Somatic disorders and antidepressant use in suicides: A population-based study from the Friuli Venezia Giulia region, Italy, 2003-2013

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Abstract

Background: Many somatic disorders are complicated by depression and increase the risk of suicide. Little is known ~~about the~~ whether antidepressants might reduce the ~~role that antidepressant treatment might play in decreasing~~ suicidal risk in patients with somatic disorders.

Methods: Data on diagnoses and antidepressant prescriptions were derived from the Social and Health Information System of the Friuli Venezia Giulia (FVG) Region. Cases were all suicides that occurred in the region during the years 2003-2013 and were sex- and age-matched to controls from the general population. Conditional logistic regression analysis was used to assess the association between suicide and somatic disorders.

Results: The suicide rate in FVG decreased from 11.3 to 10.7 per 100,000 inhabitants during years 2003-2013. The risk of suicide increased almost 3-fold in suicide cases with ~~any~~ somatic disorders. ~~The highest risk was carried by respiratory disorders.~~ Elderly somatic patients were at twice as high risk as compared to younger patients. The risk ~~was~~ increased from 2.6 to 9.8 times ~~by~~ as the number of comorbid disorders increased. Although no significant risk of suicide in patients with somatic disorders was found when patients were adherent to antidepressant treatment, only 11.5% of the ~~in 10~~ suicides was adequately treated in the year prior to death.

Conclusions: ~~Recent s~~Severe medical illnesses and underlying depressive symptoms may have a synergy effect on the risk of ~~subsequent~~ suicide, particularly in older patients and in patients with multiple morbidities. Since medically ill subjects adherent to antidepressant treatment did not show a significant risk of suicide, early identification and adequate treatment of depression in somatic patients should be considered a suitable strategy in order to prevent suicide.

KEY WORDS

Suicide, Somatic Disorders, Antidepressants, Case-control

Introduction

Many somatic disorders, particularly neoplasms, are known to increase the risk of suicide. Few comprehensive population-based studies, however, have investigated a broad range of somatic risk factors of suicide at an individual level (1-4). Some studies focused only on suicides among the elderly (5-8) and one study focused on suicides among the young (9). Moreover, underlying depression has been shown in patients with somatic disorders such as cancer (10, 11), stroke (12), neurological disorders (13), myocardial infarction (14-16), gastrointestinal diseases (17), cirrhosis (18), chronic obstructive pulmonary disease (COPD)(19), endocrine disorders (20), and musculoskeletal disorders (21). Such patients might benefit from antidepressant medication. Fluoxetine has been shown to be effective in reducing depressive symptoms among patients with HIV, stroke, and diabetes (22). A potential role of antidepressants in preventing suicide has been suggested in depressed patients with cancer (23, 24), neurological disorders (13), stroke (12) and after myocardial infarction (25). It is not established, however, whether antidepressants can reduce the risk of suicide in patients with somatic illnesses.

The aim of the present study was to explore the main demographic and somatic risk factors of suicide, to describe the prescription patterns and adherence to antidepressant treatment in suicides and controls, and to explore whether antidepressant treatment can decrease the risk of suicide in patients with somatic disorders.

Material and methods

Study design and subjects

A matched case-control design was used. The Regional Social and Health Information System (SISSR) was used to select cases and controls. The SISSR links data from different regional databases (i.e. the Death Register, the Hospital Discharge Register, and the Drug Prescription Register), using a unique anonymous key.
Cases were all suicides that occurred during an 11- year period (from 1st January 2003 to 31st December 2013) in the Friuli Venezia Giulia (FVG) Region, Italy. They were identified through the Death Register, which uses ICD-9 codes E95* and E98* for intentional self-harm and events of undetermined intent, as provided by the National Institute of Statistics (Istat) (26).
For each case, 10 controls were selected from the FVG general population by using incidence density sampling (27). Controls were matched for gender and year of birth and were alive at the time of suicide of their corresponding case (index date),
The time range for all registered variables was the 365 days prior to the index date.

Psychiatric and somatic diagnoses

The main in-patient diagnosis, recorded in the first position on the medical record on discharge from public hospitals or private hospitals covered by the Regional Health System, was obtained from the Hospital Discharge Register. In-patients diagnoses were recorded as ICD-9 codes. Out-patients diagnoses were not available.
Diagnoses were arranged into18 groups: affective disorders (codes 296, 300.4, 311); non-affective psychiatric disorders (codes 290-295, 297-300.3, 300.5-310, 312-319); infectious and parasitic diseases (codes 001-139); malignant neoplasms (codes140-208); benign neoplasm (codes 210-229); carcinoma in situ and neoplasm of uncertain or unknown behavior (codes 230-239); endocrine, nutritional and metabolic diseases and immunity disorders (codes 240-279); diseases of the blood and blood-forming organs (codes 280 -289); neurological disorders (codes 320-359): diseases of sense organs (codes 360-389); heart and vascular diseases (codes 390-459); diseases of the respiratory system (codes 460-519); diseases of the digestive system (codes 520-579); diseases

of the genitourinary system (codes 580-629); diseases of the skin and subcutaneous tissue (codes 680-709); diseases of the musculoskeletal system and connective tissue (codes 710-739); congenital anomalies (codes 740–759); and symptoms, signs, and ill-defined conditions (codes 780–799). Complications of pregnancy, childbirth, and the puerperium (codes 630–679); certain conditions originating in the perinatal period (codes 760–779); injury and poisoning (codes 800–999) and external causes of injury and supplemental classification (codes E and V) were not included in the definition of somatic disorders (1) and were not considered.

Antidepressant prescriptions

All antidepressant prescriptions filled in FVG in the 365 days prior to the index date were obtained from the Drug Prescription Register. These were prescriptions reimbursed by the National Health System (i.e. prescribed by a general practitioner or other public physician) and corresponded to more than 90% of all prescriptions (28). The retrieved data included the date of each prescription of antidepressants, as well as the number of packages and the volume (expressed in defined daily doses, DDD).

The medication possession ratio (MPR) ~~(29)~~ was used to assess adherence to antidepressant treatment, as indicated in previous studies (29, 30). MPR was defined as the proportion of days supply obtained during a specified time period, as provided by Andrade et al. (29). Since one DDD was assumed to cover one day of treatment and, consequently, the total number of DDD approximated the number of days of treatment, t~~T~~he MPR was calculated as:

$$\frac{\text{Total number of DDD in the 365 days prior to the index date}}{\text{365 days}} \times 100$$

~~One DDD was assumed to cover one day of treatment. The total number of DDD approximated the number of days of treatment.~~

Based on previous studies on adherence measures of various drugs (29), and antidepressants specifically (30), an individual was defined adherent to treatment when the MPR was ≥ 80%. An individual with an MPR ≤ 79% was defined as non-adherent. The individuals defined adherent to treatment, thus, were covered by antidepressants for at least 292 days during the 365 days prior to the index date.

Statistical analyses

Continuous variables were summarized using the median as a measure of central tendency and the range as a measure of dispersion, whereas dichotomous or categorical variables were tabulated into contingency tables. For categorical variables, the chi-square statistic (χ^2) was used to test the differences between observed and expected frequencies.

Conditional logistic regression analysis was used to assess the associations between outcome (suicide) and predictors (psychiatric and somatic disorders).

Crude and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were estimated from the logistic regression coefficients and their respective standard errors. A P-value (P) < 0.05 was set as the threshold for statistical significance.

Descriptive and inferential analyses were conducted using the statistical software SAS-Enterprise Guide 4.3 (SAS Institute Inc, Cary, NC, USA). Conditional logistic regression was estimated using the SAS procedure *PhReg*.

Results

The population of FVG was about 1.2 million in the years 2003–2013. The annual number of suicides was around 130 subjects during the study period. The suicide rate decreased from 11.3 per 100,000 inhabitants in 2003 to 10.7 per 100,000 inhabitants in 2013.
The total number of suicides during the study period was 1,308 and the number of controls was 13,080. The median age was 55.8 years (range = 12 - 98).
There were 746 cases (57%) aged between 0 and 59 years, 98 of whom (13%) were younger than 30 years, and 562 cases (43%) aged 60 years or older. The number of males was 957 (73.2%) and the number of females 351 (26.8%).

Psychiatric and somatic disorders

All psychiatric and somatic disorders were more common in cases than in controls (Table 1). Affective disorders were diagnosed in 4.7% of cases (N = 61) and in 0.1% of controls (N =15) with somatic disorders. Non-affective psychiatric disorders were diagnosed in 8.7% of cases (N = 114) and in 0.2% of controls (N = 24) with somatic disorders.
Affective disorders were 3-fold more prevalent in female cases than in male cases (16.5%~~; N = 58~~ vs 5.0%~~; N = 48; χ^2 = 45.7;~~ P < 0.001), whereas in controls they were twice as prevalent in females as in males (0.2%~~; N = 8~~ vs 0.1%~~; N = 13; χ^2 = NS~~).
Non-affective psychiatric disorders were more prevalent in female cases ~~(23.9%; N = 84)~~ than in male cases (23.9% vs 13.5%~~;; N = 48; χ^2 = 20.6;~~ P < 0.001), whereas among controls the prevalence was 0.4% in both genders ~~(N = 13 and N = 40, respectively; χ^2 = NS)~~.
Somatic disorders had a more equal gender distribution than psychiatric disorders. They were diagnosed in 53.6% ~~(N = 188)~~ of female cases and in 48.8% ~~(N = 467)~~ of male cases ~~(χ^2 = NS)~~, whereas in controls they were diagnosed in 25.9% ~~(N = 909)~~ of females and in 23.3% ~~(N = 2232)~~ of males (~~χ^2 = 9.3;~~ P < 0.005). A single somatic diagnosis and more than one somatic diagnosis in the 365 days prior to the index date were both more common in cases compared to controls ~~was found in 28% of cases and in 16% of controls, whereas more than one somatic diagnosis was found in 22% of cases and in 7.5% of controls~~ (Table 2). Cardiovascular, digestive and musculoskeletal disorders were the most common somatic disorders among both cases and controls (Table 1).
Both affective and non-affective disorders were about twice as prevalent in cases aged 0-59 years as in cases aged 60 years and over ~~(χ^2 = 19.4;~~ (P < 0.001). In contrast, somatic disorders were twice as prevalent in the older age group as in the younger age group ~~(χ^2 = 136.5;~~ (P < 0.001) (Table 3).

Antidepressants

In the 365 days prior to index date, antidepressants were prescribed to 40.9% of cases (N = 535) and to 6.2% (N = 810) of controls (~~χ^2 = 1700; P < 0.001~~). Gender distribution in cases was: 315 males ~~(32.9%)~~ and 220 females ~~(62.7%)(χ^2 = 94.1; P < 0.001~~). Gender distribution in controls was: 455 males ~~(4.7%)~~ and 355 females ~~(10.1%)(χ^2 = 127.0; P < 0.001).~~
Antidepressants were prescribed to ~~38.1% (N =~~ 284~~) of~~ cases in the age group 0-59 years, and to ~~44.6% (N =~~ 251~~)~~ in the age group 60 years and over ~~(χ^2 = NS)~~. Among controls, the ~~proportions~~ numbers were ~~5.0% (N =~~ 375) and ~~7.7 % (N =~~ 435~~)~~, respectively ~~(χ^2 = NS)~~.
The differences in the distribution of antidepressants were statistically significant when comparing genders (P < 0.001), but not age groups.
Adherence to antidepressant treatment was found in 11.5% ~~(N = 151)~~ of cases and in 1.5% of controls ~~(N = 195)~~. ~~Among cases, 7.4% of males (N = 71) and 22.8% of females (N = 80) were adherent to treatment (χ^2 = 54.4; P < 0.001), whereas among controls the proportions were 1.1% (N = 102) and 2.6% (N = 93), respectively (χ^2 = 43.9; P < 0.001).~~
Adherence to treatment differed significantly between males and females in both cases and controls (Table 4), but did not differ ~~significantly~~ between the two age groups.

The patterns of antidepressant prescriptions in relation to diagnoses are summarized in Table 54.

Conditional logistic regression models

The crude risk of suicide was almost 3-fold increased in individuals with somatic disorders (Model 1; Table 1). After adjusting for psychiatric disorders, 9 out of 16 specific somatic disorders increased the risk of suicide, with the highest risk associated with respiratory disorders (Model 2; Table 1).
After adjusting for psychiatric disorders, the risk of suicide was similar in females (OR = 3.0; 95% CI =2.3–3.9) and in males (OR = 3.1; 95% CI =2.7–3.7).
When specific somatic disorders were analyzed separately, neurological, genitourinary and dermatological disorders did not significantly increase the risk of suicide in females (data not shown), but diseases of the blood and blood-forming organs were associated with an increased risk (OR = 3.5; 95% CI = 1.1–11.6) only in females.
After adjusting for psychiatric disorders, somatic disorders increased the risk of suicide more than 4-fold in subjects aged more than 60 years, whereas they increased the risk of suicide only 2-fold in subjects aged 0-59 years (Table 3).
Respiratory and digestive disorders increased the risk of suicide in both age groups. Infectious and parasitic, cardiovascular, genitourinary, sense organs disorders (data not shown) and malignant neoplasms (OR = 2.2; 95% CI = 1.7–3.0) increased the risk of suicide in the older age group.
Neurological and dermatological disorders increased the risk of suicide only in the younger age group (data not shown ~~respectively OR = 2.2; 95% CI = 1.2–4.1 and OR = 2.1; 95% CI = 1.1–4.2~~).
The risk of suicide was further increased by the number of comorbid somatic diagnoses (Table 2).
After adjusting for psychiatric disorders, somatic disorders increased the risk of suicide ~~(3-fold)~~ only in subjects either not prescribed or non-adherent to antidepressant medication (OR = 2.8; 95% CI = 2.5–3.3). In adherent subjects, somatic disorders did not increase the risk of suicide (OR = 1.0; 95% CI = 0.7–1.5) (Figure 1). This difference by treatment status persisted when the analysis was applied to genders, age groups, and specific somatic disorders separately (data not shown).

Discussion

Our 11-year case-control study of all suicides in the FVG Region showed that both psychiatric and somatic disorders were strongly associated with death by suicide, although the magnitude of risk was somewhat weakened by the adjustment for psychiatric disorders, as previously observed (1-4). The risk also increased with the number of somatic comorbidities, consistent with the Danish findings by Qin et al.(1, 31).
In our study, affective as well as non-affective psychiatric disorders increased the risk of suicide almost 50 times, albeit only 4.7% and 8.7% of suicides hospitalized for somatic disorders was also hospitalized for affective and non-affective psychiatric disorders respectively. Thus, it is likely that psychiatric disorders, particularly depression, were underdiagnosed among the cases with somatic disorders, although depression has been indicated as underlying many somatic disorders (1, 10, 17-21, 25, 32). Since depression is considered one of the major risk factors for suicide (33), the treatment of depression appears an appropriate measure to prevent suicide (31, 34, 35). This notion is supported by our finding of a 3-fold increased suicide risk in somatic patients who were not prescribed or did not adhere to antidepressant treatment. This increased risk, however, was not observed in patients who adhered to treatment.
Nonetheless, we found that antidepressants were prescribed to 40% of suicides in the year prior to death, and only one-third of them were adherent to treatment. This fact was even more pronounced in males, whose adherence to antidepressants was less than 8%, compared to 23% in females. Low adherence to antidepressants was also found in suicides with a previous hospitalization for affective

disorders (57%). A low percentage of prescriptions is consistent with our previous findings from the same Region, although the period considered was the last 90 days of life (28).
The risk of suicide in subjects with somatic disorders was about the same in males and females, as also found by Qin et al.(1). The elderly, however, were at twice as high risk as the young, both in crude and adjusted analysis. This discrepancy between age groups has not been reported in other studies of hospitalized patients (1, 2). Nonetheless, in a psychological autopsy study from Italy (36), the authors observed that the rate of medical illness in older suicides was from three to six times higher as adult suicides and young adult suicides, respectively. Our finding of a more than 4-fold higher risk among medically ill in-patients older than 60 years, further ~~however~~, was similar to another study based only on elderly patients (5). Since suicide rates are generally higher among the elderly (28), these findings are of importance for suicide prevention.
Furthermore, we observed a significant increased risk in only 9 out of 16 diagnostic categories, in contrast to previous findings from Denmark, which showed an increased risk of suicide in all somatic diagnostic categories (1). An explanation for this may be that, in our study, the risk of suicide had been strongly influenced by a larger number of disorders associated with higher suicidal risk in given ICD-9 categories. In other categories, however, a similar distribution of less or more severe disorders may have diluted the risk of suicide. For instance, respiratory disorders carried the highest suicidal risk, which was increased by 2.5-fold and was somewhat higher than the Danish findings (1). This may be due to the high burden of chronic obstructive pulmonary disease (COPD) on the risk of suicide, as recently indicated in a large population-based study (37).
Furthermore, since cancer has been often indicated as an independent risk factor of suicide (2, 4, 38), we avoided the dilution of suicidal risk in cancer patients by analyzing malignant neoplasms separately from other neoplasms. We confirmed previous findings (2, 4, 38). However, in the analysis stratified by age groups, the risk of suicide remained significant only in the elderly, with an increase of more than 2-fold. The same risk of suicide was found by Miller et al. in a case-control study based on subjects older than 65 years (8).
Finally, our finding of a greater suicidal risk among subjects with unspecified symptoms, signs, and ill-defined conditions is noteworthy. We agree with Qin et al.(1), whose explanation was that a plethora of unexplained symptoms and signs may have often been somatizations associated with psychiatric disorders such as depression and anxiety.

Strengths and limitations

The strength of this population-based register study is that it compares data of all suicides occurred during 11-year period to matched controls from the general population. This avoids bias, such as information and selection bias (1, 5). To our knowledge, this is also the first study to investigate prescription patterns of antidepressants among somatic patients.
However, several limitations should be taken into account. Firstly, out-patient diagnoses were not available. We only considered diagnoses after recent discharges from hospital, representing severe psychiatric and somatic disorders, with a relatively high suicidal risk (1, 4, 16, 37, 39). According to previous findings, further, the risk of suicide in somatic out-patients was not pronounced when adjusted for clinical depression (3).
Secondly, only antidepressant prescriptions issued by GPs and other public physicians were available in the regional Drug Prescription Register. Patients can also receive prescriptions from private physicians or obtain free medication at hospitals, but this amounts to less than 10 % of the prescriptions (28). Thirdly, patients' compliance could not be directly assessed, but was estimated through prescription patterns. In addition, we did not assess whether the prescription was made before or after discharge from hospital. The period considered for discharge diagnoses as well as for prescriptions of antidepressants was the 365 days prior to index date and it might not be possible to determine whether depression or somatic disorders came first.

Fourthly, we were not able to adjust our analysis for many factors of possible or probable importance for suicidal behavior, such as socio-economic status. Further, we were not able to assess whether suicide methods, particularly antidepressant poisoning, may had had an impact on our results.
Finally, the low number of subjects in some somatic diagnostic categories did not allow stratified analysis in specific age groups within genders and in antidepressant users, due to the low cell sizes and the consequent loss of statistical power.

Conclusions

Somatic disorders are associated with an increased risk of suicide, which to a large extent, but not totally, is mediated by depression. Clinicians, thus, should be aware of this when discharging patients from hospital, particularly in the case of older patients and patients with multiple morbidities. In order to better integrate hospital care and primary care, general practitioners should also be involved, after the patient's discharge, since adequate treatment of depression in primary care settings has been shown to be crucial in suicide prevention (40-42). This may be demonstrated by our finding that the risk of suicide was not increased among the subjects who were adherent to antidepressants treatment. This information is of particular concern, since only 1 in 10 suicides was adequately treated in the year prior to death.
Nonetheless, more investigations are needed to better assess the suicidal risk in specific somatic disorders. Research is also needed to better establish whether an adequate treatment of depression through antidepressant medication is a key issue in suicide prevention among somatic patients.

Competing Interest Statement

The authors have no competing interests to report

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