Impact of antidepressants use on risk of myocardial infarction: A systematic review and meta-analysis

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ABSTRACT

Aims: The aim of the study was to perform a systematic review and meta-analysis to determine the association between antidepressants use and risk of myocardial infarction (MI), and whether this association differs between tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).

Methods: A PubMed/MEDLINE search was conducted for studies published up to December 2013. Included studies were evaluated for publication bias and heterogeneity. Depending on the presence of heterogeneity, a random or fixed effects model was used to identify the pooled relative risk (RR) with 95% confidence intervals (CIs). Cumulative meta-analysis, subgroup and sensitivity analyses were also performed. All analyses were performed using comprehensive meta-analysis software.

Results: Fourteen (five cohort and nine case–control) studies were included. There was heterogeneity among the studies ($P_{\text{het}} = 0.02$; $I^2 = 68\%$) but no publication bias ($Begg’s P = 0.30$ and $Egger’s P = 0.45$). Antidepressants use significantly increases the risk of myocardial infarction (MI) ($RR = 2.03$; $95\% \text{ CI} = 1.30–3.18$; $P < 0.01$). On subgroup analysis by study design, cohort studies show significant positive association ($RR = 2.16$; $95\% \text{ CI} = 1.42–3.29$; $P < 0.01$), but not case–control studies ($RR = 2.47$; $95\% \text{ CI} = 0.69–8.90$; $P = 0.17$). Sensitivity analysis and cumulative meta-analysis confirmed the stability of results. TCAs users are having 36% increased risk of MI after excluding one outlier ($RR = 1.36$; $95\% \text{ CI} = 1.10–1.67$; $P < 0.01$), but SSRIs showing no association ($RR = 0.84$; $95\% \text{ CI} = 0.57–1.22$; $P = 0.35$).

Conclusions: We found evidence that the use of antidepressants was associated with elevated risk of MI. Further research is needed to identify the underlying biological mechanisms.

KEY WORDS: Myocardial infarction, selective serotonin reuptake inhibitors, tricyclic antidepressants

Introduction

Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration.[1] Globally, more than 350 million people of all ages suffer from depression.[1] Myocardial infarction (MI) occurs when there is reduced blood flow to a part of the heart muscle resulting in necrosis of that part of the myocardium.[2] MI is a major cause of morbidity and mortality worldwide. It is estimated to be more than 3 million people each year have an acute ST-elevation MI, and more than 4 million have a non-ST-elevation MI.[3]

Emerging evidence suggests that depression may increase the risk of coronary heart disease in healthy individuals, and is associated with cardiac morbidity and mortality in individuals with established coronary heart disease.[4,5] A 1.5-fold increase in risk of fatal coronary heart disease and MI has been reported in persons with self-reported depressive symptoms.[4,6] Antidepressants are psychiatric medications given to patients with depressive disorders to alleviate symptoms. Thirty different kinds of antidepressants available can be divided into five main types: Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase
inhibitors (MAOIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs). TCAs are not recommended in patients with cardiovascular disease (CVD) owing to their arrhythmic effects. On the other hand, SSRIs appear to lack adverse cardiovascular effects when compared to other antidepressants. Despite the growing use of SNRIs, little is known about the potential cardiovascular risks associated with this relatively new class of antidepressants.

Several observational studies conducted to examine the association between use of different classes of antidepressants and risk of MI has generated inconsistent results and till date, no definite conclusion has been made on this issue. In this present systematic review and meta-analysis, we reviewed and examined the association between any antidepressant use and also the use of individual classes of antidepressants and risk of MI using all studies published up to December 2013.

Methods

Data Sources and Search Strategy

Two authors (KU and SSJ) independently performed the literature search by using PubMed/MEDLINE database up to December 31, 2013; this search was supplemented by review of bibliographies of retrieved articles. The MEDLINE MeSH terms were as follows: “Antidepressants OR TCAs OR SSRIs OR MAOIs OR SNRIs OR NaSSAs AND CVDs OR MI” with a limit; humans. Initially the titles and abstracts of resulting articles were reviewed to identify the relevant studies, followed by reading the selected full text articles.

Inclusion and Exclusion Criteria

No randomized controlled trials were found relevant for this study. All observational studies were included if they fulfilled the following criteria: (a) Cohort or case–control study design; (b) antidepressants included as an exposure of interest; (c) MI included as an outcome of interest; (d) conducted for at least 1 year; and (e) relative risk (RR) in cohort studies or odds ratio (OR) in case–control studies and their 95% confidence intervals (CI) (or sufficient data to calculate them) reported. If data on the same population were reported in multiple publications, the recent and informative publication was selected. Any discrepancies between authors on the inclusion of a study were resolved by joint evaluation of the manuscript. Reviews, case reports, letters to the editor without original data, and editorials were excluded.

Data Extraction

Two authors (KU and GP) independently reviewed the included studies and extracted the following information from each study: (i) First author’s last name, year of publication, and country of the population studied; (ii) study design; (iii) number of study subjects and number of MI cases; (iv) RR/OR estimates with 95% CIs; (v) definitions of antidepressants exposure; (vi) MI assessment; and (vii) control for confounding factors by matching or adjustments, if applicable. RR reflected the greatest degree of control for potential confounders were considered for pooled analysis.

Quality Assessment

Two authors (GP and SSJ) independently assessed the quality of each study using the Newcastle–Ottawa scale (NOS). The NOS has three parameters of quality: Selection, comparability, and outcome for cohort studies or exposure for case–control studies. It assigns a maximum of four points for selection, two points for comparability, and three points for exposure/outcome. Therefore, nine points considered as highest quality. Any discrepancies were addressed by a joint revaluation of the original article with a third author (KU).

Statistical Analysis

Because the risk of MI is low, the RR in prospective cohort studies mathematically approximates the OR in case–control studies, therefore it permits the combining of cohort and case–control studies to calculate pooled RR. Begg and Mazumdar adjusted rank correlation test, and Egger regression asymmetry test was used to assess publication bias. Heterogeneity among the studies was assessed by Cochran Q and F statistics; for the Q statistic, a P < 0.10 was considered statistically significant for heterogeneity; for F, a value > 50% is considered a measure of heterogeneity. Pooled RR estimates with 95% CIs were calculated using random-effects model if heterogeneity presents or otherwise fixed-effects model. Altman and Bland method was used to assess the test for interaction. All statistical tests were two-sided and P < 0.05 was considered statistically significant, except otherwise specified. All analyses were performed using comprehensive meta-analysis software.

The primary outcome of this meta-analysis was reported as pooled RR with 95% CI of developing MI in antidepressants users. To assess link between individual classes of antidepressants like (i) TCAs use and risk of MI; (ii) SSRIs use and risk of MI; (iii) non-SSRIs use and risk of MI, we used the available data from studies which reported RR estimates for these particular associations.

Subgroup analyses were performed according to (i) study design (cohort and case–control); and (ii) adjustment for “other CVDs,” to examine the impact of these factors on the association. We performed a one-way sensitivity analysis to evaluate the stability of our results. The scope of this analysis was to evaluate the influence of individual studies by estimating the average RR in the absence of each study. We also conducted a cumulative meta-analysis to examine the influence of a single study on the summary risk estimate by adding one study in each turn. The present work was performed as per the guidelines proposed by the meta-analysis of observational studies in epidemiology group and preferred reporting items for systematic reviews and meta-analyses [Supplementary Material].

Results

Search Results

A total of 2,288 articles were identified during the initial search [Figure 1]. After reviewing the titles and abstracts of these articles, 2,257 were found to be ineligible as they were reviews, case reports, letters, editorials, and others which did not meet the inclusion criteria. After detailed evaluation of the remaining 31 full-text articles, 17 were excluded due to nonantidepressant exposure and non-MI outcome [Figure 1].

Study Characteristics

Fourteen relevant studies were identified, including five cohort and nine case–control studies involving more than 838,993 subjects and more than 83,941 MI cases.
### Supplementary material: PRISMA 2009 checklist

| Section/topic                | Number | Checklist item                                                                 | Reported on page number |
|------------------------------|--------|---------------------------------------------------------------------------------|-------------------------|
| **Title**                    | 1      | Identify the report as a systematic review, meta-analysis, or both               | 1                       |
| **Abstract**                 |        |                                                                                  |                         |
| **Structured summary**       | 2      | Provide a structured summary including, as applicable: Background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number | 1                       |
| **Introduction**             |        |                                                                                  |                         |
| **Rationale**                | 3      | Describe the rationale for the review in the context of what is already known | 2                       |
| **Objectives**               | 4      | Provide an explicit statement of questions being addressed with reference to PICOS | 3                       |
| **Methods**                  |        |                                                                                  |                         |
| **Protocol and registration**| 5      | Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information including registration number | NA                      |
| **Eligibility criteria**     | 6      | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale | 3                       |
| **Information sources**      | 7      | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched | 3                       |
| **Search**                   | 8      | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated | 3                       |
| **Study selection**          | 9      | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis) | 3                       |
| **Data collection process**  | 10     | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators | 4                       |
| **Data items**               | 11     | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made | 5                       |
| **Risk of bias in individual studies** | 12   | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis | 5                       |
| **Summary measures**         | 13     | State the principal summary measures (e.g., risk ratio, difference in means)     | 5                       |
| **Synthesis of results**     | 14     | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis | 5                       |
| **Risk of bias across studies** | 15   | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies) | 5                       |
| **Additional analyses**      | 16     | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified | 5                       |
| **Results**                  |        |                                                                                  |                         |
| **Study selection**          | 17     | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram | 6                       |
| **Study characteristics**    | 18     | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations | 6                       |
| **Risk of bias within studies** | 19   | Present data on risk of bias of each study and, if available, any outcome level assessment (item 12) | 7                       |
| **Results of individual studies** | 20   | For all outcomes considered (benefits or harms), present, for each study: (a) Simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot | 15                      |
| **Synthesis of results**     | 21     | Present results of each meta-analysis done, including confidence intervals and measures of consistency | 7                       |
| **Risk of bias across studies** | 22   | Present results of any assessment of risk of bias across studies (see item 15) | 7                       |
| **Additional analysis**      | 23     | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [item 16]) | 8                       |
| **Discussion**               |        |                                                                                  |                         |
| **Summary of evidence**      | 24     | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers) | 9                       |
| **Limitations**              | 25     | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias) | 10                      |
| **Conclusions**              | 26     | Provide a general interpretation of the results in the context of other evidence and implications for future research | 10                      |

Contd...
Supplementary material: Contd...

| Section/topic | Number | Checklist item | Reported on page number |
|---------------|--------|----------------|-------------------------|
| Funding       | 27     | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review | NA |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA group (2009). PLoS Med 6 (6): e1000097. doi: 10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org. PICOS = Participants, interventions, comparisons, outcomes, and study design, NA = Not available, PRISMA = Preferred reporting items for systematic reviews and meta-analyses

Figure 1: Flowchart representing the selection process of studies

Participants were followed up for 4–13 years and the studies were published between 1996 and 2011.

Five cohort studies of antidepressants use and risk of MI were published between 2000 and 2011 which included more than 242,419 participants, followed up for 4–13 years, reporting 1.111 incident MI cases among 97,207 antidepressants users, and 1,558 incidents of MI cases among 88,784 nonantidepressants users. Three studies assessed MI diagnosis through the database, and two studies assessed diagnosis through hospital chart review. All studies were conducted in United States of America (USA), except one study in Europe.

Nine case–control studies have been published between 1996 and 2011. These studies included more than 596,574 participants, conducted for 1–13 years, reporting a total of 9,741 antidepressants users among 83,266 MI cases and 42,648 antidepressants users among 513,308 controls. Antidepressant use was ascertained by the database in five studies and by a patient interview in four studies. Of these, six studies were conducted in Europe and three in USA.

Among the total 14 studies, four were fond the risk of MI in any antidepressant users, six studies in TCAs users, 11 studies in SSRIs users, four studies in non-SSRIs users, one study in SNRIs users and one study in MAOIs users. Almost all the studies were controlled for potential confounding factors (at least for age) by matching or adjustment. The characteristics of the selected studies are presented in Table 1.

Quality Assessment Results

All the cohort studies were found to be high-quality studies with NOS score of eight. In the case–control studies, 7 (78%) were of high quality (NOS score > 6) with an average NOS score of 7.6.

Main Analysis

No publication bias was observed among four studies with any antidepressant use by Begg’s test (P = 0.30), Egger’s test (P = 0.45) and the funnel plot with an expected funnel shape. Because of heterogeneity (I² = 0.02; F = 68%) among the studies, a random-effects model was chosen over a fixed-effects model. We observed a significant increased risk of MI among any antidepressants users (RR = 2.03; 95% CI = 1.30–3.18; P < 0.01). Both multivariable-adjusted RR estimates with 95% CIs of each study and pooled RR are shown in Figure 2.

Secondary Analysis

We observed no association between TCAs use and risk of MI (RR = 1.14; 95% CI = 0.67–1.96; P = 0.62) with significant heterogeneity (I² = 0.01; F = 98%) but no publication bias (Begg’s P = 0.70 and Egger’s P = 0.45) [Figure 2]. But, the sensitivity analysis revealed that the TCAs users are having 36% increased risk of MI after excluding one outlier study, that is, Scherrer et al. (RR = 1.36; 95% CI = 1.10–1.67; P < 0.01) with less heterogeneity (I² = 0.01; F = 78%) [Figure 3]. We found a nonsignificant association between SSRIs and non-SSRIs use and risk of MI (RR = 0.84; 95% CI = 0.57–1.22; P = 0.35 and RR = 0.92; 95% CI = 0.82–1.04; P = 0.20, respectively). There was heterogeneity among the group of studies using SSRIs but not for non-SSRIs and no publication bias was observed among these groups [Table 2].

Subgroup Analyses

On subgroup analysis by study design, we found significant positive association between any antidepressants use and risk of MI among cohort studies (RR = 2.16; 95% CI = 1.42–3.29; P < 0.01), but not for case–control studies (RR = 2.47; 95% CI = 0.69–8.90; P = 0.17). Case–control studies of TCAs users showed increased risk of MI among TCAs users (RR = 1.41; 95% CI = 1.37–1.45; P < 0.01), but not cohort studies (RR = 0.94; 95% CI = 0.40–2.23; P = 0.89). The results were not deviated from main analysis of SSRIs and non-SSRIs use after subgroup analysis by study design and adjustment for other CVD [Table 2].

Sensitivity Analysis

Sensitivity analysis showed no significant variation in pooled RR by excluding any one study; RR lied between...
The table below summarizes the studies included in the meta-analysis:

| Study period  | MI cases | MI use | Study design | Statistic for each study | MI risk | p value | MI risk and 95% CI | Relative weight |
|---------------|----------|--------|--------------|--------------------------|---------|---------|------------------|----------------|
| Pratt et al. 1996 (USA) | 6 | a | A | 1-5 |
| Penttinen and Valonen 1996 (Europe) | 83 | b | A | NR |
| Cohen et al. 2000 (USA) | 207 | b | B | 2, 4, 6-11 |
| Cohen et al. 2001 (USA) | 112 | b | A | 1-3, 7, 8, 12-21 |
| Meier et al. 2001 (Europe) | 3319 | c | B | 13, 21 |
| Sauer et al. 2001 (USA) | 653 | d | A | 1, 2, 4, 7-9, 13, 16, 21-26 |
| Sauers et al. 2003 (USA) | 1080 | e | A | 2, 4, 6, 8, 9, 13, 16, 21, 22, 24, 25, 27 |
| Monster et al. 2004 (Europe) | 5238 | f | B | 4, 8, 18, 20, 28-36 |
| Schienger et al. 2004 (Europe) | 8688 | c | B | NR |
| Tata et al. 2005 (Europe) | 63,512 | b | B | 2 |
| Blanchette et al. 2008 (USA) | 11,908 | 65 | NR | 2, 6, 8, 10, 13, 21, 22, 37 |
| Coupiland et al. 2011 (Europe) | 2350 | h | B | 1, 2, 4, 7, 8, 11, 13, 18, 24, 37-52 |
| Scherrer et al. 2011 (USA) | 613,522 | 25-80 | NR | j | B | 7, 10, 37, 53, 54 |
| Kimmel et al. 2011 (Europe) | 693 | j | B | 4, 7-9, 24, 55-57 |

**Table 1:** Studies included in the meta-analysis

**Figure 2:** Forest plot representing the association between antidepressants use and risk of myocardial infarction. The size of the square is proportional to the weight of the corresponding study in the meta-analysis; the length of the horizontal line represents the 95% confidence interval (CI); the diamond indicates the pooled relative risk with 95% CI (random effects model).

1.66–2.47 among studies with any antidepressants use, 0.77–0.92 among studies with SSRIs and 0.90–0.93 among studies with non-SSRIs, confirming the stability of present results. Sensitivity analysis of studies with TCAs use shifted pooled RR with 95% from no association (RR = 1.14; 95% CI = 0.67–1.96; P = 0.62) to positive association.
after excluding Scherrer, et al. study\cite{21} (RR = 1.36; 95\% CI = 1.10–1.67; \( P < 0.01 \)) [Figure 3].

**Cumulative Meta-analysis**

Cumulative meta-analysis of studies with any antidepressant use shows decreasing trend of reporting RR from 5.4 in 1998\cite{11} to 2.03 after adding three studies published from 2000 to 2005.\cite{7,12,18} There was a change observed in reporting MI risk among TCAs users from no association in 1996\cite{20} (RR = 1.30; 95\% CI = 0.52–3.27; \( P = 0.58 \)) to positive association (RR = 1.36, 95\% CI = 1.10–1.67; \( P < 0.01 \)) after adding four studies published between 2000 and 2011\cite{7,15,18,20} and again into no association (RR = 1.14, 95\% CI = 0.67–1.96; \( P = 0.62 \)) after adding a study published in 2011.\cite{21} There was no change observed in association between SSRIs use and risk of MI from 2000 to 2011 (RR = 0.80; 95\% CI = 0.19–3.34 to RR = 0.84 95\% CI = 0.57–1.22).

**Figure 3:** Sensitivity analysis of studies with tricyclic antidepressants use and risk of myocardial infarction

**Table 2:**

| Overall effect estimates for myocardial infarction in ADs users according to study characteristics |
|-----------------------------------------------|
| **Number of studies** | **Pooled estimate** | **Tests of heterogeneity** | **Pinteration** | **Tests of publication bias** |
|-----------------------------------------------|
| | RR (95\% CI) | \( P \) | Q (df) | \( P \) | \( I^2 (%) \) | Begg’s \( P \) | Egger’s \( P \) |
| Any AD use | 4 | 2.03 (1.30-3.18) | <0.01\* | 9.38 (3) | 0.02 | 68 | 0.30\* | 0.45\* |
| Cohort studies | 2 | 2.16 (1.42-3.29)* | <0.01\* | 0.01 (1) | 0.92 | 0 | 0 \( ^1 \) | 0.84^| |
| Case-control studies | 2 | 2.47 (0.69-8.90) | 0.17 | 5.65 (1) | 0.02 | 82 | - | - |
| TCAs use | 6 | 1.14 (0.67-1.96) | 0.62 | 377.04 (5) | <0.01 | 98 | 0.70\* | 0.45^| |
| Except study Scherrer et al\cite{21} | 5 | 1.36 (1.10-1.67) | <0.01\* | 18.46 (4) | <0.01 | 78 | 0.35\* | 0.46^ | 0.80^ |
| Cohort studies | 3 | 0.94 (0.40-2.23) | 0.89 | 143.06 (2) | <0.01 | 98 | 1.00^ | 0.80^ |
| Case-control studies | 3 | 1.41 (1.37-1.45)* | <0.01\* | 0.26 (2) | 0.88 | 00 | 1.00| | 0.72\* |
| SSRIs use | 11 | 0.84 (0.57-1.22) | 0.35 | 598.61 (10) | <0.01 | 98 | 0.87\* | 0.30^ |
| Cohort studies | 4 | 0.95 (0.49-1.87) | 0.89 | 188.09 (3) | <0.01 | 98 | 0.64^ | 1.00^ | 0.70^ |
| Case-control studies | 7 | 0.79 (0.53-1.17) | 0.24 | 80.06 (6) | <0.01 | 92 | 0.36^ | 0.00 |
| Adjusted for other CVD | 6 | 0.80 (0.60-1.07) | 0.13 | 22.85 (5) | <0.01 | 78 | 0.67\* | 0.45^ | 0.03 |
| Not adjusted for other CVD | 5 | 0.94 (0.47-1.88) | 0.86 | 570.08 (4) | <0.01 | 99 | 1.00^ | 0.60^ |
| NonSSRIs use | 4 | 0.92 (0.82-1.04)* | 0.20 | 0.55 (3) | 0.91 | 00 | 1.00| | 0.53^ |
| Adjusted for other CVD | 2 | 0.95 (0.75-1.19)* | 0.64 | 0.47 (1) | 0.49 | 00 | 0.75^ | - | - |
| Not adjusted for other CVD | 2 | 0.91 (0.79-1.06)* | 0.23 | 0.02 (1) | 0.89 | 00 | - | - |
| SNRIs use | 1 | 0.35 (0.32-0.40) | - | - | - | - | - | - |
| MAOIs use | 1 | 1.26 (1.00-1.59) | - | - | - | - | - | - |

*Relative risk from fixed-effects model due to no heterogeneity among the studies. \( P \) value representing significant association between ADs use and myocardial infarction. \( ^{1} \)Statistically significant for homogeneity. \( ^{2} \)Test of interaction was not statistically significant. \( ^{3} \)Statistically significant for no publication bias. RR = Relative risk, CI = Confidence interval, df = Degree of freedom, SSRIs = Selective serotonin reuptake inhibitors, CVD = Cardiovascular diseases, TCAs = Tricyclic antidepressants, SNRI = Serotonin-norepinephrine reuptake inhibitors, MAOIs = Monoamine oxidase inhibitors, ADs = Antidepressants

**Discussion**

In the past decade, the role of antidepressants use in the development of MI has been widely debated. With the combined analysis of four observational studies currently available, it appears that 2-fold increased risk of MI among antidepressants users compared to nonusers, and this association remained stable even after the sensitivity analysis. Our results support the hypothesis that TCAs use may increase the risk of MI but not SSRIs use may reduce the risk of MI. A study by Scherrer, et al.\cite{21} found 65\% decreased risk of MI among subjects who were using SNRIs and a study by Tata, et al.\cite{18} found 26\% increased risk of MI among MAOIs use, compared to the subjects who were not taking any antidepressant.

Depression could increase heart rate, decrease heart rate variability, or contribute to electrical instability secondary to inhibition of parasympathetic activity, or may stimulate sympathetic activity with subsequent changes in serum levels of catecholamines.\cite{7} The patients with depression are at an increased risk for MI due to abnormalities in platelet function such as up-regulation of platelet imidazoline and serotonin receptors and enhanced intra-platelet calcium mobilization.\cite{14} SSRIs may reverse this sequel and reduce MI risk by affecting serotonin-mediated platelet activation due to inhibition of serotonin uptake into platelets and blocking of intracellular calcium mobilization.\cite{14} It is also possible that SSRIs prevent MI through treatment of depression which would lead to a reversal of the abnormal platelet function, modification of lifestyle, and better compliance with medication, diet, and exercise.\cite{14}

Our findings are consistent with the hypothesis that the use of TCAs may increase the risk of MI in depression. TCAs are...
class I antiarrhythmic drugs, a group of medications that have been associated with an increased risk of sudden death.[31] They have also been shown to increase heart rate and reduce heart rate variability.[32] Cardiac complications of TCAs therapy were observed decades ago and since 1981 several investigators have warned about the use of tricyclic agents, particularly among those with CVD.[7]

In the subgroup analysis, stratification by study design substantially affects the result among subgroups of any antidepressant use and TCAs use, but there is no deviation in the result among subgroups with SSRIs and non-SSRIs use. Cohort studies with any antidepressant use showed 2.2-fold increased risk of MI, but case–control studies showed no association. Cohort studies with TCAs showed no association, whereas case–control studies showed 41% increased risk of MI. Subgroup analysis based on the adjustment of other CVD among studies with SSRIs use, and non-SSRIs use did not substantially influence the results.

The strength of the present analysis lies in the inclusion of 14 observational studies reporting data of more than 800,000 participants, including 85,941 MI cases.

Our meta-analysis has following limitations. First, we did not search for unpublished studies for original data, which may or may not be in agreement with our results. Second, the included studies were different in terms of study design, confounder adjustments, and definitions of drug exposure.

In summary, our results found a harmful association between antidepressant use and risk of MI. However, we cannot rule out an increased risk of MI in TCAs users and decreased risk of MI among SSRIs users. A randomized trial is needed to determine whether the antidepressant use in general and the different classes of agents, in particular, affect the association between depression and MI along with underlying biological mechanisms.

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