Discontinuation of antidepressants in suicides findings from the Friuli Venezia Giulia Region, Italy, 2005-2014

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Abstract

Although continued use of antidepressants (AD) has been found to be associated with a lower risk of suicide, AD discontinuation is reported repeatedly. The aim of this case-control study, thus, was to assess whether discontinuation to AD was associated with an increased risk of suicide, according to different genders and age groups. The Social and Health Information System of Friuli Venezia Giulia Region, Italy, was used to collect data on suicides, diagnoses and AD use from 2005 to 2014. We selected, as cases, all suicides that had at least one prescription of AD in the 730 days before death (N = 876), and we matched with regard to age and sex each case with five controls from the general population. Conditional logistic regression analyses were used to assess the association between suicide and modifications of AD treatment. We found that 70% of suicides and controls from the general population discontinued AD in the 2 years before the index date. In two-thirds of them, discontinuations were two or more. Discontinuation of AD, however, did not represent a significant risk factor for suicide. More appropriate care of depression, particularly by primary care physicians who widely prescribe AD, should be fostered in order to prevent suicide. However, more research is needed to assess to which extent AD discontinuation can affect suicidal risk.

KEYWORDS
antidepressants, case-control, discontinuation, drug utilization, suicide

1 | INTRODUCTION

Suicide prevention is a public health priority, since suicide accounts for 1%-4% of global mortality.[1] Depression has been indicated as one of the main risk factors behind suicide.[2] A logical consequence for prevention of suicide, thus, should be to identify and treat individuals with depressive disorders through health interventions, which include antidepressant medication.[3] Although the efficacy of antidepressants in major depressive disorders has been demonstrated in several clinical trials,[4] inappropriate use in clinical practice has been reported.[5] Antidepressant discontinuation, for instance, has been reported repeatedly.[6-12] Furthermore, several studies observed that depression often remains untreated in suicidal individuals.[13-17] Conversely, observational studies from many countries observed that suicide rates decreased in parallel to an increase of antidepressant prescriptions.[3,18] Moreover, studies at the individual patient level found that continued use of antidepressants was associated with a lower risk of suicide deaths.[19-22] In our previous studies from Friuli Venezia Giulia region, Italy, we found an inverse association between continuous use of antidepressants and suicide risk,[23] as well as a decreasing trend of suicide risk, when

subjects were adherent to antidepressant medication.[17,24] Nonetheless, a better focus on the effect of antidepressants on suicide risk using qualitative parameters had been claimed.[17] In this regard, it appears important to assess whether discontinuation to antidepressants can affect suicide risk. Further, it is crucial to explore suicide risk patterns according to the use of antidepressants in different genders and age groups, since important differences in antidepressant utilization have been observed in women compared to men, as well in older age groups compared to younger age groups.[9,12,25-27]

The aim of the present case-control study was to assess whether discontinuation to antidepressants is associated with an increased risk of suicide, according to different genders and age groups.

2 | MATERIAL AND METHODS

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[28]

2.1 | Selection of cases and controls

The Regional Social and Health Information System (SISSR) of the Friuli Venezia Giulia (FVG) Region, Italy, was used to select cases and controls. A unique anonymous key is used by SISSR for the data linkage of different regional databases (the Death Register, the Hospital Discharge Register and the Drug Prescription Register).[17,24]

All residents in the region who died by suicide from 1 January 2005 to 31 December 2014 were identified from the Death Register using ICD-9 codes E95* and E98* for intentional self-harm and events of undetermined intent. To be selected as cases, subjects who committed suicide had to receive at least one prescription for an antidepressant during their last 730 days of life. Five controls from the FVG general population were matched, using incidence density sampling method,[29] by gender and year of birth to each case. Additionally, controls had to be alive at the date of suicide of their corresponding case (index date) and had to have been dispensed at least one antidepressant in the 730 days prior to the index date.

2.2 | In-patient diagnoses

The main in-patient diagnoses were identified from the Hospital Discharge Register, in case suicides and controls had been hospitalized during the 730 days prior to the index date. As in our previous study,[17] we only used diagnoses recorded in the first position on the medical record on discharge from public and private hospitals covered by the Regional Health System. They were arranged into three groups, according to ICD-9 codes: affective disorders (codes 296, 300.4, 311); non-affective psychiatric disorders (codes 290-295, 297-300.3, 300.5-310, 312-319); and somatic disorders (codes 001-289; 320-629; 680-759; 780-799). Complications from 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 considered and consequently excluded from further analyses.

2.3 | Antidepressant discontinuation and other treatment modifications

All prescriptions for antidepressants filled in FVG during the 730 days prior to the index date were included in the study. Prescriptions are reimbursed by the National Health System, if prescribed by a general practitioner (GP) or other public physician. They cover more than 90% of all antidepressant prescriptions in the region.[14] In the present study, retrieved prescriptions included the date, the number of packages, the volume (expressed in defined daily doses, DDD) and the antidepressant substance name according to its ATC code.[30]

Four classes of antidepressants were then merged and used in the study: tricyclic antidepressants (TCA; ATC code N06AA), selective serotonin reuptake inhibitors (SSRI; N06AB), serotonergic-noradrenergic reuptake inhibitors (SNRI; N06AX21, N06AX16) and "other" antidepressants (N06AX49, N06AX12, N06AX11, N06AF03, N06AX03, N06AX18, N06AX05).

The total number of prescriptions and the dispensed volume of each antidepressant were analysed in order to assess modifications of treatment, namely discontinuations, combinations and switches.

Discontinuation of antidepressants was assessed by analysing each patient's dispensing time-line applying two conditions:

1. The total number of DDD supplied in each prescription for an antidepressant class was not sufficient to cover the time up to the next prescription;
2. A gap lower than 31 days, starting from the last day covered by the DDDs supplied at the index prescription, until the date of next prescription for an antidepressant, was allowed.

A sensitivity analysis was performed to assess the effect of changing the gap to define discontinuation, that is, assessing 15, 45, 60 and 90 days.

Discontinuation was assessed for each antidepressant class. Type of antidepressant discontinuation was further

obtained, with regard to each class and to more than one class (ie, discontinuation of SSRI plus SNRI or discontinuation of SSRI plus TCA and so on).

Moreover, it was determined whether a subject was discontinuing antidepressants during the 90 days before the index date.

We also assessed the number of other treatment modifications:

1. Switch of antidepressant, defined as the discontinuation of an index antidepressant and the dispensing of a prescription of another specific antidepressant. A gap up to 31 days, starting from the last day covered by the DDDs supplied at the index prescription, until the date of prescription for the new antidepressant, as well as an overlap of the two drugs up to 31 days, was allowed.[7]
2. Combination of antidepressant prescriptions, defined as the duration of prescription for the index antidepressant overlapping the duration of prescription of a second antidepressant for more than 31 days.[7]

Figure 1 summarizes the evaluation of discontinuations, combinations and switches.

Finally, we assessed for each individual the duration of treatment, calculated as the time elapsed from the date of first to the date of last prescription for an antidepressant.

2.4 | Antidepressant data processing

Algorithms developed for interval temporal reasoning in artificial intelligence[31,32] were used to process data for discontinuations, combinations and switches. Data were reorganized for each patient as a sequence of intervals, corresponding to the temporal duration of different prescriptions, computed using DDD information available in the dataset. We then inspected these temporal data and extracted, for each patient, the presence and duration of discontinuation events, filtering them for minimum length (a parameter we varied for sensitivity analysis). We further identified all events corresponding to a change in therapy, distinguishing only different classes of drugs.

2.5 | 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 are tabulated into contingency tables. For continuous variables (ie, number of antidepressant prescriptions), Mann-Whitney test was used to test the differences between means. 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 (discontinuation,

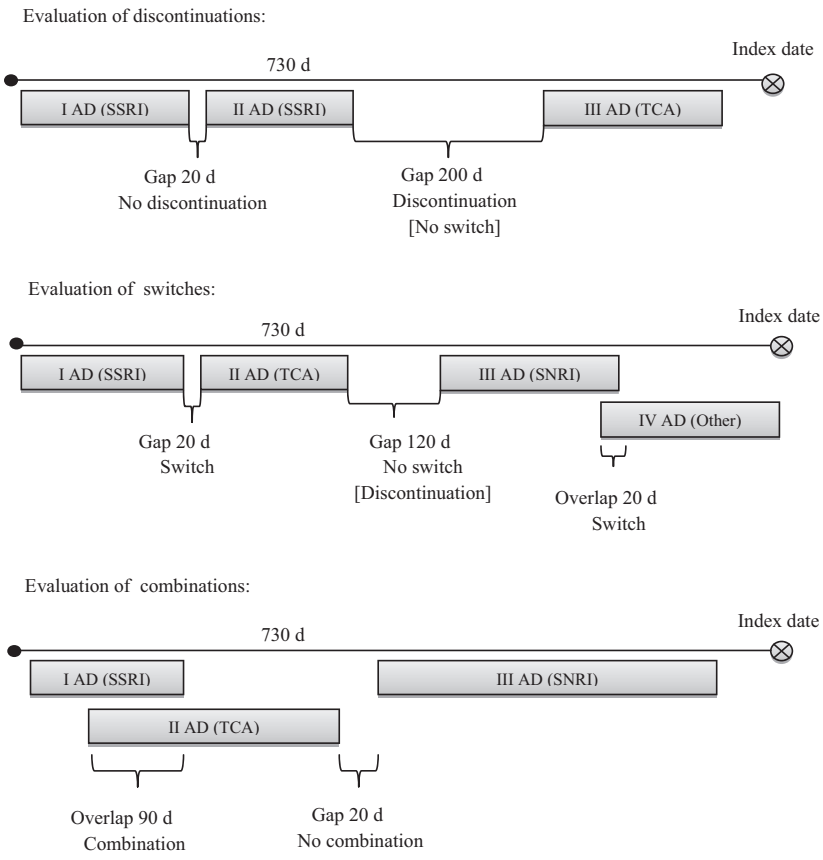

FIGURE 1 Schematic examples for describing the evaluation of discontinuations, switches and combinations. Each bar represents the number of DDDs supplied at each prescription. AD, antidepressants; DDD, defined daily doses; Other, "other" antidepressants; SNRI, serotonergic noradrenergic reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants

suicide) and predictors (time from first antidepressant prescription to index date, antidepressant discontinuation).

Crude and adjusted odds ratios (OR) and 95% confidence intervals (95% C.I.) were estimated from the logistic regression coefficients and their respective standard errors. ORs were adjusted for gender, age, hospital diagnoses, length of treatment and antidepressant treatment modifications. A *P*-value (P) < 0.05 was set as the threshold for statistical significance. Stratified analyses were performed according to male and female gender and age groups (0-59 and ≥60 years).

Descriptive and inferential analyses were conducted using the statistical software Stata/SE (version 13.1).

3 | RESULTS

Three-hundred thirty-two women and 928 men committed suicide in FVG during the years 2005-2014, while individuals older than 60 years of age were 527 and younger were 733. The percentage of suicides treated with antidepressants was more than 80% in women and in persons older than 60 years, while it was around 60% in men and in younger persons.

3.1 | Prescriptions of antidepressants

Overall, the mean number of prescriptions filled in the 2 years before the index day was 14.3 in cases (median = 10; range = 1-138) and 10.6 in controls (median = 6; range = 1-98; Mann-Whitney test (P) < 0.001).

As shown in Table 1, significant differences were found when genders and age groups were compared with regard to the mean number of prescriptions.

Selective serotonin reuptake inhibitors accounted for more than 90% of the prescriptions in cases and in controls, in all genders and age groups.

3.2 | Antidepressant discontinuation

Overall, 241 cases (27.5%) discontinued antidepressant treatment once during the 2 years prior to death, and 388 cases (44.3%) discontinued treatment twice and more, while controls were 938 (21.4%) and 2079 (47.5%), respectively ($\chi^2(P) < 0.001$). SSRIs accounted for 75% of discontinuations in both cases and controls.

The proportion of subjects who discontinued antidepressants was higher among SSRI users, varying from 75% to 55%, with regard to cases and controls of different gender and age groups. Lower proportions of discontinuations were found in subjects prescribed other antidepressant classes (Table S1).

In the 90 days prior to suicide, 65 women (24.4%) and 145 men (23.8%) discontinued antidepressants ($\chi^2(P)$ = NS), while suicides aged 0-59 years were 82 (19.9%) and suicides aged 60 years and older were 128 (27.6%; $\chi^2(P) < 0.05$). SSRI accounted for more than 90% of discontinuations, in all genders and age groups.

3.3 | Other antidepressant treatment modifications

Almost half of female and male cases modified antidepressant treatment during the 2 years prior to the index date, while this proportion was greater in male controls than female $\chi^2(P) < 0.05$). The older age group was more likely to modify antidepressant treatment than the younger age group in both cases and controls ($\chi^2(P) < 0.001$; Table 2).

3.4 | Psychiatric and somatic diagnoses

Among cases, 6% were diagnosed with affective disorders, 12% with non-affective psychiatric disorders and 44% with somatic disorders. Controls were 0.3%, 1.4% and 53%, respectively.

TABLE 1 Numbers (N), mean, standard error, median and range of antidepressant prescriptions in suicides and controls during the 730 d prior to the index date

	Suicides				Controls			
	N. of patients with AD prescriptions	Mean n. of AD prescriptions	Median n. of AD prescriptions	Range n. of AD prescriptions	N. of patients with AD prescriptions	Mean n. of AD prescriptions	Median n. of AD prescriptions	Range n. of AD prescriptions
Females	268	16.1	11	1-138	1340	9.6	5	1-71
Males	608	13.4	9	1-94	3040	11.0	6	1-98
Mann-Whitney test (P)	<0.001				<0.05			
Age group 0-59	412	9.4	5	1-60	2073	5.6	3	1-67
Age group ≥60	464	18.6	14	1-138	2307	15.1	11	1-98
Mann-Whitney test (P)	<0.001				<0.001			

AD, antidepressants; N, numbers.

TABLE 2 Numbers (N), percentages (%), crude and adjusted odds ratio (OR) and 95% confidence intervals (95% C.I.) of suicide in antidepressants users in the 730 d prior to index date, according to psychiatric and somatic in-patient diagnoses, antidepressant treatment modifications and discontinuations

	Cases		Controls		Crude suicide risk		Adjusted suicide risk[a]	
	N	%	N	%	OR	95% C.I.	OR	95% C.I.
Females								
Affective disorders	32	11.9	4	0.3	**52.4**	**16.0-171.1**	**28.8**	**8.2-101.1**
Non-affective disorders	49	18.3	22	1.6	**13.0**	**7.6-22.4**	**8.7**	**4.7-16.2**
Somatic disorders	122	45.5	683	51.0	0.8	0.6-1.0	**0.7**	**0.5-0.9**
Time from first to last AD prescription ≥270 d	202	75.4	868	64.8	**1.8**	**1.3-2.5**	1.3	0.8-2.1
Treatment modifications[b]	134	50.0	454	34.0	**2.1**	**1.6-2.8**	**1.8**	**1.3-2.6**
Discontinuations	203	75.5	941	70.2	1.3	1.0-1.8	1.0	0.6-1.5
Males								
Affective disorders	21	3.4	9	0.3	**12.8**	**5.7-28.9**	**5.8**	**2.4-14.1**
Non-affective disorders	58	9.5	40	1.3	**7.6**	**5.0-11.5**	**6.5**	**4.2-10.1**
Somatic disorders	267	43.9	1638	54.0	**0.5**	**0.5-0.8**	**0.5**	**0.4-0.7**
Time from first to last AD prescription ≥270 d	416	68.4	1974	64.9	1.2	1.0-1.4	1.0	0.7-1.4
Treatment modifications[b]	282	46.4	1164	38.3	**1.5**	**1.2-1.8**	**1.4**	**1.2-1.8**
Discontinuations	426	70.1	2076	68.3	1.1	0.9-1.3	1.1	0.8-1.4
Age group 0-59								
Affective disorders	34	8.2	6	0.3	**33.4**	**13.1-85.5**	**18.4**	**6.3-53.2**
Non-affective disorders	71	17.2	23	1.1	**19.9**	**11.7-33.8**	**16.4**	**9.3-29.0**
Somatic disorders	135	32.8	856	41.3	**0.7**	**0.5-0.8**	**0.5**	**0.4-0.7**
Time from first to last AD prescription ≥270 d	232	56.3	967	46.6	**1.5**	**1.3-1.9**	1.0	0.7-1.5
Treatment modifications[b]	144	34.9	420	20.3	**2.2**	**1.7-2.8**	**1.9**	**1.5-2.6**
Discontinuations	258	62.6	1157	55.8	**1.4**	**1.1-1.7**	1.1	0.8-1.6
Age group ≥60								
Affective disorders	19	4.1	7	0.3	**15.4**	**6.1-38.6**	**8.1**	**3.0-21.5**
Non-affective disorders	36	7.8	39	1.7	**4.7**	**2.9-7.4**	**3.3**	**2.0-5.6**
Somatic disorders	254	54.7	1465	63.5	**0.7**	**0.5-0.8**	**0.6**	**0.5-0.8**
Time from first to last AD prescription ≥270 d	386	83.2	1875	81.3	1.2	0.9-1.5	1.0	0.7-1.5
Treatment modifications[b]	272	58.6	1198	51.9	**1.3**	**1.1-1.6**	**1.3**	**1.1-1.7**
Discontinuations	371	80.0	1860	80.6	1.0	0.7-1.2	0.9	0.7-1.3

Statistically significant ORs are highlighted in bold.

AD, antidepressant.

[a]Adjusted for affective psychiatric disorders, non-affective psychiatric disorders, somatic disorders, time from first to last AD prescription and treatment modifications.

[b]Switches and combinations.

Number and proportions of diagnoses with regard to genders and age groups are summarized in Table 2.

3.5 | Conditional regression analyses

As summarized in Table 2, in the adjusted analyses, discontinuation did not significantly affect suicide risk in all genders and age groups.

No differences in suicide risk were observed when the analysis was stratified per type of discontinuation (ie, SSRI, SNRI, TCA, other antidepressants and more classes of antidepressants; data not shown).

In crude and adjusted analyses, the risk of suicide was significantly increased by treatment modifications in both genders and age groups (ORs varying from 2.0 to 1.4 in adjusted analyses; Table 2).

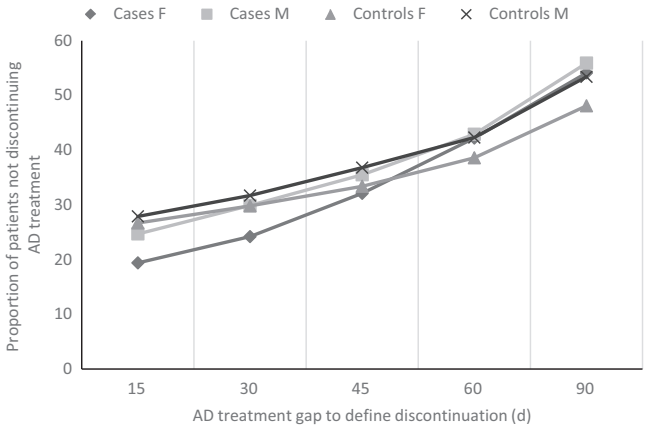

FIGURE 2 Proportions of male and female cases and controls who did not discontinue antidepressant treatment during the 730 d prior to the index date. Sensitivity analysis of different gaps defining discontinuation of treatment

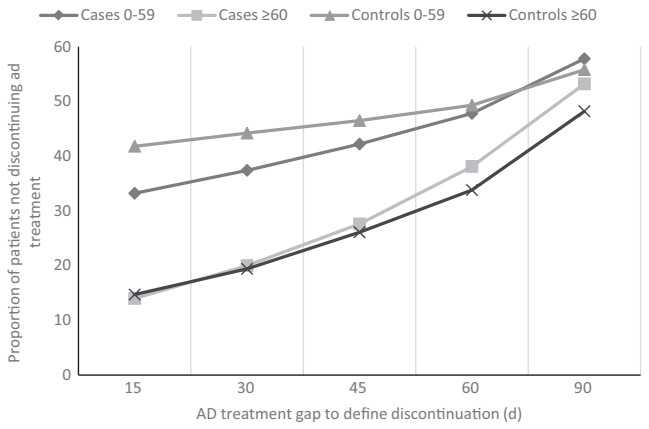

FIGURE 3 Proportions of cases and controls aged 0-59 y and 60 y and older who did not discontinue antidepressant treatment during the 730 d prior to the index date. Sensitivity analysis of different gaps defining discontinuation of treatment

3.6 | Sensitivity analysis

As summarized in Figures 2 and 3, a longer treatment gap to define discontinuation would increase the estimated proportion of subjects remaining on antidepressant treatment in both cases and controls. Nonetheless, this relation did not change the association between discontinuation of antidepressants and suicide risk, which was still found non-significant in all genders and age groups (data not shown).

4 | DISCUSSION

4.1 | Antidepressant prescriptions

Antidepressants were more dispensed to females and to older subjects, consistent with international findings and previous findings from the region.[12,14,24,25,33] Moreover, differences between genders and age groups were found with regard to the mean number of prescriptions, with suicides in the older age group having filled the greatest number. However, subjects older than 60 years were more likely to discontinue antidepressant treatment compared to younger subjects, in contrast to previous findings.[7,9] An explanation for this may be that elderly may have been dispensed with lower doses of antidepressants and, consequently, a lower number of DDDs, which might have affected the discontinuation gaps.[34]

The antidepressant class most commonly dispensed was SSRI, in line with international and Italian literature.[6,10,22,27,35,36]

4.2 | Antidepressant discontinuation and suicide

In the present study, we demonstrated that 70% of suicides and controls from the general population discontinued antidepressant treatment in the 2 years before the index date. In two-thirds of them, the number of discontinuations was two or more. Further, one in four suicides discontinued antidepressants in the 90 days prior to death. Discontinuation of antidepressants has been reported repeatedly, with proportions varying from 20% to 75% according to the study period considered, the definition of discontinuation (ie, using treatment gaps or only treatment abandonment), the type of subjects included (ie, patients with a depressive disorder or general population) and the class of antidepressants considered.[6,8-11] Serna,[10] for instance, observed that 75% of subjects in their cohort discontinued treatment after 11 months, consistently with our findings. An Italian study,[6] however, found that only 27.5% of antidepressant users discontinued treatment during 1-year follow-up. We found a proportion of discontinuations in controls from the general population three times higher, compared to this previous study. Since most of prescriptions in FVG are filled by general practitioners (GPs),[17] we agree with Trifiro et al[6] that reasons for discontinuation may be a lower awareness of GPs in following clinical practice guidelines, as well as a higher tendency of filling inappropriate prescriptions for vague symptoms. Interestingly, we also found that about 40% of controls modified treatment during the study period, which may reflect a general difficulty by GPs in identifying a beneficial medication. Differently, the high percentage of discontinuations and treatment modifications found in suicides may be explained by the fact that many of them may be resistant to antidepressants, as previously observed.[17] In support of this hypothesis, treatment modifications were an independent suicidal risk factor in both genders and age groups.

Further, few studies analysed whether antidepressant discontinuation can affect suicidal behaviour risk. A study

from the United States found an increased rate of suicidal behaviour after discontinuation of antidepressants.[37] Similarly, Valuck et al[38] observed a 60% increase of suicide attempts after antidepressant discontinuation. A Danish study,[15] however, did not find differences in suicide risk in subjects aged 50 years and over who discontinued antidepressant treatment compared to those who continued treatment. This was consistent with our results, which could not identify discontinuation as a significant risk factor for suicide in subjects of all genders and age groups.

In contrast to other studies,[7,9,34] SSRIs accounted for more than 70% of discontinuations. Treatment discontinuation may be related to different factors, such as a lack of effect or the onset of adverse effects, as well as patient compliance, which can be related to psychological reasons or interactions with doctors.[21,37,39,40] Further, a Danish study[11] had observed that the more GPs prescribed antidepressants, the more they were discontinued. GPs are more likely to prescribe SSRIs, due also to their safety in overdose compared to older antidepressants.[6,17] This prescribing pattern,[11] thus, might occur also in case of patients at a greater risk of suicidal behaviour.[37] Conversely, this may explain the lower discontinuation rate observed in the present study among TCA users compared to other antidepressant classes. Consistent to our study, however, Yerevanian et al[37] found no differences in suicidal behaviour risk when comparing SSRI and TCA discontinuation.

4.3 | Strengths and limitations

The main strength of this study is that it used population-level data from real-world subjects treated with antidepressants during a 10-year period. Further, several confounding factors were taken into account, such as gender, age, hospital diagnoses, length of treatment and antidepressant treatment modifications. Selection bias was minimized, since the study was based on register data of all suicides and matched controls derived from the regional population.[17,24] To our knowledge, this is also the first study analysing types of discontinuation within different antidepressant classes in suicides and controls, as well as discontinuation of antidepressant as independent risk factor for suicide in all genders and age groups.

A number of limitations, however, should be taken into account. Firstly, the case-control study design did not allow to analyse to which extent subjects dispensed antidepressants before the study period was started (ie, 730 days prior to the index date). Secondly, only antidepressant prescriptions issued by GPs and other public physicians were available from the health database, albeit we demonstrated that this constitutes 90% of the prescriptions.[14] Thirdly, actual adherence to treatment could not be assessed, as seen in the literature based on prescription registers.[7,9,10,21,23,24] Fourthly, we had no information on the reasons for discontinuation and treatment changes. Fifthly, our results could have been influenced by the treatment gap used to define discontinuation and the DDDs may not have been representative of the actual doses given. However, our additional sensitivity analysis, in which different lengths of treatment gap were considered, did not change the association between discontinuation of antidepressants and suicide risk. In this regard, it is noteworthy that the number of days without medication between fills had been demonstrated to improve the ability to predict antidepressant persistence.[41] Sixthly, some discontinuations may have been representing the conclusion of an adequate treatment for a proper length of time, which is set between 9 and 12 months after recovery.[42] Nonetheless, this seems to have influenced minimally our results, since only a small proportion of subjects were prescribed antidepressants for more than 9 months without discontinuation. Further, no differences in suicide risk were found in subjects discontinuing antidepressants, after adjusting for the duration of treatment. Seventhly, the database provided only diagnoses received at hospital and outpatient diagnoses were not available. As a consequence, an overestimate of suicide risk may have occurred, since inpatients are usually more severely ill.[17,24] On the other hand, an underestimate of depression as an indication for antidepressant may also have occurred.[17] However, a previous database study found that antidepressants are prescribed for depression in more than half of the cases.[43] Still, it cannot be excluded that there is residual confounding-by-indication potentially leading to lack of association between discontinuation and suicide. Finally, other limitations regarded the fact that we could not adjust the analyses for other factors, such as socio-economic features, as well as we had no information on suicide methods, like antidepressant poisoning.[17,24]

5 | CONCLUSIONS

Although we could not identify antidepressant discontinuation as an independent suicidal risk factor, our finding of three subjects out of four discontinuing treatment is of major interest. An adequate antidepressants treatment, in fact, is likely to be a crucial factor for preventing suicide.[15,17,37] In a number of studies, adherence to antidepressants was also associated with a decrease in suicide rates.[19-22] Further, the fact that other modifications of treatment were positively associated with suicide in all genders and age groups may indicate that more efforts are needed to monitor antidepressants in individuals who are likely to be treatment-resistant. Since antidepressants are widely prescribed by primary care physicians, our findings might suggest that GPs should be more aware when antidepressants are frequently combined or switched.

Notwithstanding the limitations, this study adds evidence that a more appropriate care of depression should be fostered in the prevention of suicide. More research is needed to assess to which extent antidepressant discontinuation can affect suicidal risk.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Zalsman G, Hawton K, Wasserman D, et al. Suicide prevention strategies revisited: 10-year systematic review. *Lancet Psychiatry*. 2016;3(7):646-659.
2. Isometsa E. Suicidal behaviour in mood disorders–who, when, and why? *Can J Psychiatry*. 2014;59(3):120-130.
3. Isacsson G. Suicide prevention–a medical breakthrough? *Acta Psychiatr Scand*. 2000;102(2):113-117.
4. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. 2018;391 (10128):1357-1366.
5. Ho SC, Chong HY, Chaiyakunapruk N, Tangiisuran B, Jacob SA. Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: a systematic review. *J Affect Disord*. 2016;193:1-10.
6. Trifiro G, Tillati S, Spina E, et al. A nationwide prospective study on prescribing pattern of antidepressant drugs in Italian primary care. *Eur J Clin Pharmacol*. 2013;69(2):227-236.
7. Milea D, Guelfucci F, Bent-Ennakhil N, Toumi M, Auray JP. Antidepressant monotherapy: a claims database analysis of treatment changes and treatment duration. *Clin Ther*. 2010;32(12):2057-2072.
8. Sawada N, Uchida H, Suzuki T, et al. Persistence and compliance to antidepressant treatment in patients with depression: a chart review. *BMC Psychiatry*. 2009;9:10.
9. Wu CS, Shau WY, Chan HY, Lai MS. Persistence of antidepressant treatment for depressive disorder in Taiwan. *Gen Hosp Psychiatry*. 2013;35(3):279-285.
10. Serna MC, Cruz I, Real J, Gasco E, Galvan L. Duration and adherence of antidepressant treatment (2003 to 2007) based on prescription database. *Eur Psychiatry*. 2010;25(4):206-213.
11. Hansen DG, Vach W, Rosholm JU, Sondergaard J, Gram LF, Kragstrup J. Early discontinuation of antidepressants in general practice: association with patient and prescriber characteristics. *Fam Pract*. 2004;21(6):623-629.
12. Sundell KA, Gissler M, Petzold M, Waern M. Antidepressant utilization patterns and mortality in Swedish men and women aged 20-34 years. *Eur J Clin Pharmacol*. 2011;67(2):169-178.
13. Isacsson G, Holmgren A, Osby U, Ahlner J. Decrease in suicide among the individuals treated with antidepressants: a controlled study of antidepressants in suicide, Sweden 1995-2005. *Acta Psychiatr Scand*. 2009;120(1):37-44.
14. Castelpietra G, Morsanutto A, Pascolo-Fabrici E, Isacsson G. Antidepressant use and suicide prevention: a prescription database study in the region Friuli Venezia Giulia, Italy. *Acta Psychiatr Scand*. 2008;118(5):382-388.
15. Erlangsen A, Agerbo E, Hawton K, Conwell Y. Early discontinuation of antidepressant treatment and suicide risk among persons aged 50 and over: a population-based register study. *J Affect Disord*. 2009;119(1-3):194-199.
16. Barak Y, Aizenberg D. Association between antidepressant prescribing and suicide in Israel. *Int Clin Psychopharmacol*. 2006;21 (5):281-284.
17. Castelpietra G, Gobbato M, Valent F, De Vido C, Balestrieri M, Isacsson G. Antidepressant use in suicides: a case-control study from the Friuli Venezia Giulia Region, Italy, 2005-2014. *Eur J Clin Pharmacol*. 2017;73(7):883-890.
18. Gusmao R, Quintao S, McDaid D, et al. Antidepressant utilization and suicide in Europe: an ecological multi-national study. *PLoS ONE*. 2013;8(6):15.
19. Haukka J, Arffman M, Partonen T, et al. Antidepressant use and mortality in Finland: a register-linkage study from a nationwide cohort. *Eur J Clin Pharmacol*. 2009;65(7):715-720.
20. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. *Arch Gen Psychiatry*. 2006;63(12):1358-1367.
21. Sondergard L, Kvist K, Andersen PK, Kessing LV. Do antidepressants prevent suicide? *Int Clin Psychopharmacol*. 2006;21 (4):211-218.
22. Sondergard L, Lopez A, Andersen PK, Kessing LV. Continued antidepressant treatment and suicide in patients with depressive disorder. *Arch Suicide Res*. 2007;11(2):163-175.
23. Castelpietra G, Bovenzi M, Clagnan E, Barbone F, Balestrieri M, Isacsson G. Diagnoses and prescriptions of antidepressants in suicides: register findings from the Friuli Venezia Giulia Region, Italy, 2002–2008. *Int J Psychiatry Clin Pract*. 2016;20:121-124.
24. Castelpietra G, Gobbato M, Valent F, et al. Somatic disorders and antidepressant use in suicides: a population-based study from the Friuli Venezia Giulia region, Italy, 2003-2013. *J Psychosom Res*. 2015;79(5):372-377.
25. Loikas D, Wettermark B, von Euler M, Bergman U, Schenck-Gustafsson K. Differences in drug utilisation between men and women: a cross-sectional analysis of all dispensed drugs in Sweden. *BMJ Open*. 2013;3(5):8.
26. Krivoy A, Balicer RD, Feldman B, et al. The impact of age and gender on adherence to antidepressants: a 4-year population-based cohort study. *Psychopharmacology*. 2015;232 (18):3385-3390.
27. Wu CS, Shau WY, Chan HY, Lee YC, Lai YJ, Lai MS. Utilization of antidepressants in Taiwan: a nationwide population-based survey from 2000 to 2009. *Pharmacoepidemiol Drug Saf*. 2012;21(9):980-988.
28. Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies. *Basic Clin Pharmacol Toxicol*. 2018;123:233-35.

29. Satchi T, Mounib EL. Automating the selection of controls in case-control studies. SUGI: SAS Users Group International Annual conference; 25th: SAS Users Group International, 2000.
30. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2015. Oslo; 2015.
31. Allen JF. Maintaining knowledge about temporal intervals. *Commun ACM*. 1983;26(11):832-843.
32. Maler O, Pnueli A, eds. *On Recognizable Timed Languages*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2004.
33. Cheung K, Aarts N, Noordam R, et al. Antidepressant use and the risk of suicide: a population-based cohort study. *J Affect Disord*. 2015;174:479-484.
34. Braunstein D, Hardy A, Boucherie Q, et al. Antidepressant adherence patterns in older patients: use of a clustering method on a prescription database. *Fundam Clin Pharmacol*. 2017;31(2):226-236.
35. Degli Esposti L, Piccinni C, Sangiorgi D, Fagiolini A, Buda S. Patterns of antidepressant use in Italy: therapy duration, adherence and switching. *Clin Drug Investig*. 2015;35(11):735-742.
36. Balestrieri M, Carta MG, Leonetti S, Sebastiani G, Starace F, Bellantuono C. Recognition of depression and appropriateness of antidepressant treatment in Italian primary care. *Soc Psychiatry Psychiatr Epidemiol*. 2004;39(3):171-176.
37. Yerevanian BI, Koek RJ, Feusner JD, Hwang S, Mintz J. Antidepressants and suicidal behaviour in unipolar depression. *Acta Psychiatr Scand*. 2004;110(6):452-458.
38. Valuck RJ, Orton HD, Libby AM. Antidepressant discontinuation and risk of suicide attempt: a retrospective, nested case-control study. *J Clin Psychiatry*. 2009;70(8):1069-1077.
39. Claxton AJ, Li ZM, McKendrick J. Selective serotonin reuptake inhibitor treatment in the UK: risk of relapse or recurrence of depression. *Br J Psychiatry*. 2000;177:163-168.
40. Bull SA, Hunkeler EM, Lee JY, et al. Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother*. 2002;36(4):578-584.
41. Bushnell GA, Sturmer T, White A, et al. Predicting persistence to antidepressant treatment in administrative claims data: considering the influence of refill delays and prior persistence on other medications. *J Affect Disord*. 2016;196:138-147.
42. NICE Clinical Guidelines CG90. Depression in adults: The treatment and management of depression in adults. Appendix 19: Clinical evidence forest plots. National Institute for Health and Clinical Excellence, 2010.
43. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts ACG. Indications for antidepressant drug prescribing in general practice in the Netherlands. *J Affect Disord*. 2007;98(1-2):109-115.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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