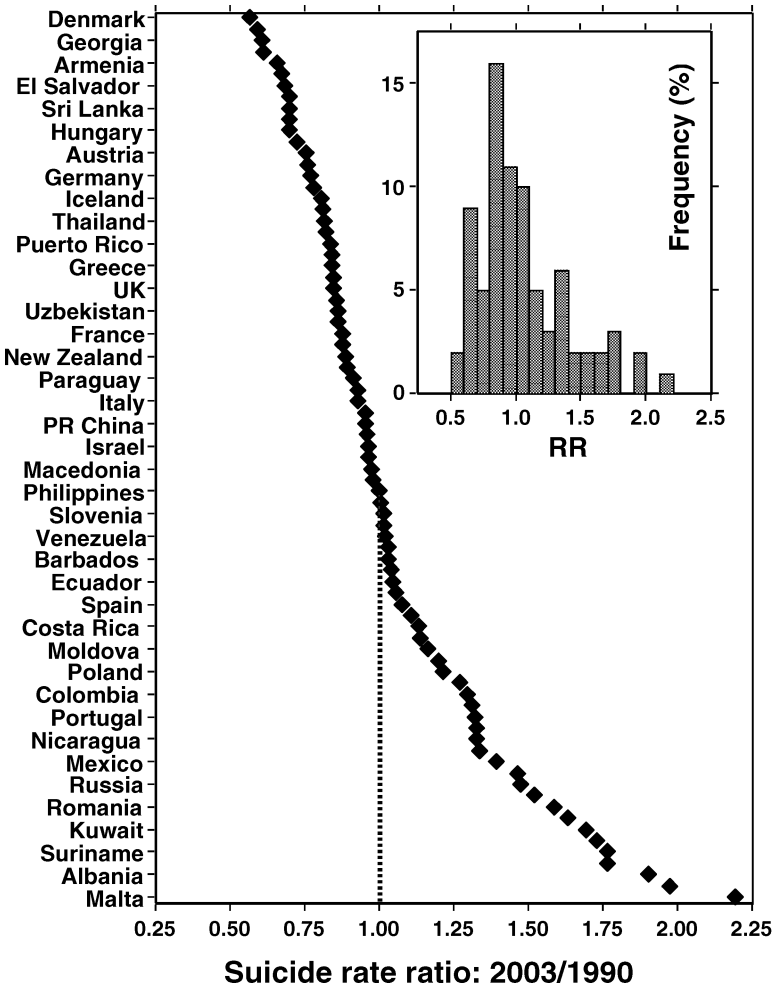

FIGURE 2. Changes in annual suicide rates in 79 countries between 1990 and 2003, as a ratio, in rank order from greatest decrease to greatest increase. Values <1.0 (left of dotted vertical line) indicate *reductions* in suicide rate during the decade of rapid increases in international use of modern antidepressants, as observed in 42/79 countries (53.2%), with no change or *increases* (to the left of 1.0) in 37/79 (46.8%). The pooled rate ratio (RR), based on random effects meta-analysis, is 1.01 (95% CI, .99–1.02 [not significant]). The inset is a histogram of the same data, indicating some skewing toward low values, with a modal value of approximately 0.85. Data are from World Health Organization.[60]

only about half of the world (42, or 53%, of 79 reporting nations) experienced decreases in reported suicide rates in the 1990s, whereas 47% experienced *increases* or no change between 1990 and 2003, with large variations in rates and trends among specific countries, within world regions, and within countries over time (Figure 2), as also noted recently by Safer and Zito.[65]

It is important to reemphasize a major general limitation of ecological, or aggregate correlational, studies.[35–38] They do not identify the presence or absence of a measure of interest (taking of antidepressant treatment) at the level of individual persons, and they rely on indirect indices of drug usage (sales or prescription rates). Therefore, it is possible for unidentified intervening variables to yield apparent, but misleading, correlations with suicide rates. Despite the fundamental limitations of correlational analyses, an important overall conclusion from this large body of population-based research is that it provides little or no support for a potential *adverse* association between growing clinical application of SRIs or other modern antidepressants and increased risk of suicide in countries or regions—a question that has been under intense discussion recently.[9–14] A second conclusion is that inverse associations between massive increases in antidepressant usage and recent decreases in suicide rates were found, but inconsistently and of much lesser magnitude (14%) than the 4-fold rise in antidepressant availability (Table 2). As noted, this variability in reported suicide rates is not explained by the degree of increase in antidepressant

usage, by national population, or by year of publication. However, there was a significant correlation of higher initial suicide rate at the start of the 1990s and greater decrement during the decade. There also were indications of greater decreases in suicide rates among men (Table 2) and in older persons—both being subgroups with relatively high suicide risks.[61]

The recent changes in suicide risk associated with the advent of the modern antidepressant era of the 1990s were at least partly anticipated in earlier decades in some countries,[40,41,43,44,51,53] including Sweden and the United States (Figure 1), in which strong inverse correlations between antidepressant sales and suicide rates were found in the 1990s either as temporal (secular) trends[41,43,47,55–58] or as differences among subregions (counties) of both countries.[41,51,56] Decreasing trends in suicide rates during the decades before the 1990s suggest that factors in addition to the massive recent growth in clinical application of SRIs and other modern antidepressants have contributed to declining suicide rates. Among patients at high risk of suicide, the 1990s were associated with major gains in rates of diagnosis and treatment generally—when recognition and treatment of persons with probable major depression rose from 28% to 44% in the United States, following much smaller increases in the 1980s.[66,67] No doubt, these recent gains were encouraged by greatly expanded use of relatively safe and effective new antidepressants by primary care physicians as well as psychiatrists, and for a wide range of psychiatric conditions such as anxiety disorders.[68] However, treatment of major depression patients increased only 1.6-fold (44% vs. 28%) in the 1990s, in contrast to the nearly 4-fold increase in use of antidepressants generally (Table 2), suggesting that much of the increase occurred in conditions other than major affective disorders, such as anxiety disorders, in which suicidal risk is much lower.[69]

Improved recognition and intervention in disorders with especially high suicidal risks (including severe major depression and bipolar disorders), as well as greater access to clinical care (including wider use of lithium and other mood-stabilizing agents), also are likely to have contributed to the decline in suicide rates since the 1970s.[23,24,70] For example, a recent U.S. study found that indices of access to health care services in general were associated with suicide rates in individual states across America in 2001.[71] Factors strongly correlated with lower state suicide rates included greater average federal aid for mental health services and a lower rate of uninsured persons, followed by greater population density of psychiatrists or physicians, and by higher population density per square mile.[71] Some of the reported studies attempted to address such factors by adjusting correlations for covariates of interest, including sex and age, and sometimes economic factors, although usually not population density.[44,51,52,54,57,58] Two recent studies[51,56] enhanced statistical power greatly by analyzing suicide rates and antidepressant prescription rates in over 3000 counties in the United States. Based on tabulated data provided in one of those reports,[51] the multivariate correlation of suicide rates with antidepressant sales was somewhat less ($r = -0.16$ [95% CI, -0.035 to $+0.026$]; $p = 0.08$) than for population density ($r = -1.43$ [95% CI, -2.23 to -0.63]; $p = 0.004$), an index of access to health care services[71] that would include use of modern antidepressants but also many other services.

Of note, the reported recent decreases in rates of completed suicide considered above have not been paralleled by changes in risks of suicide attempts or in suicidal ideation in the general population. Kessler and colleagues[72] found little change in U.S. rates of suicide attempts or ideation between 1990 and 1992 versus 2001 and 2003, despite increased use of antidepressants. In addition, the estimated rate of suicide attempts among U.S. high school students remained stable ($r_s = +0.238$; $p = 0.529$) from 1990 to 2005,[73] as was also found between 1997 and 2003.[60] Moreover, the nearly $17 billion annual world antidepressant market has tended to become saturated over the past decade, and U.S. sales of SRIs have undergone minor decreases since 2003, particularly among primary care physicians.[65,74–76] These new developments may reflect, in part, the impact of recent U.S. Food and Drug Administration warnings about evidence of associations of treatment with antidepressants and possibly increased suicidal risk (ideation and possibly attempts) in juveniles and perhaps young adults, with reduced risks in older patients.[14] Finally, it is noteworthy that annual U.S. suicide rates, overall, have tended to *rise* slightly since the end of the 1990s ($r_s = +0.929$; $p = 0.038$), from 10.4 per 100,000 in 1999 to 11.1 in 2004.[77,78] Whether these two new trends (less antidepressant use, more suicide) are meaningfully related remains to be clarified.

In conclusion, pooled analysis of the findings of the ecological studies reviewed here suggests that markedly greater availability of antidepressant treatment in the 1990s has correlated with moderate decreases in suicidal rates in some countries. However, the findings were inconsistent and their variability is not readily explained, although higher initial suicide rate, male sex, and older age appear to favor finding inverse correlations between antidepressant sales and suicide rates. Finally, the ecological studies reviewed provide no evidence that antidepressants, including SRIs, might increase risk of suicide. They also accord with a growing body of evidence, from large cohort and case-control studies (as cited above) and also from randomized controlled trials in adults with major depression, that antidepressants lack major adverse effects on suicidal behavior.

Dr. Baldessarini is a consultant or research collaborator with Auritec, Biotrofix, Eli Lilly, IFI, Janssen, JDS, Merck, MK-BioPharmaceuticals, NeuroHealing, Novartis, and Solvay

Corporations. Dr. Tondo has research collaborations or contracts with Eli Lilly, Janssen, and JDS. Dr. Licinio is a consultant and research collaborator with Eli Lilly. Dr. Valuck is a consultant and research collaborator with Eli Lilly and Janssen. Dr. Oquendo is a consultant or research collaborator with Eli Lilly and Pfizer, and has received drug products for federally supported studies from Abbott, JDS, Lilly, and Solvay. Dr. Fawcett is a consultant and research collaborator with Eli Lilly. Drs. Strombom and Tohen and Ms. Dominguez are employees of Eli Lilly. Dr. Tollefson is a former employee of Eli Lilly and is currently CEO of Orexigen Therapeutics and an adviser to Avera, Cortex Pharmaceuticals, Cypress Bioscience, LifeCycle Pharma, and XenoPort.

REFERENCES

1. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990;147:207–10.
2. Beasley CM, Dornseif BE, Bosomworth JC, et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. BMJ 1991;303:685–92.
3. Laughren TP. [U.S. Food and Drug Administration memorandum on review of SRIs]. Jan. 1994. http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006B1_03_Background%20Memo%2001–05-04.doc
4. Teicher MH, Glod CA, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. Drug Safety 1993;8:186–212.
5. Matthews JD, Fava M. Risk of suicidality in depression with serotonergic antidepressants. Ann Clin Psychiatry 2000;12:43–50.
6. Healy D. Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors. Psychother Psychosom 2003;72:71–9.
7. Lapierre YD. Suicidality with selective serotonin reuptake inhibitors: valid claim? J Psychiatry Neurosci 2003;28:340–7.
8. Mann JJ, Emslie G, Baldessarini RJ, et al. ACNP task force report on SRIs and suicidal behavior in youth. Neuropsychopharmacology 2006;31:473–92.
9. UK Medicines and Health Regulatory Agency, Committee on Safety of Medicines (CSM). Selective serotonin reuptake inhibitors (SSRIs): overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescent, including a summary of efficacy and safety data. Dec. 2003. At: http://www.mhra.gov.uk [search for "regulatory status and CSM advice"].
10. U.S. Food and Drug Administration. Antidepressant use in children, adolescents, and adults. Mar. 2004, updated June 2006. At: http://www.fda.gov/cder/drug/antidepressants [see Draft Medication Guide for Antidepressant Drugs; Revisions to Product Labeling].
11. U.S. Food and Drug Administration. Background information on the suicidality classification project. Mar. 2004, updated May 2007. http://www.fda.gov/cder/drug/antidepressants/classificationProject.htm
12. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332–9.
13. Baldessarini RJ, Pompili M, Tondo L. Suicidal risk in antidepressant trials. Arch Gen Psychiatry 2006;63:246–8.
14. Laughren TP. [U.S. Food and Drug Administration memorandum on suicidal risk in trials of antidepressant drugs in juvenile and adult patients]. Nov. 2006. At: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006–4272b1-index.htm [see Briefing Document].
15. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant trials: an analysis of the FDA database. Arch Gen Psychiatry 2000;57:311–7.
16. Storosum JG, van Zwieten BJ, van den Brink W, Gersons BP, Broekmans AW. Suicide risk in placebo-controlled studies of major depression. Am J Psychiatry 2001;158:1271–5.
17. Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials with SRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry 2003;160:790–2.
18. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomized controlled trials submitted to the MHRA's safety review. BMJ 2005;330:385–8.
19. Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomized controlled trials. BMJ 2005;330:396–8.
20. Acharya N, Rosen AS, Polzer JP, et al. Duloxetine: meta-analyses of suicidal behaviors and ideation in clinical trials for major depressive disorder. J Clin Psychopharmacol 2006;26:587–94.
21. Meltzer HY, Alphs L, Green AI, et al.; International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia. Arch Gen Psychiatry 2003;60:82–91.
22. Hennen J, Baldessarini RJ. Reduced suicidal risk during treatment with clozapine: a meta-analysis. Schizophrenia Res 2005;73:139–45.
23. Baldessarini RJ, Tondo L, Davis P, Goodwin FK, Hennen J. Decreased suicidal risk during long-term lithium treatment: a meta-analysis. Bipolar Disord 2006;8:625–39.
24. Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. Lithium treatment reduces suicidal risk in recurrent major depressive disorder. J Clin Psychiatry 2007;68:380–3.
25. Pedersen AG. Escitalopram and suicidality in adult depression and anxiety. Int Clin Psychopharmacol 2005;20:139–43.
26. Jick SS, Dean AD, Jick H. Antidepressants and suicide. BMJ 1995;310:215–8.
27. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. JAMA 2004;292:338–43.
28. Martinez C, Rietbrock S, Wise L, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. BMJ 2005;330:389–92.
29. Didham RC, McConnell DW, Blair HJ, Reith DM. Suicide and self-harm following prescription of SRIs and other antidepressants: confounding by indication. Br J Clin Pharmacol 2005;60:519–25.
30. Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. CNS Drugs 2004;18:1119–32.

31. Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and suicide in severely depressed children and adults: a case-control study. Arch Gen Psychiatry 2006;63:865–72.
32. Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. Am J Psychiatry 2006;163:41–7.
33. Søndergård L, Kvist K, Andersen PK, Kessing LV. Do antidepressants prevent suicide? Int Clin Psychopharmacol 2006;21:211–8.
34. Søndergård L, Lopez AG, Andersen PK, Kessing LV. Continued antidepressant treatment and suicide in patients with depressive disorder. Arch Suicide Res 2007;11:163–75.
35. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Tanskaren A, Haukka J. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry 2006;63:1358–67.
36. Greenland S, Robins J. Ecologic studies: biases, misconceptions, and counter-examples. Am J Epidemiol 1994;139:747–60.
37. Schwartz S. The fallacy of the ecological fallacy: the potential misuse of a concept and the consequences. Am J Pub Health 1994;84:819–24.
38. Morgenstern H. Ecologic studies in epidemiology: concepts, principles, and methods. Ann Rev Pub Health 1995;16:61–81.
39. World Health Organization. New ADDs. At: http://www.whocc.no/atcddd [see New ATC/DDD].
40. Barbui C, Campomori A, D'Avanzo B, Negri E, Garattini S. Antidepressant drug use in Italy since the introduction of SRIs: national trends, regional differences and impact on suicide rates. Soc Psychiatry Psychiatr Epidemiol 1999;34:152–6.
41. Isacsson G. Suicide prevention—a medical breakthrough? Acta Psychiatr Scand 2000;102:113–7.
42. Rihmer Z, Appleby L, Rihmer A, Belso N. Decreasing suicide in Hungary [Letter]. Br J Psychiatry 2000;177:84.
43. Carlsten A, Waern M, Ekedahl A, Ranstam J. Antidepressant medication and suicide in Sweden. Pharmacoepidemiol Drug Saf 2001;10:525–30.
44. Hall WD, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P. Association between antidepressant prescribing and suicide in Australia, 1991–2000: trend analysis. BMJ 2003;326:1008–11.
45. Kelly CB, Ansari T, Rafferty T, Stevenson M. Antidepressant prescribing and suicide rate in Northern Ireland. Eur Psychiatry 2003;18:325–8.
46. Oravecz R, Czigler B, Leskosek F. Correlation between suicide rate and antidepressant use in Slovenia. Arch Suicide Res 2003;7:279–85.
47. Grunebaum MF, Ellis SP, Li S, Oquendo MA, Mann JJ. Antidepressants and suicide risk in the United States, 1985–1999. J Clin Psychiatry 2004;65:1456–62.
48. Gunnell D, Ashby D. Antidepressants and suicide: what is the balance of benefit and harm? BMJ 2004;329:34–8.
49. Helgason T, Tómasson H, Zoëga T. Antidepressants and public health in Iceland: time series analysis of national data. Br J Psychiatry 2004;184:157–62.
50. Dahlberg M, Lundin D. Antidepressants and the suicide rate: is there really a connection? [Working paper 2005–4, Department of Economics, University of Uppsala]. 2005. http://www.nek.uu.se/Pdf/wp2005_4.pdf
51. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry 2005;62:165–72.
52. Guaiana G, Andretta M, Corbari L, et al. Antidepressant consumption and public health indicators in Italy, 1955 to 2000. J Clin Psychiatry 2005;66:750–5.
53. Ludwig J, Marcotte DE. Antidepressants, suicide, and drug regulation. J Policy Anal Manage 2005;24:249–72.
54. Barak Y, Aizenberg D. Association between antidepressant prescribing and suicide in Israel. Intl Clin Psychopharmacol 2006;21:1281–4.
55. Fazel S, Grann M, Goodwin GM. Suicide trends in discharged patients with mood disorders: associations with selective serotonin uptake inhibitors and comorbid substance misuse. Int Clin Psychopharmacol 2006;21:111–5.
56. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry 2006;163:1898–904.
57. Milane MS, Suchard MA, Wong M-L, Licinio J. Modeling of the temporal patterns of fluoxetine prescriptions and suicide rates in the United States. PLoS Medicine 2006;3:190–9. At: http://www.plosmedicine.org
58. Reseland S, Bray I, Gunnell D. Relationship between antidepressant sales and secular trends in suicide rates in the Nordic countries. Br J Psychiatry 2006;188:354–8.
59. U.S Centers for Disease Control and Prevention. National vital statistics reports 2006. At: http://www.cdc.gov/nchs/ deaths.htm [see Deaths: Final Data for 2003].
60. World Health Organization. Country reports and charts available [on suicide]. At: http://www.who.int/mental_health/prevention/suicide/country_reports/en/index.html
61. Conwell Y, Heisel MJ. The elderly. In: Simon RI, Hales RE, eds. Textbook of suicide assessment and management. Washington, DC: American Psychiatric Press, 2006:57–76.
62. Markowitz S, Cuellar A. Antidepressants and youth: healing or harmful? Soc Sci Med 2007 (in press).
63. Korkeila J, Salminen JK, Hiekkanen H, Salokangas RK. Use of antidepressants and suicide rate in Finland: an ecological study. J Clin Psychiatry 2007;68:505–11.
64. Bramness JG, Walby FA, Tverdal A. The sales of antidepressants and suicide rates in Norway and its counties 1980–2004. J Affect Disord 2007;102:1–9.
65. Safer DJ, Zito JM. Do antidepressants reduce suicide rates? Public Health 2007;121:274–7.
66. Cleanthous P. Patient welfare: implications of innovation in the US antidepressant market. Oct. 2002. http://www.econ.yale.edu/seminars/apmicro/am02/cleanthous-021219.pdf
67. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry 2003;64:1465–75.
68. Baldessarini RJ. Drug therapy of depression and anxiety disorders. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2005:429–59.
69. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998;173:11–53.
70. Tondo L, Baldessarini RJ. Risks of suicidal ideation, attempts and suicides among 2826 Sardinian men and women with types

I and II bipolar, and recurrent major depressive disorders. Acta Psychiatr Scand 2007 (in press).

71. Tondo L, Albert MJ, Baldessarini RJ. Suicide rates in relation to health care access in the United States: an ecological study. J Clin Psychiatry 2006;67:517–23.
72. Kessler RC, Berglung P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990–1992 to 2001–2003. JAMA 2005;293:2487–95.
73. Eaton DK, Kann L, Kinchen S, Ross J. Youth risk behavior surveillance—United States, 2005. MMWR Surveil Summ 2006;55(5):1–108. http://www.cdc.gov/mmwr/PDF/SS/SS5505.pdf
74. Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry 2007;164:884–91.
75. Nemeroff CB, Kalali A, Keller MB, et al. Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States. Arch Gen Psychiatry 2007;64:466–72.
76. Valuck RJ, Libby AM, Morrato EM, Orton HD, Allen R, Baldessarini RJ. Recent changes in the use of modern antidepressants in the United States. Am J Psychiatry 2007 (in press).
77. Heron MP, Smith BL. Deaths: leading causes for 2003. Natl Vital Stat Rep 2007;55(10):1–92. http://www.cdc.gov/nchs/data/nvsr/nvsr55/nvsr55_10.pdf
78. American Association of Suicidology. U.S.A. suicide: 2004 official final data. 2006. http://www.suicidology.org/ associations/1045/files/2004datapgs.pdf