Journal of Affective Disorders 174 (2015) 479–484

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

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

Kiki Cheung [a], Nikkie Aarts [a,b], Raymond Noordam [a,b], Jan C. van Blijderveen [a,c], Miriam C. Sturkenboom [c], Rikje Ruiter [a], Loes E. Visser [a,d], Bruno H. Stricker [a,e,*]

[a] Department of Epidemiology, Erasmus MC – University Medical Centre Rotterdam, The Netherlands
[b] Department of Internal Medicine, Erasmus MC – University Medical Centre Rotterdam, The Netherlands
[c] Department of Medical Informatics, Erasmus MC – University Medical Centre Rotterdam, The Netherlands
[d] Apotheek Haagse Ziekenhuizen – HAGA, The Hague, The Netherlands
[e] Inspectorate of Health Care, The Hague, The Netherlands

ARTICLE INFO

Article history:
Received 5 July 2014
Received in revised form
9 December 2014
Accepted 10 December 2014
Available online 18 December 2014

Keywords:
Depression
Selective Serotonin Reuptake Inhibitors
Tricyclic
Antidepressants
Suicide

ABSTRACT

Background: 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.

Limitations: Although a large healthcare database was used, the number of reported cases of suicide (attempt) was low.

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.

1. Introduction

Suicide accounts for almost one million deaths worldwide each year and is therefore a major problem in many countries (Goldsmith et al., 2002). Depression is the most important risk factor (Brent, 1993). From the various treatments that are available to treat depression, Selective Serotonin Reuptake Inhibitors (SSRIs) are prescribed most frequently (Usala et al., 2008). This preference to prescribe SSRIs, compared to tricyclic antidepressants (TCAs), is due to their milder adverse effect and toxicity profile (Anderson, 2000).

Compared to non-use as well as compared to TCAs and other antidepressants, SSRIs were associated with an increased risk of suicidal behavior, especially in children and adolescents (Martinez et al., 2005; Hall and Lucke, 2006; Fergusson et al., 2005). The risk seems to be increased especially during the first month of therapy (Hall and Lucke, 2006; Juurlink et al., 2006). As a causal pathway, it is hypothesized that SSRIs may cause agitation and subsequently potential ill-considered behavior, before their beneficial effect relieves depression (Mihanovic et al., 2010). However, others could not confirm the increased risk of suicide during use of SSRIs (Isacsson et al., 2009; Arias et al., 2010; Gibbons et al., 2007). It therefore remains controversial whether SSRI use is associated with suicidal behavior. For studies comparing SSRIs and TCAs, findings might be influenced by confounding by indication, as indications for prescribing TCAs and SSRIs are different (Jick et al., 2004; Didham et al., 2005).

* Corresponding author at: Department of Epidemiology, Erasmus Medical Centre, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.
Tel.: +31 10 70 44294; fax: +31 10 70 44657.
E-mail address: b.stricker@erasmusmc.nl (B.H. Stricker).

http://dx.doi.org/10.1016/j.jad.2014.12.032
0165-0327/

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.

2. Methods

2.1. 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 (van der Lei et al., 1993; Vlug et al., 1999; Lamberts et al., 1992). 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).

2.2. 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 (or less) prior to the end of the study period were excluded, to ascertain that everybody had at least 6 weeks of follow-up.

2.3. 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.

2.4. 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.

2.5. Co-variables

Several co-variables were considered as potentially confounding factors: year of first antidepressant prescription, indication for antidepressant use (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.

2.6. 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 (Stricker and Stijnen, 2010). 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 $>10\%$ 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, and 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.

3. Results

3.1. Baseline characteristics

Table 1 describes the baseline characteristics of the study population. A total of 27,712 patients were identified as having