Antidepressant use and the risk of suicide: a population-based cohort study

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ABSTRACT

Background and objectives: The existing literature provides contradictory evidence on antidepressant use and risk of suicide. Some studies have shown that the use of Selective Serotonin Reuptake Inhibitors (SSRIs) is associated with an increased risk of suicide, especially during the first months of treatment, whereas other studies did not confirm this association. For this reason, our objective was to investigate the association between antidepressant use and risk of suicide in incident antidepressant users in relation to time since starting therapy.

Methods: We conducted a population-based cohort study within the Dutch Integrated Primary Care Information (IPCI) database, in incident users of antidepressant therapy between 1994 and 2012 (n=27,712). Cox proportional hazard models were used to study the association between current use of SSRIs, tricyclic antidepressants (TCA) and other antidepressants and risk of suicide or attempted suicide.

Results: During follow-up, a total of 280 incident antidepressant users attempted or committed suicide. Current use of SSRIs (hazard ratio (HR): 0.78, 95% CI: 0.57-1.07), TCAs (HR: 0.82, 95% CI: 0.48-1.42) or other antidepressants (HR: 0.75, 95% CI: 0.47-1.18) was not statistically significantly associated with suicide compared to past use of any of the antidepressants.

Conclusions: This study did not indicate an increase in risk of suicide after starting treatment with SSRIs, TCAs or other antidepressants compared with past antidepressant use.

INTRODUCTION

Suicide accounts for almost one million deaths worldwide each year and is therefore a major problem in many countries [183]. Depression is the most important risk factor [184]. From the various treatments that are available to treat depression, Selective Serotonin Reuptake Inhibitors (SSRIs) are prescribed most frequently [185]. This preference to prescribe SSRIs, compared to tricyclic antidepressants (TCAs), is due to their milder adverse effect and toxicity profile [186]. Compared to non-use as well as compared to TCAs and other antidepressants, SSRIs were associated with an increased risk of suicidal behaviour, especially in children and adolescents [187-189]. The risk seems to be increased especially during the first month of therapy [188, 190]. As a causal pathway, it is hypothesized that SSRIs may cause agitation and subsequently potential ill-considered behaviour, before their beneficial effect relieves depression [191]. However, others could not confirm the increased risk of suicide during use of SSRIs [192-194]. It therefore remains controversial whether SSRI use is associated with suicidal behaviour. For studies comparing SSRIs and TCAs, findings might be influenced by confounding by indication, as indications for prescribing TCAs and SSRIs are different [195, 196].

Because of the lack of consistency between studies and the limitations of some of these, our objective was to investigate the association between incident use of antidepressants and the risk of suicide or suicide attempts in a large population-based study with prospectively gathered healthcare information, under the hypothesis that the risk of suicide would be higher during the first weeks of treatment with SSRIs, TCAs or other antidepressants.

METHODS

Setting

Data from the Integrated Primary Care Information (IPCI) database were used. The IPCI database contains computer-based patient records of more than 600 Dutch General Practitioners (GPs). In the Dutch healthcare system, the GP acts as the gatekeeper of all individual healthcare information and all inhabitants are registered with a GP. The IPCI database currently contains patient information of 1.5 million subjects, including age, sex, date of birth, symptoms, diagnoses, laboratory results, summaries of specialist letters and drug prescription data. Drug prescription data, included product name, quantity prescribed and dosage regimen. The International Classification of Primary Care (ICPC) coding system is used to code diagnoses [20, 157, 197]. We used the Anatomical Therapeutic Chemical (ATC) classification scheme to classify drugs that were prescribed to patients. The IPCI database follows the European Union guidelines on the use of medical data for medical research and has been validated to be used for pharmacoepidemiological research. The scientific and ethical advisory board of the IPCI project approved the study design and use of the data (project number: 07/49).

Study population

The study population comprised all patients with an incident antidepressant prescription between 1994 and 2012 who had ≥1 year of data registered in the database before entering the study. Patients were followed from the date of first antidepressant drug prescription (baseline) until their first attempted suicide, completed suicide or end of the study period on 1 February 2012 whichever came first. We excluded patients under the age of 10, patients with a recorded diagnosis of a psychotic disorder (ICPC code P71) and patients who had multiple different antidepressant drug classes dispensed on the same day. Patients who received an antidepressant prescription 6 weeks prior to the end of the study period were excluded, to ascertain that everybody had at least 6 weeks of follow-up.

Outcome measures

The study outcomes were defined as a notification of either a completed suicide or as an attempted suicide, either coded as P77 (ICPC code 'suicide') or p77.01 (ICPC code 'suicide attempt'), or as similar free text through automated text search. All cases identified with the automated text search were validated manually using the electronic medical records. The first date of suicide or suicide attempt served as the index date.

Exposure definition

The exposure of interest was antidepressant drug use. We categorized these drugs into three classes based on ATC code (4th level): TCAs (N06AA), SSRIs (N06AB) and other antidepressants (N06AG, N06AF and N06AX). Throughout the follow-up time, each individual could provide person-time to one or more periods of current or past exposure over the course of the study period. Patients were classified as currently or previously exposed to an antidepressant, based on the exposure status on the index date. If the date of event fell between the start date and end date of an antidepressant prescription, these patients were considered as current users. If the index date was after the last date of prior antidepressant use, the patient was considered a past user.

Co-variables

Several co-variables were considered as potentially confounding factors: year of first antidepressant prescription, indication for antidepressant use (at date of first antidepressant prescription and at index date), age, sex, history of previous suicide attempts, history of self-harm (both within 1 year prior to the date of first antidepressant prescription), psychotropic drug use at index date (antipsychotics: ATC-code N05A, anxiolytics: N05B, hypnotics and sedatives: N05C) and sequential use of different antidepressants (switching). The latter was considered as a potential risk factor, as some patients may be resistant to antidepressant medications possibly indicating a more severe depression. The indication for antidepressant drug use was identified through the diagnoses in the medical records and includes the following indications:

depression (ICPC code P76 and P03), anxiety (P01 and P74) and depression and anxiety combined. We used the ICPC codes and corresponding free text to identify patients with depression using an automated text search. When the indication was not grouped in the above mentioned categories, the indication was stated as 'other indication'. A subsample was validated manually to determine whether the automated text search correctly identified 'depression' and 'anxiety' as the indications for antidepressant use.

Statistical analyses

A Cox proportional hazards model was used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for the associations between the use of different antidepressants and suicide or suicide attempt [110]. Use of antidepressants was included in the model as a time-varying determinant. Co-variables were included in the multivariable model if they changed the point estimate of the association between antidepressant use and suicide > 10 percent or were considered clinically relevant. Sub-analyses were performed to investigate whether the risk varied in relation to time since starting therapy (1-14 days, 15-28 days and >28 days). To evaluate potential confounding by indication, we investigated current antidepressant use in depressed patients and current use for other (unknown) indications separately. Dose response analyses were performed to assess whether the risk varied between high and low dose of antidepressant use. A low dose was defined as the median dose or less and a dose higher than the median dose was defined as a high dose. Analyses with regard to the duration of past use were performed to assess whether this influenced the risk of suicide in our population. In the analyses, we took less than 1 year and more than 1 year past use as separate reference groups. In another sub-analysis potential effect modification by age and sex was tested, stratified analyses were presented accordingly. All analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY). P-values below 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Table 1 describes the baseline characteristics of the study population. A total of 27,712 patients were identified as having received an antidepressant drug prescription, of whom the majority were women (61.2%). SSRI users tended to be younger (median: 44 years, IQR: 42.0 – 70.0) than those prescribed TCAs (median: 55 years, IQR: 28) and SSRI users comprised the largest group of patients for whom a diagnosis of depression was registered (37.6%) compared to TCAs (7.3%) and other antidepressant types (19.4%).

Table 1 *Characteristics of study population at baseline according to first antidepressant type prescribed*

Characteristic	All anti-depressants (n= 27,712), N (%)	TCAs (n=7,732), N (%)	SSRIs (n=12,686), N (%)	Other anti-depressants (n=7,294), N (%)
Age, years				
10-24	2,169 (7.8)	399 (5.2)	1,305 (10.3)	465 (6.4)
25-40	7,388 (26.7)	1,364 (17.6)	4,082 (32.2)	1,942 (26.6)
41-55	8,442 (30.5)	2,179 (28.2)	3,721 (29.3)	2,542 (34.9)
56-70	5,187 (18.7)	1,953 (25.3)	1,820 (14.3)	1,414 (19.4)
>70	4,526 (16.3)	1,837 (23.8)	1,758 (13.9)	931 (12.8)
Mean age (SD)	49.6 (17.9)	55.3 (18.3)	46.7 (18.5)	49.1 (16.9)
Sex, female	16,970 (61.2)	4,916 (63.5)	8,001 (63.1)	4,053 (55.6)
Indication of use				
Depression	6,752 (24.4)	564 (7.3)	4,774 (37.6)	1,414 (19.4)
Anxiety	1,103 (4.0)	191 (2.5)	655 (5.2)	257 (3.5)
Depression and anxiety	706 (2.5)	54 (0.7)	511 (4.0)	141 (1.9)
Other (unknown) indication	19,151 (69.1)	6,923 (89.5)	6,746 (53.2)	5,482 (75.2)
History of self-harm [a]	257 (0.9)	24 (0.3)	173 (1.4)	60 (0.8)
Use of psychotropic drugs				
Antipsychotics	484 (1.7)	83 (1.1)	264 (2.1)	137 (1.9)
Anxiolytics	2069 (7.5)	381 (4.9)	1190 (9.4)	498 (6.8)
Hypnotics and sedatives	1523 (5.5)	388 (5.0)	733 (5.8)	402 (5.5)

Values are given in numbers (percentages) unless stated otherwise. [a] Referred to as self-injury or previous suicide attempts, prior to date of first antidepressant prescription. Abbreviations: n; number of antidepressant users, TCAs; tricyclic antidepressants, SSRIs; Selective Serotonin Reuptake Inhibitors

Associations between known risk factors and suicide

In the total population with 280 cases, we found that a history of self-harm (HR: 6.94, 95% CI: 4.53-10.64) and psychotropic drug use (HR antipsychotics: 6.42, 95% CI: 4.19-9.85, HR anxiolytics: 5.07, 95% CI: 3.78-6.79, HR hypnotics and sedatives: 4.33, 95% CI: 3.05-6.15) were the strongest factors associated with the risk of a suicide (attempt) (table 2). Age, in particular between age 10 to 24 years (HR: 6.41, 95% CI: 3.76-11.06), was also found to be strongly associated with the risk of a suicide attempt. Other factors that were significantly associated with suicide were different antidepressant prescriptions (switching antidepressants) (HR: 2.38, 95% CI: 1.69-3.34) and depression (HR: 2.53, 95% CI: 1.82-3.50). A higher risk was observed for patients diagnosed with both depression and anxiety at the same time (HR: 4.40, 95% CI: 1.92-10.1).

Table 2 *Hazard ratios of potential risk factors for suicide and suicide attempt*

Variable	Cases, N	HR (95% CI) [c]	P
Age, years			
10-24	50	6.41 (3.76-11.06)	<0.001
25-40	90	2.87 (1.73-4.76)	<0.001
41-55	107	2.68 (1.62-4.41)	<0.001
56-70	38	1.58 (0.90-2.76)	0.11
>70	18	1 (ref)	
Sex, female[b]	182	0.92 (0.73-1.16)	0.47
Indication for antidepressant			
Depression	54	2.53 (1.82-3.50)	<0.001
Anxiety	7	1.66 (0.78-3.56)	0.19
Depression and anxiety	6	4.40 (1.92-10.06)	<0.001
Unknown/other indication	236	1 (ref)	
History of self-harm [a,b]	23	6.94 (4.53-10.64)	<0.001
Concurrent use psychotropic drugs [b]			
Antipsychotics	23	6.42 (4.19-9.85)	<0.001
Anxiolytics	59	5.07 (3.78-6.79)	<0.001
Hypnotics and sedatives	38	4.33 (3.05-6.15)	<0.001
No. of antidepressant types prescribed during follow-up			
1	253	1 (ref)	
>1	50	2.38 (1.69-3.34)	<0.001

[a] Referred to as self-injury or previous suicide attempts, prior to date of first antidepressant prescription. [b] Reference group: male, no history of self-harm and non-use for psycholeptics. [c] Adjusted for age and sex. Age was adjusted for gender and gender was adjusted for age only. Abbreviations: HR; Hazard rate ratio, CI; confidence interval, n; number of cases with completed suicide or suicide attempt, P; p-value

Association between antidepressant treatment and suicide (attempt)

Table 3 shows the association between current antidepressant use and suicide (attempt). We observed no significant associations with suicide in patients who were prescribed SSRIs (HR: 0.78, 95% CI: 0.57-1.07), TCAs (HR: 0.82, 95% CI: 0.48-1.42) or other antidepressants (HR: 0.75, 95% CI: 0.47-1.18), compared to past use, after adjustment for the known risk factors (age, sex, indication of use, antipsychotic use, anxiolytic use and number of different antidepressants prescribed). We also found no evidence of a higher suicide risk in patients prescribed TCAs currently (HR: 0.89, 95% CI: 0.26-3.06), SSRIs (HR: 0.56, 95% CI: 0.31-1.09) or other antidepressants (HR: 0.54, 95% CI: 0.20-1.45) when restricted to the indication of depression. When stratified by age or gender, no significant differences for the different strata was observed (results not shown). Patients treated with TCAs receiving a high dose compared to low dose were at a higher risk of suicide (HR: 3.52, 95% CI: 1.04-11.93, p-value: 0.043). In patients treated with

SSRIs, no significant differences were observed between high and low dose (HR: 1.44, 95% CI: 0.61-3.39, p-value: 0.409). We did not observe differences in suicide risk between the analyses where we took a reference group of less than 1 year and more than 1 year past use (results not shown).

Table 3 *Risk of suicide in patients prescribed SSRIs, TCAs and other antidepressants*

	Total population			Depression only		
Exposure	**Cases, N**	**Adjusted HR (95% CI)[b]**	**Adjusted HR (95% CI)[c]**	**Cases, N**	**Adjusted HR (95% CI)[b]**	**Adjusted HR (95% CI)[d]**
Past use [a]	202	1 (ref)	1 (ref)	27	1 (ref)	1 (ref)
Current use of TCAs	15	1.01 (0.58-1.76)	0.82 (0.48-1.42)	3	1.07 (0.32-3.59)	0.89 (0.26-3.06)
Current use of SSRIs	63	1.19 (0.88-1.62)	0.78 (0.57-1.07)	19	0.63 (0.34-1.19)	0.56 (0.31-1.09)
Current use of other antidepressants	23	1.18 (0.75-1.85)	0.75 (0.47-1.18)	5	0.61 (0.23-1.63)	0.54 (0.20-1.45)

Suicide risk by indication. [a] Includes use of all antidepressant types. [b] Model 1: adjusted for age and sex. [c] Model 2: adjusted for sex, age, antipsychotic use at index date, anxiolytic use at index date, indication at index date and the number of different antidepressants prescribed during follow-up. [d] Adjusted for all the above mentioned risk factors except for the indication at index date. Abbreviations: HR; Hazard rate ratio, CI; confidence interval, n; number of cases with completed suicide or suicide attempt, P; p-value, TCAs; tricyclic antidepressants, SSRIs; Selective Serotonin Reuptake Inhibitors

Analyses by duration of antidepressant use

Figure 1 shows the association between SSRIs and suicide risk in relation to time since starting therapy. Although a higher risk was observed in patients who recently started therapy with SSRIs (HR 1-14 days, adjusted for age and sex: 1.44, 95% CI: 0.96-2.17), this did not reach

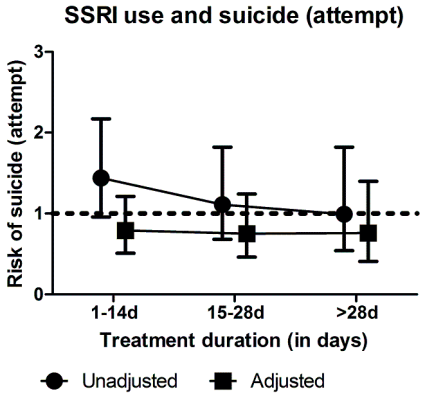

Figure 1 *SSRI treatment duration and risk on suicide (attempt)*
Current treatment with SSRIs compared to past use of all antidepressant types. Model 1: adjusted for age and sex. Model 2: adjusted for sex, age, antipsychotic use at index date, anxiolytic use at index date, indication at index date and the number of different antidepressants prescribed during follow-up. Abbreviations: SSRIs, Selective Serotonin Reuptake Inhibitors; d, days.

statistical significance. After adjustment for the other factors, we observed no increased risk in patients who recently started SSRIs (HR 1-14 days: 0.79, 95% CI: 0.51-1.21, HR 15-28 days: 0.75, 0.46-1.24 and HR >28 days: 0.76, 0.41-1.40). Similar results were observed for patients who were prescribed TCAs or other antidepressants, but with wider confidence intervals due to low numbers of cases (results not shown).

DISCUSSION

The objective of the current study was to assess the association between the use of different antidepressant drug classes and the risk of suicide or suicide attempt during the first weeks of treatment. The results of our study did not show an association between the different antidepressant drug classes and suicide (attempts) overall nor during the first weeks of treatment. In addition, we did not observe an increased risk in the initial treatment period nor did we find an increased risk when restricting analyses to specific indications. We also found no significant effect modification by age and gender. Previous studies yielded similar results [6, 21]. Patients receiving a high dose of TCAs compared to low dose were at a higher risk of suicide. A possible explanation is that these patients suffer from a more severe depression, which is associated with an increased risk of suicide [198]. Also, depressed patients use TCAs for self-poisoning or suicide [199].

In line with currently available literature, we found that classical risk factors, such as young age, depression, a history of self-harm, antipsychotic use (as a crude measure of a psychotic indication) and sequential use of different antidepressants were associated with a higher risk of suicide (attempts) [187, 191, 195, 200-202]. Previous researchers observed an increased risk of suicide with SSRI use in young individuals [187, 203, 204]. Although it might therefore be speculated that the risk of suicide in SSRI users is age dependent, age did not act as an effect modifier in our study, suggesting that risk was similar between low and high age. However, our study population consisted largely of patients aged 25 and over (92.2%), leaving only a limited number of patients aged 25 years or younger. In contrast to our results, another study observed an increased risk of suicide in patients with depression prescribed SSRIs, TCAs or other antidepressants compared with no current treatment [205]. A possible explanation for the lower risk of suicide is that 'no current treatment' may indicate no depression or less severe depression than being under treatment. Confounding by indication in the previous studies might underlie this difference in observation, as these studies did not adjust for the indication of treatment [195, 205].

Previously, an increased risk of suicidal behaviour during the first month of SSRI therapy compared with other antidepressants was found [195]. However, others could not confirm this, as the risk was found to be highest in the month before the initial prescription (because suicide attempt may prompt initiation of antidepressant treatment) and a decline in risk after initiation

of treatment [206]. In our study, estimates for the first weeks of use did not differ significantly from longer durations of use. Although it is likely that the duration of past use may influence the risk of suicide, this did not change the risk in our study population. We did not find an increased risk in current users compared with past users of less than one year nor did we find an increased risk in current users compared with past users of more than one year. Therefore we suggest that the risk is similar in both reference groups. A possible biological mechanism that might explain the phenomenon of increased suicidal risk in the first weeks after start of SSRIs may be the slow onset of drug action in patients with severe depression [207]. The serotonin levels may increase before the depression is relieved, presumably by down regulation of the postsynaptic receptor population [208]. Therefore, patients may transiently become extremely agitated and restless and commit suicide before the drug treatment starts to relieve depression [191, 207, 209]. Patients may also become more anxious following onset of SSRI treatment, which is also associated with an increased risk of suicide [210]. Our results did not support the findings of these previous studies [188, 190], as we did not find evidence or differences in risk of suicide in relation to time since starting therapy. A possible explanation for this finding is that the population used in this particular analysis, where we stratified by treatment duration, was not restricted to patients with depression only. The number of cases was too small to make precise estimates in this analysis.

Strengths and limitations of the study

An advantage of our study is the large number of GPs participating in the IPCI project, providing us with complete medical information of at least 1.5 million patients. In the Dutch healthcare system, the GP acts as the gatekeeper of all individual healthcare information. Consequently, there was information on drug use and potential confounders available. With this information we were able to assess the use of antidepressants and the potential confounders at different time points. A key advantage of this cohort design is that we were able to include all eligible incident antidepressant users, which minimizes the risk of selection bias. Also, in our opinion, the information bias is minimal as we used prescription records as the source of medication data [28, 211]. However, patients whose antidepressant treatment was initiated by a specialist (prior to cohort entry) may have been misclassified as the IPCI database largely consists of GP prescription data and it does not include information about whether prescribed medications are actually taken by the patient. However, we expect that the actual intake of antidepressant drugs will be non-differential between the different drug classes. We manually validated all potential suicide cases and grouped those who did not have a recorded suicide or suicide attempt in the control group and therefore minimizing the risk of misclassification of the outcome. Our study also has several limitations. Several studies have demonstrated that patients with a greater risk of suicide or self-harm (often with a recorded history of self-harm) are preferably prescribed SSRIs, since this antidepressant class is safer when taken in overdose than TCAs [196, 212]. As the number of history of self-harm cases in our study was low, it is likely that we were

not able to extract all cases of self-harm prior to start of therapy. Another observation is the relatively high number of patients with an indication for antidepressants other than depression or anxiety. We assumed that not all patients with depression were recognized as such, because we restricted only to synonyms for depression, and not for keywords of symptoms in the automated text search. We manually validated a subsample to determine whether the automated text search correctly identified 'depression' and 'anxiety' as the indication for antidepressant use. We found similar results for depression (47.3%) and anxiety (10.3%) as was found earlier [213]. It could be speculated that the change in the prescribing practices over the last 20 years may have affected our results. However, we believe that this is not an issue in our study as the majority of our study population received their first antidepressant prescription after 1 January 2000 (90.5%). We also included the year of first antidepressant prescription in the model as a confounding factor, but this did not change the risk of suicide (attempt). A recently published study showed that the number of cases of suicide and self-harm that was not reported in the UK health care database was relatively high, which may also be considered as a limitation in our study [214]. However, we expect that under-reporting of suicide attempts between different antidepressant drug classes will be non-differential.

Conclusion

In summary, we did not find evidence for an increased risk of suicide or suicidal attempts in the first weeks of treatment in patients who were treated with SSRIs, TCAs or other antidepressants in comparison to patients who have previously been treated with antidepressants.