



Research paper

Season of treatment initiation with antidepressants and suicidal behavior: A population-based cohort study in Sweden



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A B S T R A C T

Background: Decreased binding capacity of SERT in the prefrontal cortex has been observed in both suicide victims and suicide attempters. Moreover, some studies have shown that SERT has a seasonal variation with lower binding capacity in the spring and summer, which coincides with a seasonal peak of suicides. Our aim was to explore whether the season of treatment initiation with antidepressants is associated with suicide or suicide attempt and compare it with the underlying suicide seasonality in the general population.

Methods: Using Swedish registers, patients who initiated treatment with an antidepressant were followed up to three months for suicidal behavior. Cox regression analyses were used. Results were compared with the underlying seasonal pattern by calculating standardized mortality ratios (SMRs) for suicides and standardized incidence ratios (SIRs) for suicide attempts.

Results: Patients aged ≥ 65 years had higher risk for suicide when initiating antidepressant treatment in the summer, and also a higher risk for suicide attempt when initiating treatment in the spring and summer. Young patients (0–24 years) presented a higher risk for suicide attempt when initiating treatment in the autumn. Patients with previous suicide attempt had a seasonal pattern, with a higher risk to carry out a suicide attempt in the summer and autumn. Results from the SMR and SIR calculations numerically support these findings.

Limitations: We used information of filling an antidepressant prescription as a proxy of actual antidepressant treatment. Patients with combination, augmentation therapy or those switching antidepressant during follow-up were excluded. Thus, our results refer to less complicated psychopathology.

Conclusions: Our results indicate an interaction between biological and health care-related factors for the observed seasonal pattern of suicidal behavior in the elderly, whereas psychological and societal factors may be more important for the seasonality observed in the younger patients.

1. Introduction

Antidepressants appear to exert their pharmacological action by enhancing serotonergic neurotransmission. Antidepressants have been exhaustively investigated in randomized clinical trials and in systematic meta-analyses. Such investigations have demonstrated their efficacy for the treatment of depressive and anxiety disorders, but also that they may have the potential adverse effect of triggering suicidal behavior (Jick et al., 2004; Juurlink et al., 2006; Martinez et al., 2005; Olsson et al., 2006; Stone et al., 2009).

Investigations suggesting that antidepressants, and more specifically selective serotonin reuptake inhibitors (SSRIs), trigger suicidal behavior were first reported in the 1990s (Teicher et al., 1990). Studies

thereafter reported conflicting results, with some finding no increased risk for suicide, regardless of treatment assignment (Beasley et al., 1991; Hammad et al., 2006; Khan et al., 2000; Storoosum et al., 2001), whereas others reported increased risk for suicide attempts and self-harm behaviors (Fergusson et al., 2005; Gunnell et al., 2005; Martinez et al., 2005). Later, a differential risk of antidepressant-induced suicidal behavior across the age spectrum was suggested, 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 (Martinez et al., 2005; Olsson et al., 2006; Stone et al., 2009). Several possible mechanisms have been suggested for how antidepressants may trigger suicidality, including the resolving psychomotor retardation in depression, which may activate the patient to commit suicide before any mood

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improvement has occurred (Nutt, 2003), the development of akathisia-like symptoms (Maris, 2002), the short term effects in impulsivity and aggression, as well as the poorly defined although clinically evident jitteriness/anxiety syndrome (Sinclair et al., 2009).

Moreover, a temporal association between antidepressants and suicide may be due to non-response to antidepressant treatment itself. Meanwhile, ecological studies have reported that a higher prescription of SSRIs is associated with lower suicide rates (Gibbons et al., 2005, 2006; Grunebaum et al., 2004; Isacson and Mathe, 2008; Milane et al., 2006).

Several lines of evidence from postmortem studies of suicide victims, as well as in vivo imaging studies of suicide attempters, suggest that serotonergic neurotransmission is implicated in the suicidal process, possibly through a decreased serotonin transporter (SERT) binding in the prefrontal cortex (Arango et al., 1995; Leyton et al., 2006; Mann et al., 1996). A low concentration of the major serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid is known to be associated with suicidal behavior (Asberg et al., 1986). Suicidal or impulsive aggressive behavior in patients with mood or personality disorders has been associated with a low central serotonergic function in the limbic-hypothalamic brain regions (Coccaro, 1992).

Moreover, positron emission tomography and single-photon emission computed tomography studies in healthy and depressed individuals have reported that the SERT presents a seasonal variation pattern with increased binding capacity in winter and decreased capacity in the spring (Buchert et al., 2006; Matheson et al., 2015; Praschak-Rieder et al., 2008; Ruhe et al., 2009), although other researchers could not verify this specific finding (Cheng et al., 2011; Koskela et al., 2008). Such a seasonal pattern is suggested to be mainly driven by the short allele of SERT (Kalbitzer et al., 2010). If a seasonal variation of SERT binding capacity really exists, this variation coincides with the seasonal peak of suicide in the spring and early summer that has been reported in many ecological studies from different countries (Christodoulou et al., 2012). We have previously reported an increased seasonal pattern in suicide victims with positive forensic screening for antidepressants in blood at the time of suicide (Makris et al., 2013), which might also suggest a possible synergistic effect of other seasonal factors with antidepressants. Thus our hypothesis was that there would be a clear seasonal pattern in suicidal behavior among patients starting antidepressant treatment, which cannot be fully explained by the underlying seasonal pattern of suicides in the general population.

1.1. Aims of the study

The primary aim of this study was to assess the relationship between season of initiation of antidepressant treatment and the risk of suicide or suicide attempt. As a secondary aim, we examined the seasonal pattern of suicide among antidepressant initiators in relation to the seasonal pattern of suicide in the general population.

2. Methods

2.1. Data sources

Both individual based and aggregated data were obtained from the National Board of Health and Welfare and Statistics Sweden. The Swedish medical registers use a ten-digit national registration number (NRN), a unique personal identifier assigned to all Swedish residents, allowing accurate linkage between registers.

The National Patient Register (NPR) has nearly complete nationwide coverage for discharge diagnoses in both somatic and psychiatric settings in Sweden based on the International Classification of Diseases (ICD), with full coverage of all psychiatric inpatient care since 1987. Outpatient specialist visits, including psychiatric visits from both private and public caregivers, are included since 2001. Each record

includes admission and discharge dates, the main discharge diagnosis and secondary diagnoses.

The Cause of Death Register includes all individuals who died either in Sweden or abroad since 1952 and who were registered in Sweden at the time of death. The data are based on death certificates that provide information on date as well as underlying main and secondary causes of death using the ICD codes.

The Swedish Prescribed Drug Register contains individual-level information for all dispensed prescribed drugs in Sweden for the entire Swedish population since July 2005.

Aggregated data on monthly suicides and suicide attempts during the period July 2006 and December 2012 were also obtained from the National Board of Health and Welfare for the calculation of Standardized Mortality Ratios (SMR) and Standardized Incidence Ratios (SIR) in different seasons.

2.2. Inclusion and exclusion criteria

From the Swedish Prescribed Drugs Register, we initially identified 1 027 666 patients who filled a prescription of at least one antidepressant between July 2006 and December 2012. Patients who had filled a prescription of antidepressants (N06A), antipsychotics (N05A) or antiepileptics (N03A), or who had been admitted to a psychiatric department during the year prior to inclusion were excluded. Some 12 532 patients were excluded because they had a prescription of antipsychotics or mood stabilizers at the same time as the prescription of antidepressants. An additional 202 patients were excluded because the date of dispense was after the date of death. Finally, 224 patients were excluded because of invalid information in the prescription register. After exclusions, the total population comprised of 1 014 708 patients. We divided the total population into four groups according to seasons of treatment initiation (autumn: September–November, winter: December–February, spring: March–May and summer: June–August) and followed them up to three months for suicide or suicide attempt. During the three-month follow-up, 411 patients were censored because they moved from Sweden and 99 397 were dispensed afterwards another of the above mentioned drug groups (N03A, N05A, N06A) and were therefore censored at that time.

2.3. Calculation of SMR and SIR

In order to compare with the underlying seasonal pattern in completed and attempted suicides, we calculated the standardized mortality ratios (SMRs) for suicides and the standardized incidence ratios (SIRs) for suicide attempts among those starting an antidepressant treatment. We divided the observed suicides and suicide attempts among those starting on antidepressants in each season in our study population with the expected number, which was calculated by multiplying the age- and sex-specific rates from the general population with the corresponding contributed person-time for each season.

2.4. Exposure measure

Season of treatment initiation with an antidepressant agent.

2.5. Outcome measures

Suicide or suicide attempt (ICD-10 codes: X60–X84, Y10–Y34) during the three-month follow-up.

2.6. Follow-up

For patients who began treatment in a specific season, we assigned an exposure of that season and followed them for up to three months until outcome, loss-to-follow-up, or end of season, whichever occurred first.

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