

The effect of selective serotonin re-uptake inhibitors on the risk of myocardial infarction in a cohort of patients with depression

Stephen E. Kimmel,¹ Hedi Schelleman,² Jesse A. Berlin,³
David W. Oslin,⁴ Rachel B. Weinstein,³ Judith L. Kinman,²
William H. Sauer⁵ & James D. Lewis⁶

¹Center for Clinical Epidemiology and Biostatistics and Cardiovascular Division at the Department of Medicine, University of Pennsylvania School of Medicine, 423 Guardian Drive, Philadelphia, PA 19104-6021, ²Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, 423 Guardian Drive, Philadelphia, PA 19104-6021, ³Johnson & Johnson Pharmaceutical Research and Development, 1125 Trenton-Harbourton Road, Titusville, NJ 08560, ⁴Department of Psychiatry, University of Pennsylvania School of Medicine and the Philadelphia VAMC, 3900 Chestnut Street, Philadelphia, PA 19104-6178, ⁵Department of Medicine, University of Colorado, 12401 E 17th Avenue, B-136, Aurora, CO 80045 and ⁶Center for Clinical Epidemiology and Biostatistics and Division of Gastroenterology at the Department of Medicine, University of Pennsylvania School of Medicine, 423 Guardian Drive, Philadelphia, PA 19104-6021, USA

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Depression is associated with an increased risk of cardiovascular disease. Some studies, but not all, have identified an association between use of selective serotonin re-uptake inhibitors (SSRIs) and reduced risk of myocardial infarction (MI). There may be a difference among SSRIs based on their affinity for the serotonin receptor.

WHAT THIS STUDY ADDS

- Current use of SSRIs by patients with depression may be associated with a reduced risk of MI. However, the risk seemed to be reduced only with longer term use of SSRIs. In addition, we did not observe a relationship between the affinity of SSRIs for the serotonin transporter and risk of MI.

AIM

To evaluate whether selective serotonin re-uptake inhibitor (SSRI) exposure influences the risk of myocardial infarction (MI) in patients with depression.

METHODS

This study included 693 patients with MI (cases) and 2772 controls. Conditional logistic regression was used to calculate the odds ratio (OR).

RESULTS

SSRI exposure may be associated with a reduced MI risk (OR = 0.77, 95% CI 0.57, 1.03). However, reduced risk was only observed with longer term use (OR = 0.73, 95% CI 0.53, 1.00) and not with shorter term use (OR = 1.15, 95% CI: 0.65, 2.05).

CONCLUSIONS

Only longer term use of SSRIs was associated with reduced MI risk, suggesting that other mechanisms, besides an acute anti-platelet effect, may reduce MI risk.

Correspondence

Dr Stephen E. Kimmel MD MSCE, Center for Clinical Epidemiology and Biostatistics and Cardiovascular Division at the Department of Medicine, University of Pennsylvania School of Medicine, 717 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021, USA.
Tel.: +1 215 898 1740
Fax: +1 215 573 5325
E-mail: stevek@mail.med.upenn.edu

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Introduction

Depression is associated with an increased risk of cardiovascular morbidity and mortality [1]. Proposed mechanisms for the increased risk in people with depression, include life-style factors (such as smoking) and increased platelet activation [2]. Long term treatment with antidepressants might reduce cardiovascular risk by alleviating depression. In addition, selective serotonin re-uptake inhibitor (SSRI) antidepressants may provide additional benefit by inhibiting the increased platelet activation in depressed patients [3]. Some studies [4–6], but not all [7–10], have identified an association between SSRIs compared with non-use and reduced risk of MI. A potential limitation of these studies is that the results might have been biased by confounding by depression.

Therefore, we sought to determine, in a population of patients with a diagnosis of depression, the association of SSRI use with MI and whether there are differences among SSRIs. Our hypothesis was that shorter term exposure to SSRIs would reduce the risk of MI via their acute antiplatelet effects.

Methods

Study population

Data for this case-control study were derived from the UK General Practice Research Database (GPRD) from 1989 to 2002. GPRD is a computerized database of anonymized longitudinal medical records of over 8 million residents in the UK. All patients with a first diagnosis of depression that was recorded at least 1 year after registration with a practice were included in this study. The rationale for including only patients with a diagnosis of depression was to reduce confounding by disease indication. Patients whose first depression diagnosis was recurrent depression or who had a diagnosis for another severe mental health disorder (e.g. schizophrenia) prior to or on the same day as their first diagnosis of depression were excluded.

This study was approved by the University of Pennsylvania Institutional Review Board and the Scientific and Ethical Advisory Group of the GPRD.

Selection of cases and controls

The cohort was followed forward in time after the first diagnosis of depression until one of three events occurred: the subject had a first-recorded diagnosis of MI (cases), follow-up ended or the subject had a censoring event. Censoring events included death and diagnoses of ventricular arrhythmias or sudden death, hypertrophic cardiomyopathy, heart transplantation, myocarditis, infiltrative cardiomyopathies, malignancy of the heart and diagnoses of other severe mental health disorders.

The recorded date of the MI event was considered the index date. For each case, we identified, at random, four

controls matched on age in 5 year increments, gender and duration of follow-up from the first diagnosis of depression until the index date using incidence density sampling.

Exposure definition

Antidepressant (SSRI and non-SSRI) users were defined as people whose antidepressant prescription lasted until the index date. All other patients were considered to be non-antidepressant users.

Paroxetine, sertraline, fluoxetine, citalopram and fluvoxamine were classified as SSRIs. SSRIs were also categorized by their affinity for the serotonin transporter, i.e. high affinity: paroxetine, sertraline and fluoxetine and moderate affinity: citalopram and fluvoxamine [11]. All other antidepressants were considered to be non-SSRI agents. Because venlafaxine exhibits serotonin inhibition, as well as other actions, we performed a sensitivity analysis in which we included venlafaxine along with SSRIs.

Patients simultaneously exposed to both SSRIs and non-SSRIs at their index date were excluded.

Analysis

Conditional logistic regression was used to estimate the odds of MI in SSRI users compared with non-users of any antidepressant. Known risk factors for MI as well as variables that changed the unadjusted OR by at least 10% after adjustment were included in the multivariable models to adjust for confounding [12].

Results

There were 128 116 subjects identified with a first diagnosis of depression who did not meet the exclusion criteria. Among them, 693 patients had a subsequent MI (cases) and they were matched to 2772 controls.

The adjusted OR for MI among current SSRI users vs. non-users was 0.77 (95% confidence interval [CI] 0.57, 1.03, $P = 0.08$) (Table 1). The adjusted OR was essentially unchanged when including venlafaxine with SSRIs (OR 0.76, 95% CI 0.57, 1.01) (Table 1). Among users of non-SSRI antidepressants the adjusted OR was 0.89 (95% CI 0.67, 1.19, $P = 0.44$).

Current SSRI users without a second SSRI prescription in the 90 days prior to the index date ('shorter term use') had an OR of 1.15 (95% CI 0.65, 2.05), while current SSRI users with ≥ 1 additional SSRI prescription in the preceding 90 days ('longer term use') had an OR of 0.73 (95% CI 0.53, 1.00).

No consistent relationship was observed between SSRI affinity and odds of MI (moderate affinity OR 0.53, 95% CI 0.29, 0.99 and high affinity OR 0.83, 95% CI 0.61, 1.14 vs. non-users; multiplicative interaction $P = 0.18$). In addition, although the ORs among individual SSRIs seemed to vary (Figure 1), the global test of any differences among the different SSRIs was not statistically significant ($P = 0.11$).

Table 1

Odds ratio for myocardial infarction by SSRI use

| Current antidepressant use | Cases (n = 693) | Controls (n = 2772) | Adjusted odds ratio* (95% confidence interval) | P |
|----------------------------|-----------------|---------------------|--|------|
| None | 497 | 1985 | 1.00 (Reference) | |
| SSRI | 89 | 360 | 0.77 (0.57, 1.03) | 0.08 |

*Adjusted for: history of hypertension, diabetes, hypercholesterolaemia, congestive heart failure, stroke, ischaemic heart disease, rheumatoid arthritis, obstructive lung disease or aortic stenosis, use of aspirin or nitrates and number of prior medication prescriptions. Other variables, such as smoking and body mass index, did not alter the ORs. SSRI, selective serotonin re-uptake inhibitors.

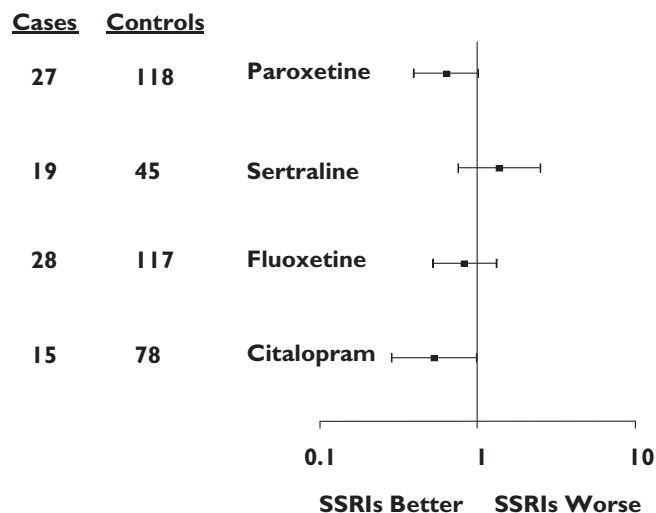


Figure 1

Adjusted odds ratio (squares) and 95% confidence intervals (bars) for myocardial infarction comparing selective serotonin re-uptake inhibitor use with no antidepressant use. Odds ratios are adjusted for all variables as described in the text

Discussion

In this study, depressed patients who were longer term users of SSRIs had lower odds of MI than depressed patients without an active antidepressant prescription. Shorter term use of SSRIs was not associated with reduced risk of MI, suggesting that longer term use may be required for beneficial effects of SSRIs. Further, no relationship was observed between affinity for the serotonin receptor and odds of MI.

There are three primary limitations of the study. First, GPRD relies on physician prescribing and therefore, some of the ‘current users’ of SSRIs in our study may not have been taking the prescribed antidepressant, which may have led to underestimation of the protective effects of SSRIs on MI risk. Second, because other antidepressants may have adverse effects among those with existing cardiovascular disease, it is possible that SSRIs were used in higher risk patients which could have biased our results towards the null, despite adjustment for available con-

founders. Third, our results may have been confounded by the severity of depression, biasing the results away from demonstrating a protective effect of SSRIs.

Within the context of the limitations of observational research, our results suggest that there may be a difference between shorter term and longer term use of SSRIs and the risk of MI. These results raise the possibility that an inhibition of platelet effect by SSRIs may not be primarily or solely responsible for the reduction of the risk of MI among depressed patients.

Competing Interests

Dr Kimmel has received research funding from Pfizer and GlaxoSmithKline and served as a consultant for Pfizer and GlaxoSmithKline, all unrelated to SSRIs. Dr Schelleman has had travel to scientific conferences paid for by pharmacoepidemiology training funds contributed by pharmaceutical manufacturers. Drs Berlin and Weinstein are full-time employees of Johnson & Johnson Pharmaceutical Research and Development. Both were full-time employees of the University of Pennsylvania at the time this work was conducted. Dr. Berlin is a shareholder in Johnson & Johnson. Dr Lewis has received research funding from Pfizer and GlaxoSmithKline and served as a consultant for Pfizer and GlaxoSmithKline. Ms Kinman and Drs Oslin and Sauer have no conflicts to declare.

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