Role of Antidepressants in Acute Coronary Syndrome: An Evidence-Based Case Report

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ABSTRACT

Background: *Acute coronary syndrome (ACS) and depression are related to each other. Detection and proper treatment of these conditions can improve functional ability and quality of life. However, there is still controversy in this population regarding the use, safety, and efficacy of antidepressant pharmacotherapy. This evidence-based case report (EBCR) aims to determine the role of antidepressants in acute coronary syndrome patients.* ***Methods:*** *Literature searching was performed using online databases such as EBSCO, Embase, PubMed, ClinicalKey, and ScienceDirect according to clinical questions. The studies were selected based on the suitability of the inclusion and exclusion criteria followed by critical appraisal.* ***Results:*** *In patients with ACS, antidepressants do not affect mortality but may reduce rehospitalization. In patients with ACS and depression who received antidepressants, there is a reduced risk of myocardial infarction (MI) recurrence. In post-ACS patients, the use of antidepressants is associated with a reduced risk of recurrent MI.* ***Conclusion:*** *In ACS patients, antidepressants do not affect mortality but can reduce the incidence of myocardial reinfarction.*

Keywords*: acute coronary syndrome, antidepressant, cardiovascular event, mortality.*

INTRODUCTION

Age, obesity, smoking, dyslipidemia, diabetes, hypertension, genetics, and stress are known risk factors for cardiovascular disease.[1] Depression is strongly associated with acute coronary syndrome (ACS), and its prevalence significantly increases in post-ACS patients.[1–6] Several studies have demonstrated a clinically significant prevalence of 31-45% depressive symptoms in patients with coronary artery disease (CAD) and 15-20% post-ACS, and since 2005 the use of antidepressants has increased after ACS.[1–5] Depression may increase the mortality rate by 2–2.5 times in patients with ACS compared to those without depression.[2,5] A recent meta-analysis showed that the hazard ratio for the association between post-myocardial infarction depression and all-cause mortality was 1.32 (95% CI 1.26–1.38, P<0.001).[2,4] The pathophysiology of post-ACS depression is still unclear, and several mechanisms have been identified, such as autonomic nervous system dysfunction, heart rate variability, and increased inflammation.[2] Inflammatory cytokines are associated with the formation, development, and rupture of atherosclerotic

plaques; therefore, depression can exacerbate the incidence of ACS.[2] However, the optimal therapeutic approach, as well as the use, safety, and efficacy of antidepressant pharmacotherapy in this population, remain controversial. The aim of this EBCR was to examine the available evidence regarding the role of antidepressants on clinical outcomes in patients with ACS.

CASE ILLUSTRATION

A 61-year-old man was admitted to hospital with complaints of pain in the left chest since a few hours before hospital admission, typical chest pain towards ACS, pain reduced by taking oral isosorbide dinitrate, no loss of consciousness and no palpitations. This complaint was not the first occurrence; he had experienced a heart attack and undergone two elective percutaneous coronary interventions last year. He has history of hypertension and diabetes. Over the past year, the patient has occasionally experienced chest pain, felt tired more easily, lost interest in many activities and hobbies, and had sleep disturbances. He often feels afraid because of those symptoms. Fortunately, the family supports the patient even though it does not eliminate the complaints. From this case illustration, a question arises whether the role of antidepressant in patient with acute coronary syndrome?

METHODS

A systematic literature search was conducted on May 11th, 2022, to answer the clinical question above by searching online databases such as EBSCO, Embase, PubMed, ClinicalKey, and ScienceDirect. The population of this study is acute coronary syndrome. The intervention of this study is antidepressant agent. The comparison of this study is placebo or no intervention. The outcomes are all-cause mortality, recent myocardial infarction, and rehospitalization. The keywords used were "antidepressant," "fluoxetine," "sertraline," "escitalopram," "SSRI," "SNRI," "TCA," "MAOi", "acute coronary syndrome," combined with Boolean operators "AND" and "OR" in the search strategy. Articles included were screened according to inclusion and exclusion criteria, also removed the duplication. We included the study of meta-analysis (MA), systematic review (SR), randomized controlled trial (RCT), and clinical trial of adult populations with acute coronary syndrome (with or without depression, included post-acute coronary syndrome) who received intervention of antidepressant agent. We included all the outcomes. Other types of studies not meeting the inclusion criteria were excluded. Studies published in languages other than English or those not relevant to the PICO framework were excluded. Articles which met the criteria were critically appraised for validity, importance, and applicability using worksheets available from the Centre of Evidence-Based Medicine, University of Oxford (www.cebm.net), in accordance with the type of article. The level of evidence for each article was classified based on the Oxford Centre for Evidence-Based Medicine.

Table 1. Quaries used to conduct literature searching in journal database

Database	Keywords	Hits	Eligible
EBSCO	(antidepressant OR fluoxetine OR sertraline OR escitalopram OR SSRI OR SNRI OR TCA OR MAOi) AND (acute coronary syndrome)	128	5
Embase	('antidepressant'/exp OR antidepressant) AND ('acute coronary syndrome'/exp OR 'acute coronary syndrome' OR (acute AND coronary AND ('syndrome'/exp OR syndrome)))	290	3
PubMed	(antidepressant OR fluoxetine OR sertraline OR escitalopram OR SSRI OR SNRI OR TCA OR MAOi) AND (acute coronary syndrome)	161	3
ClinicalKey	(antidepressant OR fluoxetine OR sertraline OR escitalopram OR SSRI OR SNRI OR TCA OR MAOi) AND (acute coronary syndrome)	17	0
ScienceDirect	(antidepressant OR fluoxetine OR sertraline OR escitalopram OR SSRI OR SNRI OR TCA OR MAOi) AND (acute coronary syndrome)	10.192	2

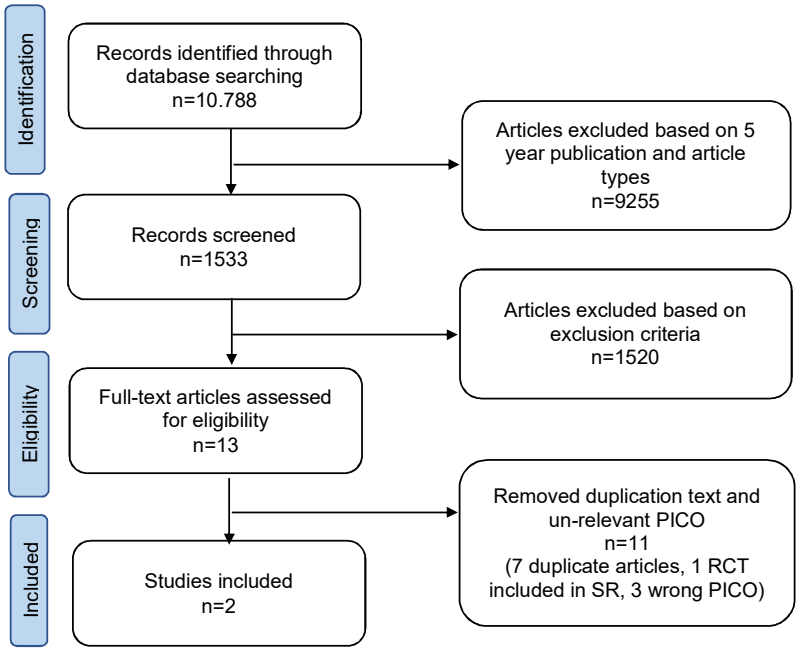

Figure 1. Flow diagram of literature searching

RESULTS

The studies included are systematic review and meta-analysis by Sweda R et al, and Fernandes et al. The summary of both articles presented in **Table 2**. The critical appraisal of the studies presented in **Table 3**.

Table 2. Summary of articles used in study

Reference / Study designs	Subjects	Determinants	Inclusion criteria	Exclusion Criteria	Outcome	Evidence Grade
Sweda R et al, (2020) / SR-MA	10 trials (12 reports) (1935 participants) with ACS	I: Bupoprion : 3 trials SSRI : 6 trials Noradrenergic and specific serotonergic antidepressant mirtazapine : 1 trial C : placebo	- Antidepressant treatment to be initiated within 1 year after ACS and continued for minimum 30 days	- Stable CAD, chronic heart failure, and other cardiac or non-cardiac conditions - Non-randomized studies, studies without primarily pharmacological intervention and without quantitative information on the outcomes of interest - Language other than English or German	- Primary : All−cause mortality. - Secondary: MI and rehospitalizations	1
Fernandes et al (2020) / SR-MA	Post ACS patients (8 RCTs) – 1148 patients	I: SSRI C : Placebo	- Stable coronary disease or post-acute coronary syndrome patients with depression - No language restriction	- Other than RCTs	- Primary outcomes : all-cause mortality, cardiovascular mortality, and MI incidence. - Secondary outcomes included PCI, hospitalization for cardiovascular causes, angina, heart failure, and stroke	1

Table 3. Critical appraisal of the studies included

	Sweda R, et al	Fernandes, et al
Q - What question (PICO) did the systematic review address? And use it to direct the search and select articles for inclusion?	Matched the PICO Framework. Yes P= ACS patients I = antidepressant therapy C = placebo / usual care O = all cause mortality, rehospitalization, recurrent myocardial infarction	Matched the PICO Framework. Yes P= CAD patients with depression I = SSRI C = placebo / no intervention O = all causes mortality, cardiovascular mortality, and myocardial infarction incidence
F – Did the search find all the relevant evidence?	Yes The study searched on PubMed, Embase, Cochrane for RCT, also scrutinized the reference lists of eligible articles for additional relevant entries. They included 10 trials.	Yes The study searched on CENTRAL, MEDLINE end PsycINFO for RCT and extended follow up analyses of RCT. They included 8 RCTs.
A – Were the criteria used to select articles for inclusion appropriate and critically appraised?	Yes This study used articles about intervention. This study included antidepressant treatment initiated within 1 year after the index ACS. ACS includes ST elevation and non-ST elevation myocardial infarct and unstable angina pectoris. In case of overlapping study populations, they included most recent results with the longest available follow up and available data of interest. Two investigators independently scrutinized articles. In case of discrepancies, they discussed it	Yes This study included SSRIs on target population such as stable coronary disease or post-acute coronary syndrome patients with depression. There were reviewers independently systematically reviewed the articles. In case any doubts and disagreements, they discussed it
I – Were the included studies sufficiently valid for the type of question asked?	Yes Studies included had similar PICO and were low risk in selection bias, performance bias, detection bias, reporting bias, and other biases except attrition bias	Yes Studies included had similar PICO, with 2 high risks bias articles
T – Have the results been totaled up with appropriate summary tables and plots?	Yes There were appropriate summary tables and plots	Yes There were appropriate summary tables and plots
H – Heterogeneity between studies assessed and explained?	Yes The magnitude of the heterogeneity variance parameter (τ) was used to assess statistically the presence of heterogeneity. All explained in the text and presented in plot	Yes The heterogeneity was assessed using I^2 and was considered to be substantial above 50%. All explained in the text and presented in plot.

DISCUSSION

The study by Sweda, et al showed that there was no difference in all-cause mortality [odds ratio (OR) 0.97, 95% credible interval (CrI) 0.66–1.42] and recurrent MI (OR 0.64, 95% CrI 0.40–1.02) between patients receiving antidepressants compared with controls, whereas antidepressant therapy was associated with fewer re-hospitalizations (OR 0.62, 95% CrI 0.40–0.94). Antidepressants reduced the risk of recurrent MI in patients with ACS and depression compared to usual care/placebo (OR 0.45, 95% CrI 0.25–0.81). In this study, they included trials that initiated antidepressant pharmacotherapy in-hospital (without further exact time data) up to 12 months thereafter. The treatment duration ranged from 8 to 52 weeks, with majority in 24 weeks. The median follow-up duration was 1 year, and only 3 out of 10 trials reported long-term outcomes. This study included 10 trials, but with a low number of participants and events. The subjects recruited in RCTs were well-selected and might not represent the general population.[6]

The study by Fernandes, et al showed that SSRIs were associated with a significantly lower risk of MI in patients with CAD and depression (RR 0.54, 95% CI 0.34–0.86), and in post-ACS patients with depression (RR 0.56,

95% CI 0.35–0.90). They found no statistically significant difference in all-cause mortality, cardiovascular mortality, hospitalizations, angina, congestive heart failure, or stroke incidence. Most patients in the study were given either sertraline or escitalopram, and that the two largest (totalling 89% of patients included in the post-ACS meta-analysis of MI risk) and the longest studies included had an intervention duration of 6 months, with clinically titrated dosages based on the reduction and tolerance of depressive symptoms.[5]

The mechanisms by which depression negatively affects the cardiovascular system and by which therapeutic interventions exert positive effects are still poorly understood. It is thought that depression cause negative effect in cardiovascular system by dysregulation of autonomic control, up-regulation of pro-inflammatory molecules, and increased platelet activation.[6] Several mechanisms involved in the potential cardiovascular benefits of SSRIs have been proposed: treatment of depression/depressive symptoms; inhibition of serotonin-mediated platelet aggregation, inflammation reduction; improved endothelial function, and increased medication adherence.[5] Antidepressant SSRI may reduce MI risk by affecting serotonin-mediated platelet activation. SSRIs inhibit serotonin uptake into platelets and block intracellular calcium mobilization, so the platelet activity is reduced.[7] SSRI paroxetine inhibits the G protein-coupled receptor kinase (GRK2), which plays a major role in the development of cardiovascular disease. This protein expression is higher in patients with ACS with depression. The SSRI paroxetine reduced the levels of GRK2 and led to a normalization of autonomic nervous system function, improved cardiac performance, and lowered the rate of recurrent infarction.[6] It is also possible that SSRIs prevent MI through reduction of other depression-mediated mechanisms, such as modification of lifestyle and better compliance with medication.[7]

Both articles are valid and can be applied to the daily practice. The results reinforce the cumulative evidence that antidepressant therapy may have a favourable risk in CAD patients with major depression and suggest a proactive approach in this population, despite the optimal strategy to identify and treat the adverse association between depression and CAD must still be determined. However, whether some SSRIs are superior to others, for example escitalopram which might be preferred over sertraline as it is the only SSRI that demonstrate cardiovascular benefit in an individual study,[4] the effectiveness of reducing MI incidence is dependent on dose, duration of treatment, continuity of therapy, or residual effects which should be investigated. It is also necessary to consider the side effects of SSRIs which contribute to mortality or morbidity such as serotonin syndrome, QT prolongation, and bleeding.

The advantage of this EBCR is the evidences obtained are included in level 1. The number of participants is also quite large, includes various type of antidepressants. Both articles included showed low heterogeneity data, even the study by Fernandes, et al showed homogenous data. The lack of this EBCR is the included studies are limited to the last 5 years and in English, although one of article had no language restriction. Keywords used in one database also generated many hits. Even the participants are quite large but the design is in the form of RCT, so the participants are selected and not represent the general population.

CONCLUSION

In patients with ACS, antidepressant has no effect on mortality but may reduce rehospitalization. In patients with ACS and depression, antidepressant reduced risk of MI recurrence. In post ACS patients, the use of antidepressant is associated with a reduced risk recurrent MI. The antidepressant therapy can be initiated within 1 year of ACS, with treatment duration of 6 months, and the dose according to therapeutic dose. Further long-term RCTs are necessary to determine the effect of antidepressant on mortality and cardiovascular events in ACS patients.

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