Two Simultaneous Increases Observed both in Youth Suicide Rates and Antidepressant Sales Amounts in Japan, 2002-2009: A Possible Link between Youth Suicides and Uses of Antidepressants

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ABSTRACT---

Objective: A relation between increases of sales amounts of antidepressants and changes in suicide rates by age brackets was investigated in Japan.

Participants and Methods: Changes of national suicide rates by age brackets from 1994 to 2009 published by Ministry of Health, Labor and Welfare Japan were compared with increases of total sales amounts of antidepressants in Japan from 1994 to 2010 reported by Cima Science Journal, Inc.

Results: The sales amounts of antidepressants significantly increased from 20 billion yen to 110 billion yen in the period of 2002-2010. Increases of suicide rates coincided in younger generation, especially in 20-29 years old. The annual suicide rates for men in the age bracket of 20-24 years old increased from 21.3 to 29.9 in 2002-2009. While significant decreases of suicide rates coincided in older generations in the same period. These changes in suicide rates are strongly age-specific.

Conclusion: Because it has been reported that the risk of suicidality associated with antidepressants is strongly age dependent, the significant increases of sales amounts of newer antidepressants probably associated with both the simultaneous suicide rates up in the younger and down in the older age groups in the period of 2002-2009 in Japan.

Keywords— antidepressant, SSRI, suicide, CYP2D6, age dependency

1. INTRODUCTION

A newspaper reported the result that in the survey of 1,016 Japanese who had lost members to suicide, 69 percent had been taking medication in Japan[1]. Hirokawa *et al*, reported that suicide completers with a history of psychiatric treatment were significantly younger than those without treatment[2]. These reports possibly suggest the link between medication and suicides especially in younger people. But there are several reports which suggest that medication reduced suicide rates. Nakagawa *et al.* reported that annual increases in prescribing of newer antidepressant medications, mainly SSRIs were associated with annual decreases in suicide rates in Japan during 1999 through 2003[3]. They did not find evidence of an interaction effect of age. Since then, suicide rates by age brackets have obviously changed in the following several years, and their results need to be investigated further. It may be helpful to prevent risks caused by medication.

2. MATERIALS AND METHODS

Suicides (N=451,486) in an age bracket 10-94 years old, from 1994 to 2009 in Japan are included in this study. National suicide rates per 100,000 person-years by age brackets for men and women in Japan, from 1994 to 2009 were obtained from the web-site[4] maintained by Ministry of Health, Labor and Welfare Japan, and plotted by using Microsoft Office Excel 2007. The suicide rates by age brackets were divided into three periods, 1994-1997, 1998-2001, and 2002-2009, based on the overall trend of increases and decreases of suicide rates by age brackets, and plotted with asymptotic lines by using Microsoft Office Excel 2007 (data not shown). The annual changes in suicide rates per 100,000 person-years for 17 age brackets in the three periods, 1994-1997, 1998-2001, and 2002-2009 obtained from slopes of the asymptotic lines are summarized in Tables 1 and 2. Antidepressant sales amounts in the period from 1994 to 2010 are referred to the values from the document content (page 7, line 9) and Fig. 10-4 in "ai report 2011" with permission[5].

3. RESULTS AND DISCUSSION

Japanese suicide rates by age brackets from 1994 to 2009

Japanese suicide rates by age brackets are available from the web-site[4]. After the economical bubble burst around 1990, large increases of Japanese suicide rates occurred in all age brackets without exception in 1998 (Figs. 1 and 2). During the following three years from 1999 to 2001, the suicide rates decreased in a recovery trend in almost age brackets. However, the changes of the suicide rates divided into two groups during the next period from 2002 to 2009. In this period, the suicide rates markedly increased in the younger age groups, especially the 20 – 29 years old group for both men and women, while decreased greatly in the older age groups (Figs. 1 and 2). The annual changes of suicide rates for age brackets in the three periods that is 1994-1997, 1998-2001, and 2002-2009 are summarized in Tables 1 and 2. The annual increase rates 1.294 for men and 0.7083 for women in both the age groups of 20 – 24 years old are highest in the period of 2002-2009. In the younger age groups, the suicide rates were on a decreasing or constant trend in the period from 1994 to 1997, and after the precipitous increase in 1998, the next decreasing trend continued from 1999 to 2001, then an increasing trend started in 2002, and has steadily continued to increase during the period from 2002 to 2009 (Figs. 1 and 2). In the middle and older age groups, inverse tendencies are observed, that is, an increasing trend in the period from 1994 to 1997 changed to a decreasing trend after 1998 taking two interrupted increases in 1998 and around 2002.

The putative suicide risk factors such as the unemployment rate cannot explain these divided tendencies. Chen *et al.* reported that the increases of the suicide rates are associated with the increases of unemployment rates in the period from1998 to 2003, but the steady decreases of unemployment rates observed in the period from 2004 to 2008, are not associated with the suicide rates remained in the constant level during this period[6].

Changes in the sales amounts of antidepressants in Japan from 1994 to 2010

The sales amounts of antidepressants are reported by CIMA SCIENCE JOURNAL, INC. [5]. Three newer antidepressants (two selective serotonin reuptake inhibitors (SSRIs) and one serotonin-norepinephrine reuptake inhibitor (SNRI))) were introduced to Japan in 1999 and 2000. After that, antidepressant sales amounts increased markedly[7], exceeded 100 billion yen in 2007, and continued to increase during the following three years from 2008 to 2010[5]. About 90% of the sales amounts are from newer antidepressants[5]. These increases led to the large increase of antidepressant prescription in Japan. Pharmaceuticals and Medical Device Agency examined the data of health insurance claims in the period from Jan, 2005 to Dec, 2008 from health insurance society, and 5,732 patients were prescribed paroxetine in the study population 399,086 patients[8]. Age distributions were 2 in 60,173(0.00%, 0-9 y), 170 in 54,350(0.31%, 10-19y), 1,182 in 71,866(1.64%, 20-29y), 2,035 in 80,416(2.53%, 30-39y), 1,455 in 64,131(2.27%, 40-49y), 653 in 40,894(1.60%, 50-59y), 151 in 21,103(0.72%, 60-69y), and 84 in 6,153(1.37%, over70y), respectively[8].

Changes of suicide rates coincided with increases of antidepressant sales amounts are strongly age dependent and correlate with CYP450 metabolism

The antidepressants reportedly show particular age dependency in several adverse effects including suicidality[9, 10]. This age dependency is able to be explained by the expression level of metabolic enzymes CYP450[11] including CYP2D6[12] and CYP3A4[13], whose expressions are suppressed in a low level from born to around 20 years old, then start to increase gradually in an age dependent manner to more than three folds in ages from 20 to 80 years old[12, 13]. The risk of suicidality associated to use of antidepressants reportedly increased in age groups under 25, and decreased over 25[9, 10]. These tendencies are exactly similar as those shown in the Japanese suicide rate changes in Figs. 1 and 2, that is, the increases of suicide rates are observed in the younger age groups, especially 20-29 years old, while the decreases of suicide rates are in the older age groups, according to the increase of the sales amounts of the newer antidepressants in 2002-2009.

SSRI and SNRI are metabolized with CYP450 enzymes. For example, paroxetine whose sales amount is highest and accounts for approximately half of the total sales amount of antidepressants in Japan in the period from 2004 to 2010[5], is mainly metabolized with CYP2D6. But the frequency of the deficient allele *CYP2D6*10* is 34.6–40.8 % in Japanese[14]. It is about 40 times higher than that of Caucasians (1-2 %) [15]. The enzymatic activity of CYP2D6*10 is about 1/10 of the normal type of CYP2D6*1. Further, Ueda *et al.* reported that the individuals who carry one normal and one deficient alleles such as *CYP2D6*1/*10* showed markedly higher blood concentration of paroxetine than that of the individuals carrying two normal alleles such as *CYP2D6*1/*1* or two deficient alleles such as *CY2D6*10/*10*[16]. It is known that paroxetine is a potent inhibitor for CYP2D6, and the normal enzyme CYP2D6*1 is inhibited about 13 times more strongly than the deficient enzyme CYP2D6*10[17]. This leads to the high blood concentration[16, 18] and occurrence of the

adverse effects including suicidality. About 40% of Japanese belong to this type of individuals carrying one normal and another deficient allele. It is very likely that the marked increase of the prescription amounts of the newer antidepressants from 2001 to 2010, among quite large number of poor metabolizers associated with the increase of suicides in younger people. Further, a high rate of benzodiazepine combination use in Japan also contributed to increases of suicides[19-21].

Understanding, knowledge, and responsibility are necessary not only for prescribing physicians, but also for patients and their families on taking antidepressants

The annual increases in prescription of newer antidepressants, mainly SSRIs, were reportedly associated with annual decrease of suicide rates in the period from 1999 through 2003 in Japan[3]. But, since then, it is important and indispensable to know that their conclusion has become different from reality. Correct understanding, accurate knowledge, and proper responsibility should be required not only for physicians but also for patients and their families to use antidepressants especially for young people with deficient metabolizing ability because of low capacity of antidepressant metabolizing enzyme CYP450s. For this purpose, prescribers should inform patients and their families about the risks associated with treatment with antidepressants. A useful medication guide about using antidepressants is available[22].

Limitations

At present, I am not able to exhibit the evidence for direct interaction between antidepressant uses and suicides. I do not have the data about the rates of suicides which were under the effect of antidepressant medication in each age bracket. In future, autopsy report system might be improved, and individual antidepressant prescription volumes might be freely available.

Generalisability

The present results are able to be sufficiently generalized in Japan, because all suicides and total sales amount of antidepressants in the period from 1994 to 2009 are included for the analyses. The results are possible to be generalized with caution in the East Asian countries including China and Korea in which deficient alleles for some of CYP450s especially CYP2D6*10 are reportedly observed in high frequencies[14]. And the results described in this report are obtained from larger populations than those obtained from trials, and thought to be generally usable to estimate adverse effects of medications on suicides.

What is already known on this topic

Annual increases in prescribing of newer antidepressant medications, mainly SSRIs were associated with annual decreases in suicide rates in Japan during 1999 through 2003, with no evidence of an interaction effect of age [3].

What this study add

Annual increases in sales amounts of antidepressants including SSRIs and SNRI were associated with both annual increases in suicide rates in the younger age brackets and annual decreases in suicide rates in the older age brackets in Japan during 2002 through 2009, with obvious evidence of an interaction effect of age.

4. CONCLUSIONS

Two simultaneous increases were observed in the period from 2002 to 2009 in Japan. One is the increase of antidepressant sales amounts. The other is the increase of suicide rates in younger age brackets. The age dependency observed in the transitions of suicide rates in the period of 2002-2009 suggests a possible relation between antidepressant prescription and suicide completion.

5. FIGURE LEGENDS

Figure 1
Suicide rates for Japanese men (a) and women (b) per 100,000 person-years by age bracket (a), obtained from the web-site http://www8.cao.go.jp/jisatsutaisaku/whitepaper/w-2011/html/honpen/part1/s1_1_04.html [4] were plotted by using Microsoft Office Excel 2007. Suicide rates by age bracket are represented by (-Δ-) for 10-14, (-□-) for 15-19, (-■-) for 20-24, (-▲-) for 25-29, (-◆-) for 30-34, (-●-) for 35-39, (-×-) for 40-44, (-✶-)for 45-49, (--▬--)for 50-54, (--▔--)for 55-59, (--┼--)for 60-64, (--□--)for 65-69, (--△--)for 70-74, (--◇--)for 75-79, (┈○┈)for 80-84, (┈✕┈)for 85-89, and (┈▬┈)for 90-94 years old, respectively.

Figure 2
Sales amounts of total antidepressants (■), paroxetine (○), sertraline (▲) , fluvoxamine (◇), and milnacipran (X) sold in Japan during the period from 1994 to 2010 are plotted respectively according to the description written in ai Report[5] .

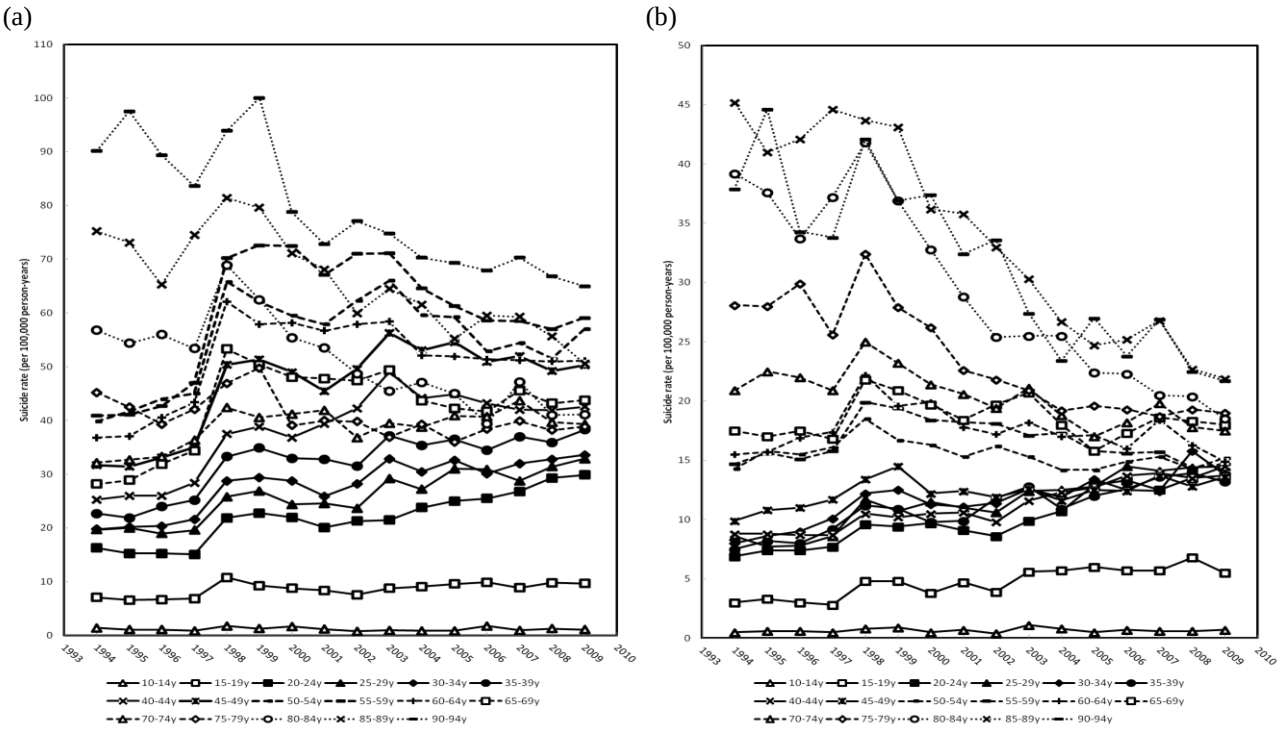

Figure 1: Suicide rates for Japanese men (a) and women (b) per 100,000 person-years by age bracket, obtained from the web-site http://www8.cao.go.jp/jisatsutaisaku/whitepaper/w-2011/html/honpen/part1/s1_1_04.html [4] were plotted by using Microsoft Office Excel 2007.

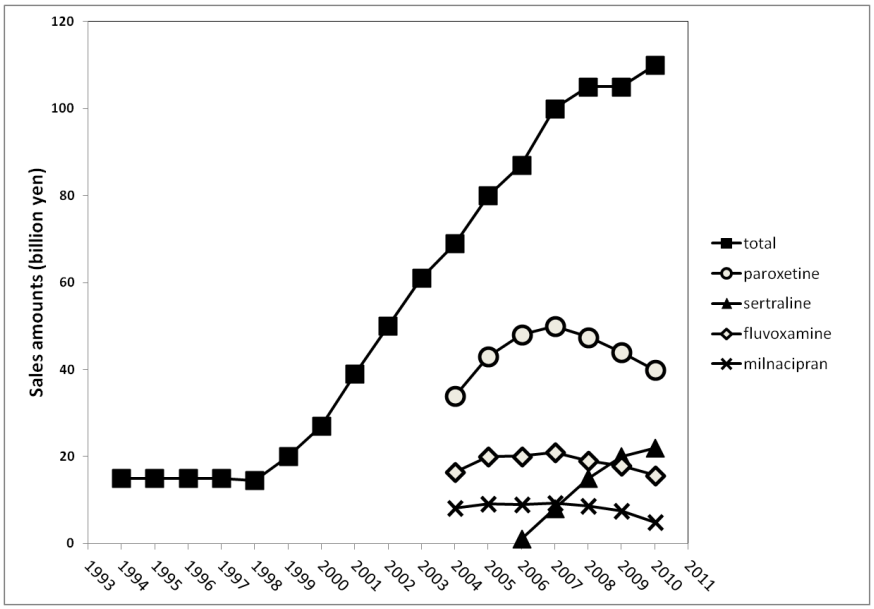

Figure 2 : Sales amounts of total antidepressants, paroxetine, sertraline and fluvoxamine sold in Japan during the period from 1994 to 2010 reported in the ai Report. **<https://www.cimanet.jp/ver4_4/pdf/aireport_sample.pdf>**[5] are plotted.

Table 1: The annual changes in Japanese men suicide rates per 100,000 person-years for 17 age brackets in the three periods, 1994-1997, 1998-2001, and 2002-2009 are obtained as described in the Method section. Positive values are shown by white characters in shaded boxes, and, negative values are shown by black characters in white boxes.

	1994-1997	1998-2001	2002-2009
10-14y	-0.15	-0.14	0.057
15-19y	-0.05	-0.77	0.231
20-24y	-0.36	-0.62	1.294
25-29y	-0.13	-0.61	0.9536
30-34y	0.56	-0.93	0.4679
35-39y	0.96	-0.34	0.5226
40-44y	0.93	0.36	-0.4964
45-49y	1.16	-1.71	-0.4476
50-54y	1.79	-2.63	-1.0452
55-59y	1.99	-0.94	-2.081
60-64y	2.33	-1.59	-1.5655
65-69y	2.16	-1.88	-0.6083
70-74y	1.32	-0.99	0.1429
75-79y	-1.25	-2.4	0.275
80-84y	-0.86	-4.94	-0.8286
85-89y	-0.99	-5.43	-1.7643
90-94y	-2.79	-6.08	-1.2643

Table 2: The annual changes in Japanese women suicide rates per 100,000 person-years for 17 age brackets in the three periods, 1994-1997, 1998-2001, and 2002-2009 are obtained in the same way as for Table 1.

	1994-1997	1998-2001	2002-2009
10-14y	0	-0.07	-0.0095
15-19y	-0.09	-0.13	0.2012
20-24y	0.24	-0.12	0.7083
25-29y	0.01	-0.13	0.5214
30-34y	0.67	-0.45	0.5738
35-39y	0.49	-0.5	0.2857
40-44y	-0.04	0.06	0.3976
45-49y	0.56	-0.53	0.2274
50-54y	0.51	-1	-0.0952
55-59y	0.28	-0.61	-0.5036
60-64y	0.69	-1.29	-0.2679
65-69y	-0.16	-1.14	-0.2452
70-74y	-0.05	-1.5	-0.3048
75-79y	-0.56	-3.11	-0.35
80-84y	-0.99	-4.31	-1.0583
85-89y	-0.07	-3.06	-1.3679
90-94y	-2.26	-2.86	-1.1964

6. ACKNOWLEDGEMENT

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