Association of Suicide and Antidepressant Prescription Rates in Japan, 1999–2003

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Objective: We examined the relationship of increasing prescription volume of newer antidepressants, introduced in Japan in 1999, to national rates of suicide.

Method: The relationship between annual changes in rates of suicide (obtained from the Japanese Ministry of Health, Labor, and Welfare Vital Statistics Database) and prescription volume of the newer antidepressants paroxetine, fluvoxamine, and milnacipran (obtained from the database of IMS Japan K.K.), stratified by gender and age groups, was modeled statistically for the years 1999 through 2003. Effects of unemployment and alcohol consumption and the interaction of gender and age with antidepressant prescribing were assessed.

Results: From 1999 through 2003 in Japan, total antidepressant prescriptions increased 57% among males and 50% among females. Approximately 80% of this increase involved the selective serotonin reuptake inhibitors (SSRIs). To reduce a limitation of ecological analysis, we compared annual change in prescription and suicide rates, which eliminates the effect of long-term (secular) linear trends. We found an inverse association between year-to-year changes in the suicide rate and prescription volume of newer antidepressants (fluvoxamine, paroxetine, and milnacipran) ($\beta = -1.34$, $p = .008$) and SSRIs specifically (fluvoxamine, paroxetine) ($\beta = -1.41$, $p = .019$). An increase of 1 defined daily dose of SSRI use/1000 population/day was associated with a 6% decrease in suicide rate. Exploratory analysis suggested a stronger association in males, who experienced a greater increase in antidepressant use. Changes in unemployment and alcohol consumption rates did not explain the association.

Conclusion: In Japan during 1999 through 2003, absent long-term linear trend effects, annual increases in prescribing of newer antidepressant medications, mainly SSRIs, were associated with annual decreases in suicide rates, particularly among males.

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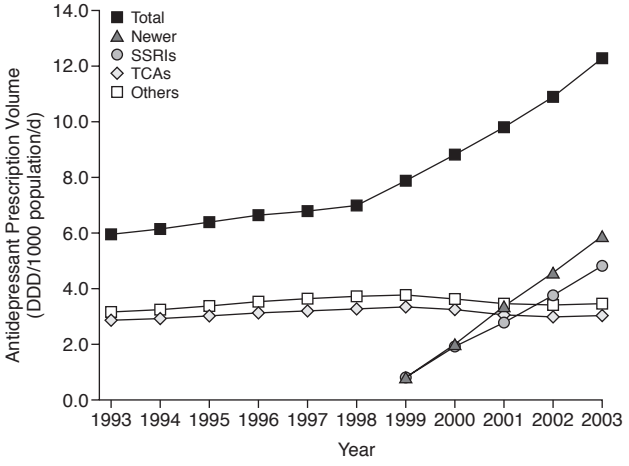
Japan has the 10th highest suicide rate in the world.[1] Its rate of 23.8 suicides per 100,000 persons in 2002 was more than double the U.S. rate in that year.[2,3] Biological, psychological, social, and cultural factors contribute to suicide risk, yet 90% or more of suicides are associated with psychiatric illness, mainly major depressive disorder.[4–8] Most depressed persons who commit suicide are untreated at the time of death.[9–11] Therefore, improved treatment of major depressive disorder is an important part of suicide prevention efforts.[12]

Until May 1999, the only antidepressants available in Japan were tricyclic antidepressants (TCAs) and the non-TCAs amoxapine, maprotiline, mianserin, trazodone, setiptiline, lofepramine, and safrazine. In mid 1999, the introduction into Japan of 3 newer antidepressants with improved side effect profiles—2 selective serotonin reuptake inhibitors (SSRIs) and 1 serotonin-norepinephrine reuptake inhibitor (SNRI)—led to a dramatic rise in antidepressant prescribing (Figure 1). This offered an opportunity to evaluate the association of antidepressant prescribing with national suicide rates in a country with a high rate of suicide and a low volume of antidepressant prescriptions. By way of comparison, in 1998, the antide-

Figure 1. Antidepressant Prescription Volume by Drug Class in Japan, 1993–2003[a]



[a]Data provided by IMS Base-JPM, IMS Japan K.K., Tokyo, Japan.
Abbreviations: DDD = defined daily dose; Newer = newer antidepressants (paroxetine, fluvoxamine, and milnacipran); Others = other antidepressants (amoxapine, maprotiline, mianserin, trazodone, setiptiline, lofepramine, and safrazine); SSRIs = selective serotonin reuptake inhibitors (paroxetine and fluvoxamine); TCAs = tricyclic antidepressants.

pressant prescription volume in the United States was 34.2 in defined daily dose (DDD) per 1000 population/day (a standard international unit of drug utilization),[13] approximately 5-fold the volume in Japan (6.99 DDD/1000 population/day, source: IMS Base-JPM prescription data). The suicide rate in the United States was less than half that of Japan in the year 2000.[2,3]

After the introduction of SSRIs in the United States[14] and other countries[13,15,16] in the late 1980s to 1990s, antidepressant prescription volumes increased markedly. This increase correlated with falls in suicide rates in national population-based studies from the United States,[17,18] Europe,[19–22] and Australia.[23] In a study of 27 countries from North America, Europe, and Australia, Ludwig and Marcotte[24] report that the suicide rate fell the most in countries with the greatest increase in SSRI prescriptions. They estimated that an increase in SSRI sales of 1 pill per capita per year in a country was associated with a 2.5% annual reduction in suicide rates.[24] Higher antidepressant prescription volumes correlated with lower suicide rates among U.S. adolescents, especially males and the poor.[25] Higher suicide rates in rural areas (with lower income levels) have been associated with less antidepressant prescribing.[18,23] In Italy, increased antidepressant prescribing was associated with lower suicide rates among women.[26,27] An exception was Iceland, where increased antidepressant prescribing did not correlate with lower suicide rates,[28] perhaps because of a very low suicide rate. In most countries studied, greater use of newer antidepressants correlated with falling suicide rates at a population level.

None of these studies involved an Asian country and most were conducted in nations with moderate annual suicide rates of less than 20 per 100,000. In this study, we examine the relationship of antidepressant prescribing to suicide rates in Japan, the world's third largest economy, and a nation with a high suicide rate and previously low antidepressant prescription volume, during the recent growth in antidepressant prescribing. We focused on the newer-generation antidepressants, mainly SSRIs, which account for most of this increase.

Recently there have been concerns about antidepressant use increasing risk of suicidal behavior. However, we hypothesize that antidepressant use on average protects against suicide. To prove that hypothesis, a clinical trial to study this relationship is needed. However, such a trial would require an extremely large sample, due to the relatively low incidence of suicide. It has been reported that increased antidepressant prescribing had no obvious effect on suicide rates in Japan,[29] but without a systematic quantitative analysis, the true relationship is unknown. Ecological analyses of the relationship of antidepressant prescribing to suicide rates have limitations. Important among these is their lack of data on which individuals were taking antidepressant medication at the time of suicide. Postmortem toxicologic studies of the presence in blood of antidepressants have found that few of the persons who committed suicide were taking antidepressants,[30,31] particularly SSRIs,[32] at the time of death.

We use population level data from Japan to investigate the relationship between prescribing of new antidepressants and suicide. Another limitation of ecological analyses is the difficulty of controlling for the many variables and long-term trends that may affect a phenomenon as complex as the suicide rate. In this ecological analysis, we used the analytic strategy of "differencing" to eliminate the effect of secular (long-term) linear trends, which could influence suicide rates. The unit of analysis in this study was the annual difference, or change, in antidepressant prescription and suicide rates. We also examined the impact of other putative suicide risk factors—the unemployment rate[33–36] and alcohol consumption.[37–39]

METHOD

Setting

Japan has a population of 127,435,000 (Male: 48.9%, Female: 51.1%).[2] The 1-year prevalence of mood disorder is 3.1% (95% confidence interval [CI] = 2.2 to 4.1).[40] The newer-generation antidepressants entered the Japanese market recently: fluvoxamine (SSRI) in 1999 and paroxetine (SSRI) and milnacipran (SNRI) in 2000. Thus, 2 SSRIs, 1 SNRI, and several older antidepressants, including TCAs, were available in Japan during the time period (1999 through 2003) of this study. In Japan, Universal Public Health Insurance covers the majority of health care

costs, and patients pay little or nothing for treatment or medication, including for major depressive disorder.[41]

Sources of Data

The following nationwide data were obtained:

(1) Annual suicide number and rate. Data on annual number of suicides and population stratified by age and gender for the years 1993 through 2003 were obtained online from the Japanese Ministry of Health, Labor, and Welfare Vital Statistics Database System.[2] We calculated annual suicide rates per 100,000 persons in 6 age groups (≤ 19, 20–29, 30–39, 40–54, 55–64, and ≥ 65 years) for males and females.

(2) Antidepressant prescribing and estimated age and gender profile. We estimated nationwide trends in the use of antidepressants in these 12 age/sex groups by calculating annual number of antidepressants sold each year. The antidepressant classes were grouped as newer antidepressants, TCAs, and other antidepressants. The newer-antidepressant group included SSRIs (fluvoxamine and paroxetine) and the SNRI milnacipran. The TCA group included amitriptyline, imipramine, clomipramine, nortriptyline, trimipramine, dosulepin, and desipramine. Other antidepressants included amoxapine, maprotiline, mianserin, trazodone, setiptiline, lofepramine, and safrazine.

Nationwide data on sales of antidepressants were obtained from the commercial database of IMS Japan K.K. (IMS Base-JPM prescription data), a leading international provider of data on drug use to the health care industry and governmental agencies. The proportion of the total antidepressant market accounted for by each medication group for 1999 vs. 2003 was as follows: newer antidepressants (10.2% vs. 47.5%), TCAs (42.1% vs. 24.4%), others (47.6% vs. 28.0%). Data were collected from 120 wholesalers, accounting for 99% of all retail pharmacies in Japan. The data included inpatient and outpatient prescriptions from hospitals and clinics. Prescription counts were converted into DDD/1000 population/day for each age/sex group. The denominator was the number of people and the numerator was the DDD in the age/sex group. The DDD is the international unit of drug utilization approved by the World Health Organization for studying trends in usage of specific drugs.[42] It is defined as the mean or typical daily maintenance dose of the drug when used by adults for its main indication (e.g., 20 mg of fluoxetine for depression) and is usually presented as DDD/1000 population/day. It does not take into account treatment duration and is an estimate of use for a particular medication. For example, one way of achieving a value of 10 DDD/1000 population/day for fluoxetine would be if 1% of the general population were prescribed fluoxetine and the daily dose for each person was 20 mg, or alternatively, if only 0.5% of the population were prescribed fluoxetine, but the daily dose for all was 40 mg. Changes in the DDD/1000 population/day in a country for a drug or group of drugs can be used to estimate trends in consumption. The age/sex stratification of antidepressant prescriptions was estimated from a series of representative large-scale surveys of prescribing (source: IMS Japan Medical Data Index), covering 5 million prescriptions each year by general practitioners and psychiatrists in Japan.

(3) Unemployment rate. Unemployment rates were obtained online from the Statistics Bureau, Japanese Ministry of Internal Affairs and Communications.[43]

(4) Alcohol consumption volume. Annual alcoholic beverage consumption data were obtained online from the National Tax Agency of Japan.[44]

Statistical Analysis

Our analyses focused on the newer antidepressants since these accounted for all of the increase in antidepressant prescribing during the time period of this study. The data were indexed by 5 levels of year, 6 of age group, and 2 of gender for a total of 60 values of suicide rate and dose of each antidepressant class. Except where noted, we differenced all time series data before model estimation. This means we subtracted each year's rate from the subsequent year's rate to calculate the annual rate change. For example, the annual change in a variable for the year 2000 is the value in 2000 minus the value in 1999. This method analyzes the effect of annual rate changes, which eliminates the effect of secular linear trends that cannot be controlled for, a major problem of ecological analyses. Thus, we analyze the relationship between annual changes in the Japanese suicide rate (the dependent variable) and annual changes in antidepressant prescribing stratified by gender and age groups for the 5 years 1999–2003. A negative association between the differenced series may not manifest itself as a negative association between the undifferenced series because the negative association could be counterbalanced by a positive linear trend in the undifferenced series.

Analyses were performed using the generalized least squares function in S-Plus and R.[45,46] The corresponding summary function computes p values for testing whether coefficients are 0. These p values are based on large-sample approximation.

We used several types of regression methods. A technical issue is that suicide rates are prima facie statistically dependent across the 3 dimensions of time (year), gender, and age. The degree of dependence will be incomparable among these 3 dimensions. Therefore, in each case we estimated the degree of dependence for each of the 3 dimensions separately. These estimates introduced extra uncertainty that was not taken into account in the p values calculated by the generalized least squares algorithm. The result was that the nominal generalized least squares p values tended to be too small. Therefore, we computed p values using the nonparametric bootstrap in those primary analyses that showed small generalized least

squares p values.[47] In each case, at least 2400 resamples were generated. The resamples are generated randomly, so the bootstrap calculation involves the intentional introduction of extraneous randomness. For this reason, bootstrap p values are best described by confidence intervals that reflect the uncertainty due to the resampling.

The analyses of SSRIs (paroxetine and fluvoxamine in DDD/1000/day) were as follows: the primary analyses consisted of 8 models including different combinations of covariates. We focused on the model with the smallest Bayes Information Criterion value,[48] which happened to be the simplest, that in which yearly change in DDD of SSRIs was the only predictor. Bayes Information Criterion is a model selection criterion that balances model fit and complexity.[48]

The analyses of all newer antidepressants (paroxetine, fluvoxamine, and milnacipran) were as follows: the primary analyses consisted of 3 models including different combinations of covariates. The model with the smallest Bayes Information Criterion was the simplest, that in which yearly change in DDD of newer antidepressants was the only predictor. The model with the second lowest Bayes Information Criterion value had yearly change in DDD of newer antidepressants and gender as independent variables. In the third model, year-to-year change in the suicide rate was the dependent variable and yearly change in DDD of newer antidepressants and age were the independent variables. For the differenced analyses above, N = 48 (4 differenced time points × 2 genders × 6 age groups). All tests were 2-sided.

RESULTS

Suicide and Antidepressant Prescription Rates

During the 10 years 1993 through 2003, the national suicide rate of Japan increased 54%, from 16.6 per 100,000 in 1993 to 25.4 per 100,000 in 1998 and then leveled off to 25.5 per 100,000 in 2003. More than twice as many suicides occurred in males compared with females.[2] The suicide rate was highest among males in the 55- to 64-year-old age group (64.8 per 100,000) and among females in the 65-year-old and older age group (22.6 per 100,000).[2] From 1999–2003, the suicide rate decreased slightly among older persons, the age group with the highest prescription volume, and leveled off in other age groups.[2] During this time period, suicides were due to the following causes: hanging (66%), jumping (10%), gas (10%), drowning (3%), stabbing (3%), overdose (1%), and other (immolation, pesticide, firearm, etc.; 7%).[49] Due to strict firearm regulation in Japan, there were fewer than 20 reported cases of suicide by firearms each year.[49]

Overlapping with this time period, newer antidepressants—the SSRIs paroxetine and fluvoxamine and the SNRI milnacipran—were approved for use in Japan. Antidepressant use in Japan, in DDD/1000 population/day, for all antidepressants, increased 56% from 7.9 in 1999 to 12.3 in 2003. All of the increase was due to the newer antidepressants (Figure 1). Approximately 80% of this increase was due to the SSRIs and the remaining 20% due to the SNRI milnacipran (IMS Base-JPM prescription data). Use of newer antidepressants increased across all age and gender groups (Figure 2). From 1999–2003, prescribing volume for all antidepressants in DDD/1000 population/day increased 50% among females (10.3–15.4) and 57% among males (6.9–10.9). The trend for SSRIs was comparable to that for newer antidepressants overall. The proportion of total antidepressant use accounted for by TCAs and other antidepressants fell, respectively, from 42% to 24% and 48% to 28% (IMS Base-JPM prescription data, Figure 1).

Alcohol Consumption and Unemployment Rates

From 1999 to 2003, the annual alcoholic beverage consumption volume, with some fluctuations, fell by 4.5%. During this period, the unemployment rate increased 6.5% for females and 12.8% for males.

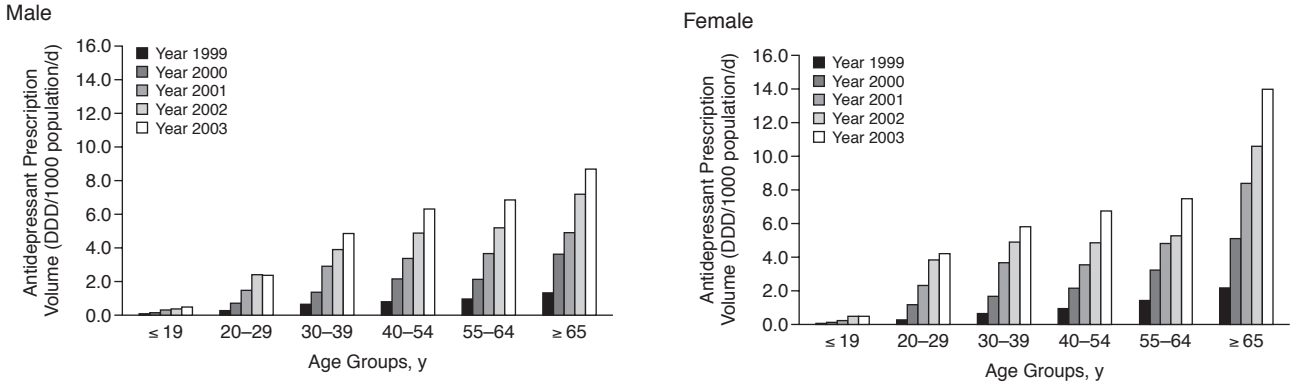
Relationship of Suicide and Antidepressant Prescription Rates

Using the time-series differencing method, we performed a regression analysis with year-to-year changes in the national suicide rate as the dependent variable and year-to-year changes in SSRI prescribing as the independent variable. Between 1999 and 2003, there was an inverse association between year-to-year changes in SSRI prescribing and suicide rates ($N = 48$, $\beta = -1.41$, SE = 0.49, bootstrap $p = .019$, 95% CI = 0.015 to 0.025). This means that, absent secular linear trends, an increase in SSRI use of 1 DDD/1000 population/day was associated with a decrease of 1.4 suicides per 100,000 persons per year.

We tested the same model, substituting year-to-year changes in prescribing of all newer antidepressants (including milnacipran) for that of SSRIs as the independent variable. The results again showed an inverse association ($N = 48$, $\beta = -1.34$, bootstrap $p = .008$, 95% CI = 0.005 to 0.012). Absent secular linear trends, an increase of 1 DDD/1000 population/day in use of all newer antidepressants was associated with a decrease of 1.3 suicides per 100,000 persons per year.

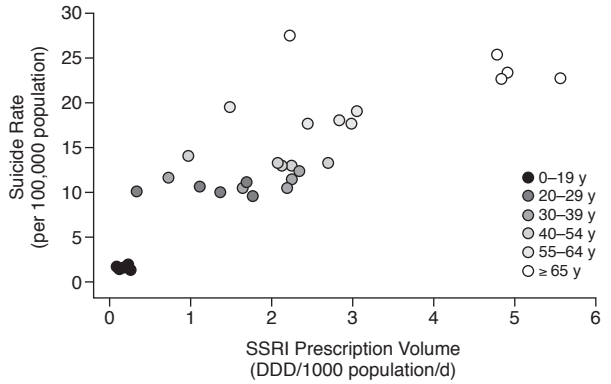
Next, we explored the interaction of gender and year-to-year changes in SSRI prescribing. The dependent variable was year-to-year changes in the suicide rate and the independent variables were year-to-year changes in SSRI prescribing, gender, and the interaction of SSRI prescribing with gender. This model showed a trend-level interaction effect suggesting a stronger impact of SSRI prescribing on the male suicide rate ($N = 48$, $\beta = -1.85$, bootstrap $p = .084$, 95% CI = 0.076 to 0.093). Using all newer antidepressants instead of SSRIs as the independent

Figure 2. Prescription Volume of Newer Antidepressants[a] by Age Groups and Gender in Japan, 1999–2003[b]



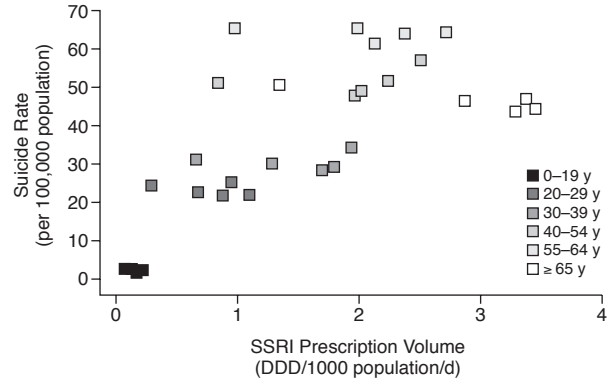
[a]Paroxetine, fluvoxamine, and milnacipran.
[b]Data provided by IMS Base-JPM, IMS Japan K.K., Tokyo, Japan.
Abbreviation: DDD = defined daily dose.

Figure 3. Female Suicide Rate (per 100,000 population) Versus SSRI Prescription Volume (defined daily dose [DDD]/1000 population/day) Stratified by Age Groups: Japan 1999–2003[a]



[a]Data provided by IMS Base-JPM, IMS Japan K.K., Tokyo, Japan, and Vital Statistics of Japan.[2]

Figure 4. Male Suicide Rate (per 100,000 population) Versus SSRI Prescription Volume (defined daily dose [DDD]/1000 population/day) Stratified by Age Groups: Japan 1999–2003[a]



[a]Data provided by IMS Base-JPM, IMS Japan K.K., Tokyo, Japan, and Vital Statistics of Japan.[2]

variable gave a similar result (N = 48, β = –1.75, bootstrap p = .076, 95% CI = 0.066 to 0.088).

We tested the effect of an interaction of age with prescribing of all newer antidepressants on the suicide rate. The dependent variable was year-to-year changes in the suicide rate and the independent variables were year-to-year changes in prescribing of all newer antidepressants, age, and the interaction of these 2 variables. The model did not show evidence of an interaction effect (N = 48, β = –.03, SE = 0.02, t = –1.4, p = .17).

Simpson's Paradox

Figures 3 and 4 show, if one looks only at the aggregate data (ignoring the age groups), SSRI prescription and suicide rates are positively correlated. A more careful examination of the data, however, reveals that within age groups, for males and females separately, the simple correlations between SSRI prescription and suicide rates are negative for most age/sex cohorts (females: –0.04, 0.06, 0.09, –0.82, –0.53, –0.89 and males: –0.64, –0.44, 0.04, 0.38, –0.32, –0.91 for age groups 0–19, 20–29, 30–39, 40–54, 55–64, and ≥ 65 years, respectively). If males and females are lumped together, all the correlations within age subgroups are negative (data not shown). This is an example of Simpson's Paradox[50]: stratification of aggregated data showing a positive correlation reveals negative associations between SSRI prescription volume and suicide rates within subgroups.

Effect of Unemployment and Alcohol Consumption

A regression analysis with year-to-year changes in the suicide rate as the dependent variable and year-to-year

changes in SSRI prescribing as the independent variable, adjusting for yearly changes in unemployment and alcohol consumption rates was performed. Results showed an inverse association between year-to-year changes in SSRI prescribing and suicide rates (N = 48, β = –1.50, bootstrap p = .008, 95% CI = 0.006 to 0.011), adjusting for the other variables. Changes in unemployment and alcohol consumption were not associated with suicide rate changes (N = 48, β = –2.62, SE = 1.52, t = –1.7, p = .09; and N = 48, β = –.001, SE = 0.003, t = –0.3, p = .76, respectively; unbootstrapped p values).

We explored the effect on the suicide rate of interaction terms of age × alcohol consumption and age × unemployment rate. The dependent variable was year-to-year changes in the suicide rate and the independent variables were year-to-year changes in prescribing of SSRIs, age, alcohol consumption, unemployment rate, and the interactions of age with alcohol consumption and unemployment rate. The model did not show evidence of interactions of age and unemployment or age and alcohol consumption (N = 48, β = –.12, SE = 0.07, t = –1.6, p = .12; and N = 48, β = .0002, SE = 0.0002, t = 1.09, p = .28, respectively). In other words, age had no effect on the relationship of alcohol consumption or unemployment rate to suicide rate.

DISCUSSION

The results of this study indicate that, after eliminating the effects of long-term linear trends, annual changes in antidepressant prescribing in Japan since the introduction of SSRIs are negatively associated with annual changes in suicide rates. It does not follow that an annual increase in SSRI prescriptions will correspond to a decrease in the suicide rate because other long-term linear trends may affect the suicide rate. For example, unemployment increased during this time period, but because the increase was nearly linear, this confound was eliminated in our differenced analysis. It might be argued that factors associated with risks of antidepressants are lost by eliminating these trend effects. However, if increased antidepressant treatment caused increased suicide rates, then in years in which the increase in prescriptions is especially great the increase in the suicide rate should also be especially great. Instead, we found evidence to support our hypothesis of an inverse relationship. This appeared to be strongest among males, who have the highest suicide rates and experienced a greater increase in antidepressant treatment.

Our findings are consistent with most studies in other countries,[17–23] and in particular with those studies[17,23] that found that demographic groups with the largest increases in antidepressant treatment had the greatest decrease in suicide rates. Using U.S. regional data, Gibbons et al.[18] and Olfson et al.[25] showed that counties with the greatest increase in SSRI and newer antidepressant prescriptions had the biggest declines in suicide rates.

Analysis of data not stratified by age and gender may have contributed to premature reports that Japan is an exception to these findings in other countries.[29] This is the first national study in an Asian country with a high annual suicide rate of more than 20 per 100,000 persons using a differenced, age/sex-stratified analysis. The results support the notion that increased use of newer antidepressants, mainly SSRIs, may have had a protective association to suicide rates in Japan.

The most likely explanation for this protective association is improved treatment of depressive disorders. Substantial literature demonstrates the efficacy of antidepressants for major depressive disorder.[12,51,52] Major depressive disorder accounts for approximately 60% and anxiety disorders for 20% of antidepressant prescriptions in Japan.[53] Greater use of antidepressants for depression and other disorders with elevated suicide risk[54] may have a beneficial effect on suicide rates.

Improved side effect profiles of newer antidepressants may have increased prescribing by general practitioners[55] and reduced negative perceptions.[56] Educational programs on depression treatment can change general practitioners' clinical knowledge and attitudes,[57,58] and reduce suicide rates.[59] Improved side effect profiles may have also increased patients' treatment adherence.[60,61] Selective serotonin reuptake inhibitors are safer on overdose compared with TCAs.[62] Clinical contact and psychosocial interventions associated with prescribing may also have beneficial effects.[63,64] A study in an isolated rural village in Japan with an aged population and very high suicide rate showed that better diagnosis and treatment of depression led to a substantial fall in suicide rates.[65]

Meta-analyses of effects of SSRIs on rates of suicide, attempts, and ideation in clinical trials report inconsistent results.[66–74] Some report that SSRIs may increase the risk of attempts, specifically in youth, on the basis of clinical trial adverse event reports,[66–69] but suicide item scores on rating scales in the same studies do not indicate such a risk.[70,71] There is a need for randomized controlled trials measuring the effects of antidepressants on suicidality, particularly in children, adolescents, and young adults.

We found a trend for a stronger protective association of both SSRIs and all newer antidepressants among males compared to females. A similar effect was found by Olfson et al.[25] Age-adjusted mortality rates from suicide are about 2-fold higher for Japanese males compared with U.S. males.[75] More widespread antidepressant treatment might be expected to more strongly affect males, since they have higher suicide rates and also experienced a greater relative increase in antidepressant prescribing during this time period compared to females. There could also be effects on impulsivity and aggression in depressed men.[76–80]

We did not find evidence of an interaction effect of age. Unlike the United States, where suicide rates are

highest among elderly males, in Japan, they are highest among middle-aged males. Yamasaki et al.[81] reported that from 1970 to 1990 in Japan, low income was associated with suicide in middle-aged males, but that study did not consider the role of mood disorders. In a cohort study of 57,714 Japanese males aged 40 to 69 years, cigarette smoking was associated with an increased risk of suicide.[82] We and others have discussed the relationship of cigarette smoking to aggressive personality traits, lower serotonin function in the brain, and the risk for suicide and nonfatal attempts.[79,82,83]

In our analysis, adjusting for alcohol consumption and unemployment rates did not significantly alter the inverse relationship between SSRIs and suicide rates. This is consistent with similar evidence from the United States,[17] Sweden,[19] and Hungary.[16]

This study has limitations associated with an ecological analysis. We cannot infer causality from statistical associations. A fundamental limitation of this type of analysis is the lack of individual level data. It is not possible to know whether individual suicides were associated with use or nonuse of antidepressant medication. Nor is it possible to control for all variables that may contribute to observed associations, such as drug abuse and access to lethal means. However, prevalence of illicit drug use and common methods of suicide, mainly hanging, did not change during the study period.[84,85] The differenced analysis of annual changes in rates eliminates the effect of long-term linear trends. Another limitation is the relatively short time period. The use of separate datasets for prescription volume and to estimate age/sex stratification of prescriptions may have introduced some error, though this method has been used by others.[23] The large national datasets allow us to estimate rates relatively accurately. We could not stratify by diagnosis since we did not have these data. Suicides tend to be underreported,[86] whereas the dose of antidepressant that patients take may be overestimated in that studies show low adherence.[87,88] However, it is unlikely that underreporting of suicides or inadequate adherence changed markedly during this time period.

In conclusion, the introduction of newer antidepressants in Japan, beginning in 1999, was associated with increased antidepressant prescribing, mainly of SSRIs. After eliminating the effects of long-term linear trends, we found annual increases in antidepressant treatment were associated with annual decreases in suicide rates. This may be a consequence of improved treatment of antidepressant-responsive psychiatric illnesses that increase suicide risk, mainly depression. Randomized controlled trials are needed to prove whether these medications have actual antisuicidal effects.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), nortriptyline (Pamelor and others), paroxetine (Paxil and others), trimipramine (Surmontil and others).

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