Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2013: 127: 117–125

DOI: 10.1111/j.1600-0447.2012.01891.x

ACTA PSYCHIATRICA SCANDINAVICA

Suicide seasonality and antidepressants: a register-based study in Sweden

Makris GD, Reutfors J, Ösby U, Isacsson G, Frangakis C, Ekbom A, Papadopoulos FC. Suicide seasonality and antidepressants: a register-based study in Sweden.

Objective: Seasonality of completed suicides with a peak in spring and early summer is a well-documented finding. The circannual serotonergic functioning is hypothesized to be central in this phenomenon. Antidepressant medications exert their pharmacological action mainly by regulating serotonin. Our aim is to study the amplitude of the seasonal effect among suicide victims positive for different classes of antidepressants or without any antidepressants at the time of death.
Method: By using Swedish Registers, 12 448 suicides with forensic data for antidepressive medication and information on in-patient-treated mental disorder were identified during 1992–2003. Seasonality was estimated with a Poisson regression variant of the circular normal distribution of completed suicides.
Results: Higher suicide seasonality was found for individuals treated with selective serotonin reuptake inhibitor (SSRIs) compared to those with other antidepressant treatment or without any antidepressant treatment. The finding is more evident for men and violent suicide methods and those without history of in-patient treatment.
Conclusion: Our results provide preliminary support for the serotonergic hypothesis of suicide seasonality and raise the question of a possible accentuation of the natural suicide seasonality in patients treated with SSRIs, a hypothesis that warrants further investigation.

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Key words: suicide; season; antidepressive agents; methods of suicide; selective serotonin reuptake inhibitor

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Accepted for publication May 8, 2012

Significant outcomes

- Higher suicide seasonality in men treated with SSRI. Especially, those who commit violent suicide and those without in-patient treatment for mental disorders the last 5 years before suicide.
- The hypothesis of a possible interaction between endogenous serotonergic system and exogenously administered agents that regulate serotonin as an underpinning mechanism of suicide seasonality is raised.
- Is the season of treatment initiation with SSRIs another contributing susceptibility factor for suicidal triggering?

Limitations

- The lack of out-patient diagnoses from primary care and psychiatric settings.
- The lack of data on treatment initiation.
- Although our statistical method is very sensitive for the detection of one-peak seasonality patterns, it is not appropriate when two or more peaks are present.

Introduction

Suicide seasonality has been consistently reported from several studies in many countries with temperate climate (1–7). There are several hypotheses for the explanation of suicide seasonality. The sociological hypothesis suggests that changes in the pattern of social interaction in spring and early summer may lead to higher suicide incidence (8). The bioclimatic hypothesis proposes that the effect of climate parameters such as sunlight, temperature, humidity, etc., on hormones and neurotransmitters such as serotonin may explain the seasonal variation in suicide (2, 5, 9). An alternative hypothesis suggests that the seasonality in suicides mainly reflects the seasonality in the availability of the means to commit suicide (3), something that may explain why the seasonal variation in suicide is most evident in violent suicides. These different explanations are not mutually exclusive.

Serotonergic neurotransmission has been considered to be central in the phenomenon of suicide seasonality, mainly due to the fact that this system also has been shown to follow a circannual rhythm. Changes of several serotonin-related measures in plasma and whole blood of healthy individuals have been reported to vary throughout the year, with maximum values during the summer and lowest values in the fall. On the contrary, 5-hydroxyindoleacetic acid (5-HIAA) follows an opposite seasonal pattern (10, 11). Postmortem studies have also reported the same finding (12). Two recent PET studies (Toronto and Copenhagen) reported significantly higher serotonin transporter binding in the fall and winter compared with spring and summer (13, 14). Another study from the Netherlands utilizing SPECT replicated this seasonal variation in serotonin transporter binding (15). Serotonin turnover assessed by measuring the concentrations of serotonin in the internal jugular vein in healthy individuals was found to be lowest in the winter (16). Interestingly, serotonin turnover in unmedicated depressed patients was found to be elevated and was reduced following successful selective serotonin reuptake inhibitor (SSRI) treatment (17).

Beside the circannual rhythm of serotonergic neurotransmission, serotonin has been implicated in suicide research with regard to impulsivity and aggressiveness. Low concentration of the major serotonin metabolite 5-HIAA in the cerebrospinal fluid is known to be related to suicidal behavior (18, 19).

Antidepressants have been thoroughly investigated in randomized clinical trials and in systematic meta-analyses for the possibility to trigger suicidal behavior (20–23).

The debate concerning whether SSRIs trigger suicidal behavior began already in the '90s, when the first series of adult patients with depression who might have been suicidal as a result of fluoxetin (Prozac) treatment were published (24). Over the following years, several groups have reported that the risk of completed suicide was the same, regardless of treatment assignment (25–27), while others assumed that SSRIs increase the risk of suicide attempts and self-harm behavior (20, 28, 29). Later on came the suggestion of a differential risk of antidepressant-induced suicide across the age spectrum, with a greater risk at the younger end of the spectrum, a declining risk with aging, and perhaps even a protective effect in elderly depressed patients (20, 22, 23). On the other hand, ecological studies have consistently reported an association between higher SSRI prescribing and lower suicide rates (30–32).

Aims of the study

The potential association between antidepressants and suicide seasonality has not been assessed. The aim of this study was to study the amplitude of the seasonal effect among suicide victims positive for different classes of antidepressants at the time of death, as well as among those without any antidepressant, using Swedish registers and forensic toxicological data.

Material and methods

Study population and definitions

The study was performed in Sweden, a country in the Northern Hemisphere. All certain suicides (codes E950-E959 in ICD-9, and X60-X84 in ICD-10) during 1992 to 2003 (n = 14 455) were identified in the Swedish Cause of Death Register (SCDR 2009), which is nationwide and covers more than 99% of all deaths in Sweden. For 1141 male suicides and 517 female suicides lacking information on day of death, their dates of death were set to the 15 day of the month of death. Those suicides that lacked information about the month of death were excluded from the analyses (313 men and 112 women).

For the remaining 14 030 suicides, forensic data from the National Board of Forensic Medicine were available for 13 076 suicides (93.2%). Toxicological analyses provided information about therapeutic levels of antidepressant medication detected in the femoral blood of suicide victims

(33) and were carried out exclusively at the Department of Forensic Chemistry of the National Board of Forensic Medicine in Linköping, Sweden, as a routine procedure for all unnatural deaths. Six hundred and twenty-eight individuals who showed toxic levels of antidepressants were excluded from the analyses because it was considered uncertain if these patients were following prescribed treatment. The SSRIs that were screened for were citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Other antidepressants included amitriptiline, clomipramine, desipramine, imipramine, maprotiline, mianserin, moclobemide, mirtazapine, nortriptiline, reboxetine, trimipramine, and venlafaxine.

The remaining 12 448 individuals were linked to the Swedish Hospital Discharge Register (NPR 2009), which has national coverage of all psychiatric hospital admissions since 1987. This register contains information on the dates of admission and discharge from hospital, the primary discharge diagnosis, and up to seven secondary diagnoses. In this way, suicide victims with a history of psychiatric disorder as a primary or secondary diagnosis (ICD-9: 290–319 and ICD-10: F00–F99) within 5 years before death were identified. The national registration numbers assigned to all Swedish residents were used for record linkage between different registers.

The study was approved by the research ethics committee in Stockholm, Sweden (Dnr 2005/1098-31).

Statistical analyses

The presence of seasonality was estimated with a Poisson regression variant of the circular normal distribution of completed suicide, as modified by Frangakis and Varadham (34). This method is an analog of the classic Edward's procedure (35). It provides an estimate of the month of maximum incidence for suicide together with 95% confidence intervals. It also gives an estimation of the relative risk (RR) of committing suicide during the peak month in comparison with the month with the minimum incidence during the year, a 95% confidence interval for RR, and a test for significance for the null hypothesis that RR = 1.0. In contrast to standard, large-sample Poisson regression inference, this method works for small samples and accounts for the fact that the null hypothesis value of RR (1.0) is at the boundary of the range of parameter values (i.e., RR ≥ 1.0). Separate stratified analyses were performed by sex, history of in-patient treatment for mental disorder, and method of suicide (violent: E953-E957/X70-X83, non-violent: E950-E952/X60-X69 according to ICD-9/ICD-10). In each of these categories, the seasonal variation of suicide was estimated for individuals with positive forensic screening for SSRIs or other antidepressants and individuals with negative forensic screening for antidepressants.

Method for comparing two samples for differential degree of seasonality

To test for differential degree of seasonality between two samples (i.e., that RR1 is different from RR2 for samples say 1 and 2), we used the distribution-free test that is derived by conditioning on the sufficient statistics under the null hypothesis that RR1 = RR2. To give a specific example, this test in Table 2 for comparing the seasonality between men with 'SSRI positive' (n = 819) and men with 'no antidepressants' (n = 7366) is calculated as follows: i) for each of the two *observed* samples separately, we estimate the *observed* RR and the peak month; we then estimate the *observed* ratio of RR (SSRI)/RR (no antidepressants) = 1.42/1.12 = 1.27; ii) we create a pool of individuals by mixing the two samples together; iii) we randomize the pooled mix to two new samples of individuals of same sizes as the original ones (i.e., 819 and 7366); iv) in the randomized new samples, we estimate the RRs and the *randomized* ratio of maxRR/minRR, namely the maximum [RR (SSRI), RR (no antidepressants)]/min [RR (SSRI), RR (no antidepressants)]; v) we repeat (iv) 1000 times thus obtaining an estimate of the null distribution of maxRR/minRR; vi) we calculate the significance level (P-value) as the fraction of the 1000 values of maxRR/minRR that are at least as large as the observed value of 1.27. The above steps work if the months of peak estimated in step (i) for the two samples are the same. If they are not, then the data for one of the two samples should be rotated by the difference between the 2 months; and then steps (ii–vi) can be applied as above. The results of the test are shown in Table 2 only for the groups that it is applicable.

For the graphical presentation of suicide seasonality, the monthly RR for suicide was calculated as the central moving average of the mean number of suicides per month over three consecutive months, divided by the average of suicides during winter months (December, January, and February) in the respective categories (Fig. 1).

The SAS software (version 9.1, SAS Institute Inc., Cary, NC, USA) and R (version 2.10, R Foundation for statistical computing, Vienna, Austria) were used for the statistical analyses.

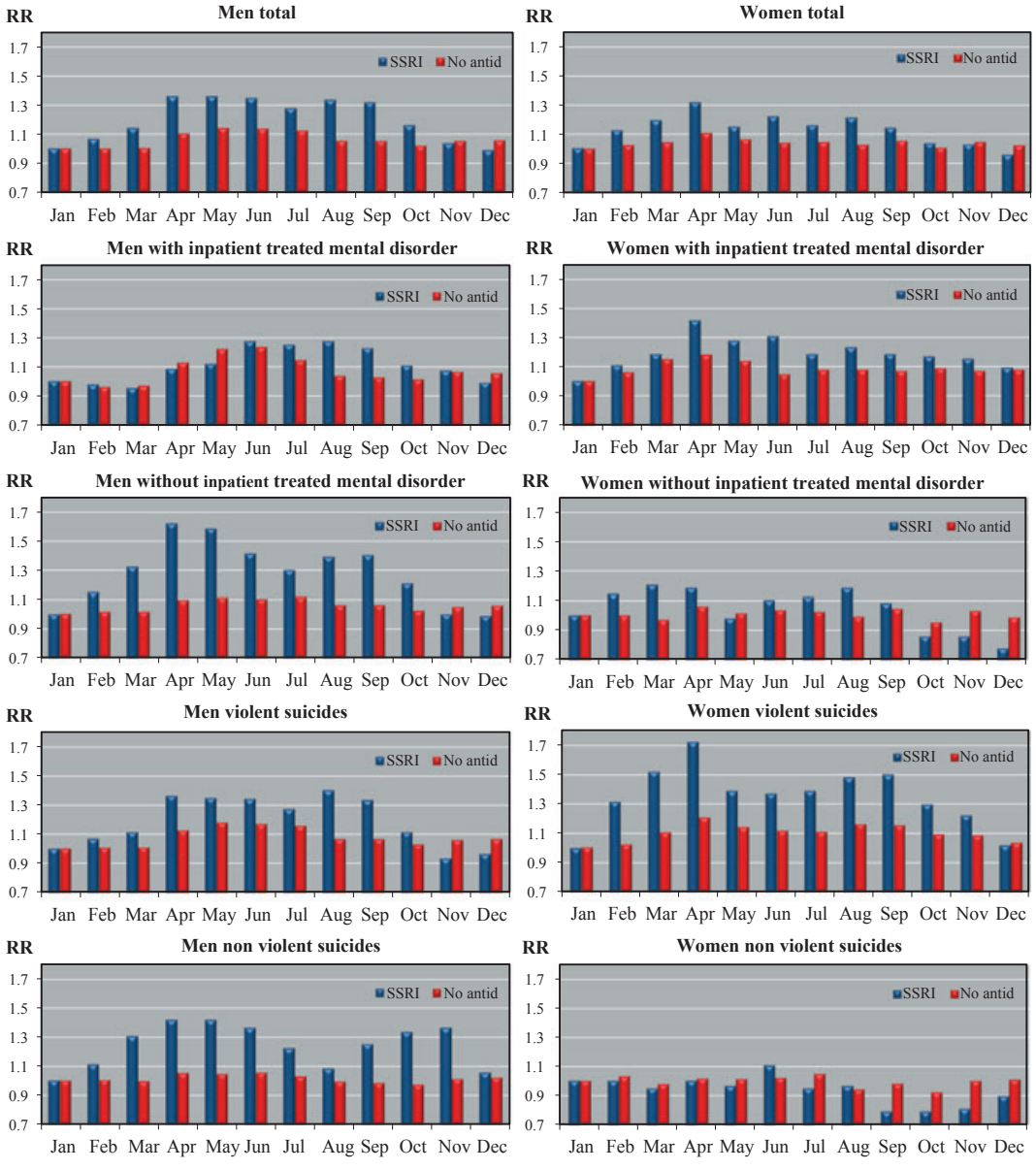

Fig. 1. Three-month moving average of the relative risk (RR) for suicide by month and treatment.

Results

There were 12 448 suicides with information about blood levels of antidepressants, month of death, sex, history of in-patient-treated mental disorder, and method of suicide in Sweden between 1992 and 2003. Of these, 9016 (72%) were men and 3432 (28%) women. Among men, 9% were positive for SSRI, 74% died by violent suicide method, and 33% were in-patient treated for at least one mental disorder during the last 5 years before suicide. Among women, 15% were positive for SSRI, 56% died by violent suicide method, and 50% were in-patient treated for at least one mental disorder during the last 5 years before suicide.

Figure 1 presents the 3-month moving average of the RR for suicide by month for those with positive screening for SSRI and those without any antidepressant and by history of in-patient-treated mental disorder, violent or non-violent suicide method, and gender.

There was a general pattern of an increased suicide incidence in late spring and summer in both men and women. Peaks in suicide incidence were found in June for men (RR = 1.14, $P < 0.001$) and in May for women (RR = 1.10, $P = 0.17$) (Table 1). Men with SSRI treatment were found to have a 42% increased suicide risk in June, compared with December (RR = 1.42, $P < 0.001$), whereas men with no-antidepressant treatment

Table 1. Suicide seasonality, expressed with the relative risk (RR) for suicide during the peak month compared to the month with the lowest suicide incidence, along with the 95% confidence intervals (CI)

	*N**,†	RR	CI‡	*P*-value	Peak month	Month CI§
Men						
Total	9016	1.14	1.08–1.20	<0.001	June	May–July
SSRI positive	819	1.42	1.00–1.65	<0.001	June	May–July
Other antidepressants	711	1.07	1.00–1.32	0.81	July	
No antidepressants	7366	1.12	1.05–1.20	<0.001	June	May–July
In-patient-treated mental disorder	2943	1.19	1.08–1.29	<0.001	June	May–August
SSRI positive	373	1.37	1.00–1.83	0.10	July	Jun–September
Other antidepressants	485	1.14	1.00–1.39	0.60	August	
No antidepressants	1992	1.20	1.00–1.33	0.01	June	May–July
No in-patient-treated mental disorder	6073	1.12	1.05–1.21	0.01	June	May–July
SSRI positive	446	1.56	1.19–2.03	<0.001	June	May–July
Other antidepressants	226	1.19	1.00–1.60	0.66	March	
No antidepressants	5374	1.10	1.00–1.16	0.06	June	May–August
Violent suicide	6696	1.18	1.00–1.24	<0.001	June	May–July
SSRI positive	631	1.49	1.00–1.86	<0.001	June	May–July
Other antidepressants	556	1.10	1.00–1.39	0.74	August	
No antidepressants	5416	1.16	1.07–1.25	<0.001	June	May–July
Non-violent suicide	2116	1.08	1.00–1.18	0.50	May	
SSRI positive	179	1.19	1.00–1.65	0.73	Jun	
Other antidepressants	146	1.23	1.00–1.95	0.67	Mar	
No antidepressants	1764	1.06	1.00–1.21	0.70	May	
Women						
Total	3432	1.10	1.00–1.18	0.17	May	
SSRI pos	514	1.27	1.00–1.62	0.17	May	
Other antidepressants	465	1.09	1.00–1.34	0.79	July	
No antidepressants	2372	1.05	1.00–1.15	0.70	May	
In-patient-treated mental disorder	1724	1.13	1.00–1.29	0.20	May	
SSRI pos	310	1.23	1.00–1.69	0.44	June	
Other antidepressants	340	1.16	1.00–1.48	0.61	May	
No antidepressants	1012	1.07	1.00–1.28	0.73	May	
No in-patient-treated mental disorder	1708	1.06	1.00–1.19	0.66	June	
SSRI pos	204	1.33	1.00–1.97	0.35	May	
Other antidepressants	125	1.34	1.00–2.21	0.51	September	
No antidepressants	1360	1.04	1.00–1.21	0.88	September	
Violent suicide	1909	1.17	1.00–1.30	0.05	June	May–July
SSRI pos	292	1.36	1.00–1.89	0.18	June	
Other antidepressants	287	1.21	1.00–1.57	0.54	June	
No antidepressants	1276	1.13	1.00–1.28	0.31	June	
Non-violent suicide	1419	1.09	1.00–1.26	0.55	April	
SSRI pos	213	1.27	1.00–1.87	0.74	April	
Other antidepressants	168	1.10	1.00–1.68	0.92	February	
No antidepressants	1012	1.06	1.00–1.26	0.82	April	

SSRI, selective serotonin reuptake inhibitor.

*Unspecified method' (ICD-9 E958 and ICD-10 X84) was included, which is why the total is higher than the sum of violent and non-violent methods.

†Suicide victims with positive screening for both SSRIs and other antidepressants were excluded from the analyses, which is why the total is higher than the sum of different antidepressants subgroups.

‡When the *P*-value is significant, the lower CI-limit is likely to be >1.00, but because of rounding effects, this is not apparent.

§Month CI presented for *P*-values <0.1.

were found to have a 12% increased suicide risk (RR = 1.12, $P < 0.001$). Men with other antidepressant treatment did not show a statistically significant seasonal pattern (RR = 1.07, $P = 0.81$). Direct comparison of the seasonal amplitude (RR) among men with SSRI treatment and those with no antidepressants yielded a statistical significant difference ($P = 0.02$). Women with SSRI treatment showed a trend of seasonality with peak incidence in May, although not statistically significant (RR = 1.27, $P = 0.17$).

Among men with a history of in-patient treatment for a mental health disorder, those with SSRI showed a statistically borderline significant seasonal pattern (RR = 1.37, $P = 0.10$), while those with no antidepressants had a statistically significant suicide peak (RR = 1.20, $P = 0.01$). On the other hand, men without history of in-patient treatment who were positive for SSRI showed the highest seasonal amplitude, with a 56% increased suicide risk in June (RR = 1.56, $P < 0.001$) compared to those without antidepressants

Table 2. Comparison of the amplitude of suicide seasonality, by estimating the ratio of the relative risk (RR1) for suicide during the peak month among suicide victims positive for SSRI, with the relative risk (RR2) for suicide during the peak month among suicide victims with no antidepressants, along with the *P*-value for this ratio (RR1/RR2). The method for comparing two samples for differential degree of seasonality was applied only among samples with a statistically significant seasonality; thus, results are presented only for men (total, no in-patient-treated mental disorder and violent suicide)

Men	RR1 (SSRI positive)	RR2 (no antidepressants)	Ratio = RR1/RR2	*P*-value
Total	1.42	1.12	1.27	0.02
No in-patient-treated mental disorder	1.56	1.10	1.42	0.08
Violent suicide	1.49	1.16	1.28	0.06

RR, relative risk; SSRI, selective serotonin reuptake inhibitor.

(RR = 1.12, $P = 0.01$). The difference in seasonal amplitude between these two groups was statistically significant ($P = 0.008$) (Table 2).

Among women with and without a history of in-patient-treated mental disorder, a trend for increased seasonality with SSRI treatment was observed, but the seasonality patterns in each of these groups were statistically very weak, and therefore, comparison of RRs between groups (SSRIs vs. no antidepressants) was not applied.

Suicides by violent methods presented significant peaks in June for both men (RR = 1.18, $P < 0.001$) and women (RR = 1.17, $P = 0.05$). Men with SSRI treatment had an increased seasonality for violent suicide (RR = 1.49, $P < 0.001$) compared to men without antidepressants (RR = 1.16, $P < 0.001$), and this difference was borderline significant ($P = 0.06$). Women with violent suicide methods did not show statistically significant seasonal peaks when stratified by treatment with SSRI (RR = 1.36, $P = 0.18$), other antidepressants (RR = 1.21, $P = 0.5$), or no antidepressants (RR = 1.13, $P = 0.31$). For non-violent suicides, no statistically significant seasonal peaks could be detected.

Discussion

In this study of all suicides in Sweden from 1992 to 2003, we found a higher seasonal variation in suicide for men treated with SSRIs compared to those with other antidepressant treatment or without any antidepressant treatment. The finding is more evident for violent suicide methods and those without history of in-patient treatment.

In our study, we observed an overall peak of completed suicides in spring–summer, which is in line with many other studies in countries with temperate climate (1–3, 5, 6, 36). Most studies show a gender difference with men having higher seasonality and one peak, while women may have a second suicide peak in fall (7, 37). Our results show also higher seasonality only among men, but the inherent limitation of our method to detect two peaks might be the reason of statistically non-significant results among women.

A central finding is that men treated with SSRI antidepressants show higher suicide seasonality compared to those with other- or no-antidepressant treatment. This might have multiple explanations.

One possible explanation is that people treated with antidepressants suffer from affective spectrum disorder that might have greater risk of seasonal suicide or that the increased suicide seasonality may reflect the nature and the seasonality of recurrence of the affective disorder. This is may be true, although the literature on the seasonality of recurrence in major depression is not consistent. In our study, analyses by specific in-patient diagnoses (e.g., major depression) were not performed because of the inadequate power to detect significant seasonal effects in such small subgroups. Other studies have shown higher suicide seasonality in individuals with a history of in-patient-treated major depression. Reutfors et al. (4), using the same statistical methodology and overlapping data set, found higher suicide seasonality for men with in-patient treatment for major depression (RR = 1.27). Postolache et al. (38) found higher suicide seasonality in both men and women with affective disorders with an approximately 20% increased suicide risk. The amplitude of suicide seasonality among men with SSRI treatment in our study was two-fold those reported in the above-mentioned studies and thus cannot be fully explained by the higher suicide seasonality among people with major depression. Moreover, the fact that suicide seasonality in individuals treated with other antidepressants was far lower or even missing compared to treatment with SSRIs does not support the explanation that higher seasonality is because of affective spectrum disorder *per se* or its natural seasonality and recurrence.

An alternative explanation might be that increased seasonality in SSRI group is because of severity of affective disorder or response failure. Again, if this was the case, then other antidepressants would have shown the same trend in seasonality, something that is not observed in our study. Moreover, if failure to respond to medication was a possible mechanism of increased seasonality, then in-patient-treated individuals would show higher seasonality assuming that refractory patient would be treated as in-patients. Our results show exactly the opposite, that is, that out-patients have higher seasonality.

A third explanation could be that this higher seasonality is because of a direct effect of SSRI. Possible mechanisms include the resolving of depression's psychomotor retardation, which may activate the patient to commit suicide before any mood improvement has occurred (39), the development of akathisia-like symptoms (40), and the short-term effects of SSRIs in impulse control and aggression. But several lines of evidence support that the absolute risk of suicide because of SSRIs is very low among older patients (21), and the number of saved lives because of antidepressive treatment has been considered far higher. Moreover, if we assume that this seasonal pattern is attributable only to SSRIs acute adverse effects, then suicide seasonality should coincide with a peak of SSRI prescription in spring. Data from the Swedish Drug Register (not shown here) on SSRI prescriptions redeemed from 2000 to 2003 indicate that there is a peak in prescription in autumn and winter. A recent report from the Netherlands with data on monthly SSRI prescription also indicates that the prescription peak of antidepressants takes place in winter (38). This raises the issue that SSRI's adverse effects alone cannot explain the spring peak of suicides and a more complex interaction between medication, endogenous neurotransmitter systems and climate is implicated.

Others would argue that seasonal affective disorder (SAD) might explain our finding of higher suicide seasonality among those treated with SSRIs. Although SAD symptoms are common (prevalence 4–10%) when populations are screened (i.e., with SPAQ), the diagnosis of SAD seems to be less common when diagnostic interviews are used (1.7%) (41). Winter SAD is much more common than spring SAD and affects more often women than men (42). Thus, it cannot explain the seasonal effect of suicide because in our study, the peak of suicide is in May–June, which is the period of symptom resolution for the majority of SAD patients. Additionally, if our finding was because of SAD, then women who are more commonly affected by SAD would show higher seasonality, which is not the case. There are no studies, to our knowledge, on the suicide risk among SAD patients, but if we assume that a proportion of SAD female patients who feel worse in autumn and winter actually commit suicide at that season, then this, at least in part, might explain the bimodal seasonality pattern among women.

The finding of statistically significant higher suicide seasonality amplitude in men with SSRI treatment but without in-patient treatment for mental disorders, during the 5 last years before suicide, deserves further investigation. These patients without psychiatric in-patient treatment were likely to have been prescribed an SSRI, either by a general practitioner in primary care or by a psychiatrist in an out-patient setting. The exact patterns of prescribing SSRI in Sweden in primary care vs. psychiatric out-patient care are not known, but it can be assumed that primary care is responsible for the majority of the prescriptions of SSRI in the general population, while psychiatric out-patient care takes care of patients after an in-patient period and other patients who need more advanced care. Under the assumption that SSRI can trigger suicidal behavior in susceptible individuals and that this phenomenon may be accentuated in specific seasons, a possible explanation for the higher suicide seasonality among those individuals could be that the majority of them received prescription of SSRI from primary care, where close follow-up is more difficult, and therefore, exacerbation of suicidal thoughts and behavior in the beginning of the treatment in spring or early summer may not have been captured on time.

The higher seasonal suicide variation among violent suicides and positive screening for SSRIs compared to violent suicides with no antidepressants is striking. A possible hypothesis can be that certain patients with affective spectrum disorder treated with SSRIs under a season of high serotonergic activity can result in an excess of suicidal and/or impulsive aggressive behavior. The alternative hypothesis of seasonal availability of means to commit suicide cannot explain the difference of seasonality between violent suicides with positive screening for SSRIs and violent suicides with no antidepressants.

Our overall finding of increased suicide seasonality in victims who were treated with SSRIs raises questions for the role of serotonin in suicide seasonality. A possible hypothesis may be that there is an accentuation of the natural suicide seasonality in patients treated with these antidepressants, owing to a possible additive effect of SSRIs upon the endogenous serotonin variation.

This is the first study to assess the association of suicide seasonality and antidepressants using data on the individual level. A recent study from Hungary reported an association between increasing prescription of antidepressants and decreasing seasonal variation in suicide over time (43). These results may seem contradicting to our findings, but there are a number of explanations why this is not necessarily the case. Sebestyen et al. used an ecological approach with no individual-based data, thus causality cannot be implied. Other known or unknown factors might have contributed

to the decreasing suicide seasonality apart from the increasing prescription of antidepressants. The suggested explanation of decreasing suicide seasonality because of decreasing depression-related suicides by the increasing of antidepressants utilization, although not indisputable, does not preclude that suicide seasonality may be accentuated in a subgroup of susceptible individuals among those who receive treatment with antidepressants. In our study with available individual-level forensic data, we have been able to show that this may be actually the case.

Assuming that an interaction between the endogenous circannual serotonergic system and the exogenously applied serotonergic agents may indeed occur in susceptible individuals, a challenging question could be if the interaction of season and antidepressant treatment might be another contributing susceptibility factor for suicidal triggering; something that so far has not been studied in the relevant literature.

The major strengths of this study are the size of the population included and the high quality of the registers that were used. This gave us the opportunity to analyze the data with regard to sex, i n-patient–non-in-patient treatment, violent–nonviolent suicide, and detection of SSRIs, other antidepressants or no antidepressants at the time of suicide. The fact that our data are population-based leads to the conclusion that the results are generalizable to other similar populations. Another advantage of this study is the statistical approach applied, which provides a sensitive estimate of the size of the seasonal peak together with a test of significance of the seasonal peak (34). The exclusion of suicides with toxic levels of antidepressants was considered advantageous because it is uncertain if those individuals were compliant to their antidepressant treatment or they just used it for the purpose of intoxication. In this way, we included individuals with therapeutic levels of antidepressants who were probably compliant up to the time of death.

Limitations include the lack of out-patient diagnoses from primary care and psychiatric settings and the lack of data on when the antidepressive treatment was initiated. Moreover, although our statistical method is very sensitive for the detection of one-peak seasonality patterns, it is not appropriate when two or more peaks are present. This limitation may have resulted in statistically nonsignificant results in women because other studies have reported that suicide seasonality varies with gender and women have a second peak in the fall (7).

In conclusion, our results provide support for the serotonergic hypothesis of suicide seasonality and raise the question of a possible accentuation of the natural suicide seasonality in patients treated with SSRIs. The additional clinical implications of an interaction between the endogenous circannual serotonergic system and exogenously applied serotonergic agents are yet to be studied.

Declaration of interest

None.

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