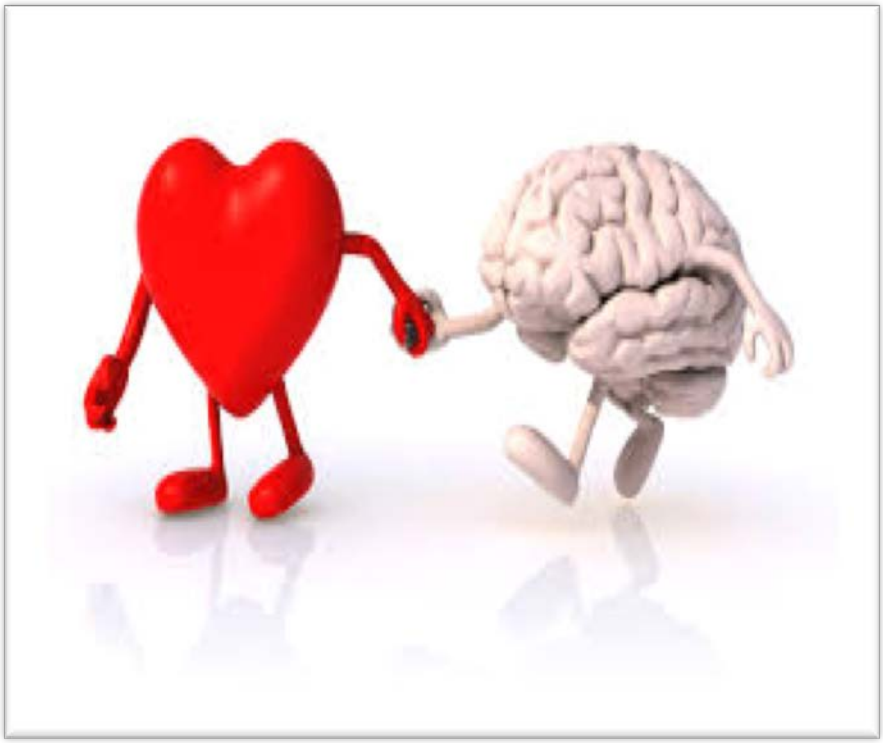
Treatment of Depression with SSRIs in Patients Post-Acute Coronary Syndromes: Better Safe Than Sorry



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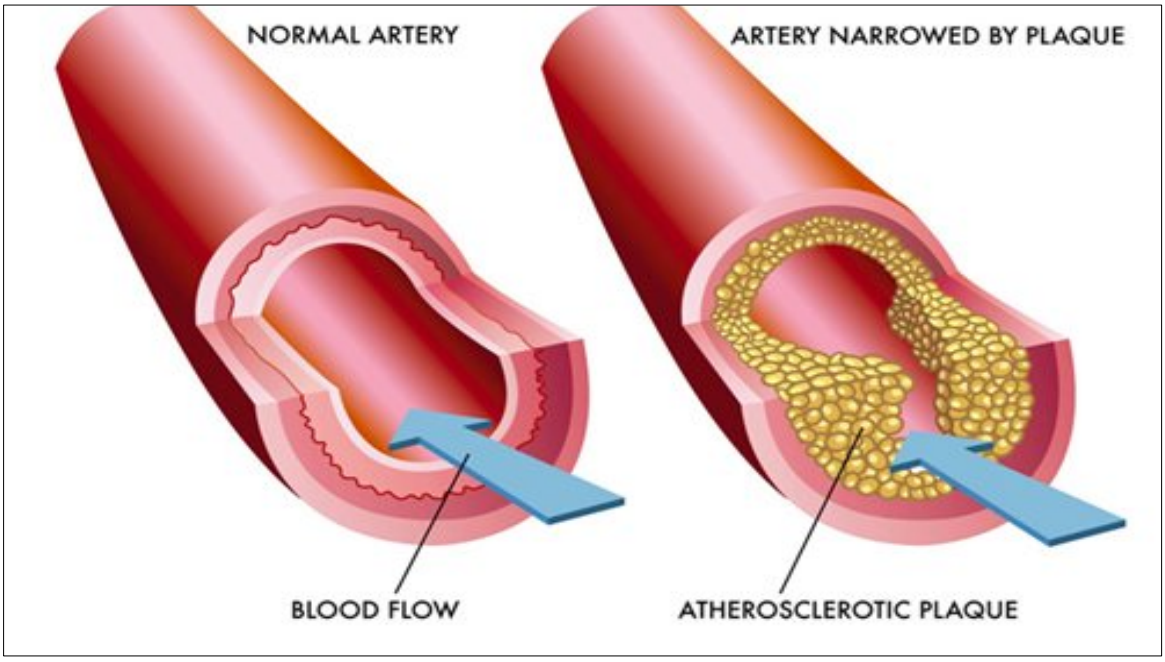
Objectives:

1. Describe the relationship between depression and acute coronary syndrome.
2. Identify the potential cardiovascular risks associated with treatment with SSRIs.
3. Develop an action plan regarding treatment of major depressive disorder in post-acute coronary syndrome patients.

Introduction:

1. Acute Coronary Syndromes:
    a. Background:[1]
        i. Heart disease is one of the highest causes of death in the United States
        ii. Incidence/Prevalence:
            1. In the recent 2018 Heart Disease and Stroke Statistics Update, roughly 92 million American adults over the age of 20 reported having some form of cardiovascular disease
            2. In the same report, 16.5 million people reported being diagnosed with coronary heart disease (CHD)
                a. This was equivalent to about 6.8% of the American population
            3. In the same report, 3.0% and 3.4% of the population, equaling to 7.9 million and 8.7 million respectively, reported having or previously having a myocardial infarction (MI) or unstable angina (UA)
            4. It is estimated that every 40 seconds someone will experience an MI in the United States
        iii. Types: STEMI, NSTEMI, and UA
            1. Definitions
                a. STEMI: ST segment elevation myocardial infarction
                b. NSTEMI: non-ST segment elevation myocardial infarction
                c. UA: unstable angina
            2. All ACS are atherosclerotic in nature
                a. Atherosclerosis being a disease in which there is plaque buildup in the arteries

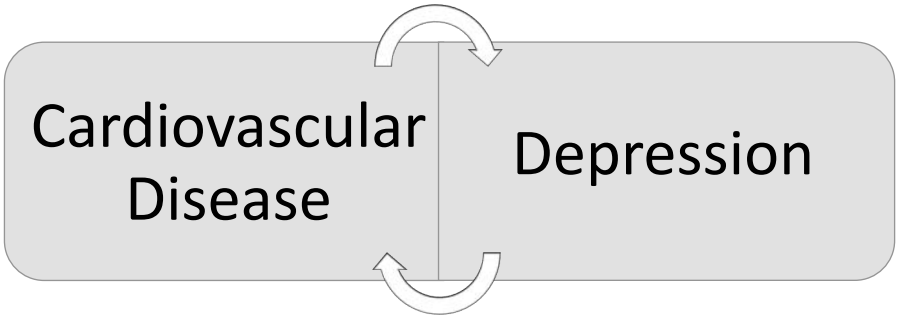
Picture 1: Atherosclerosis[2]

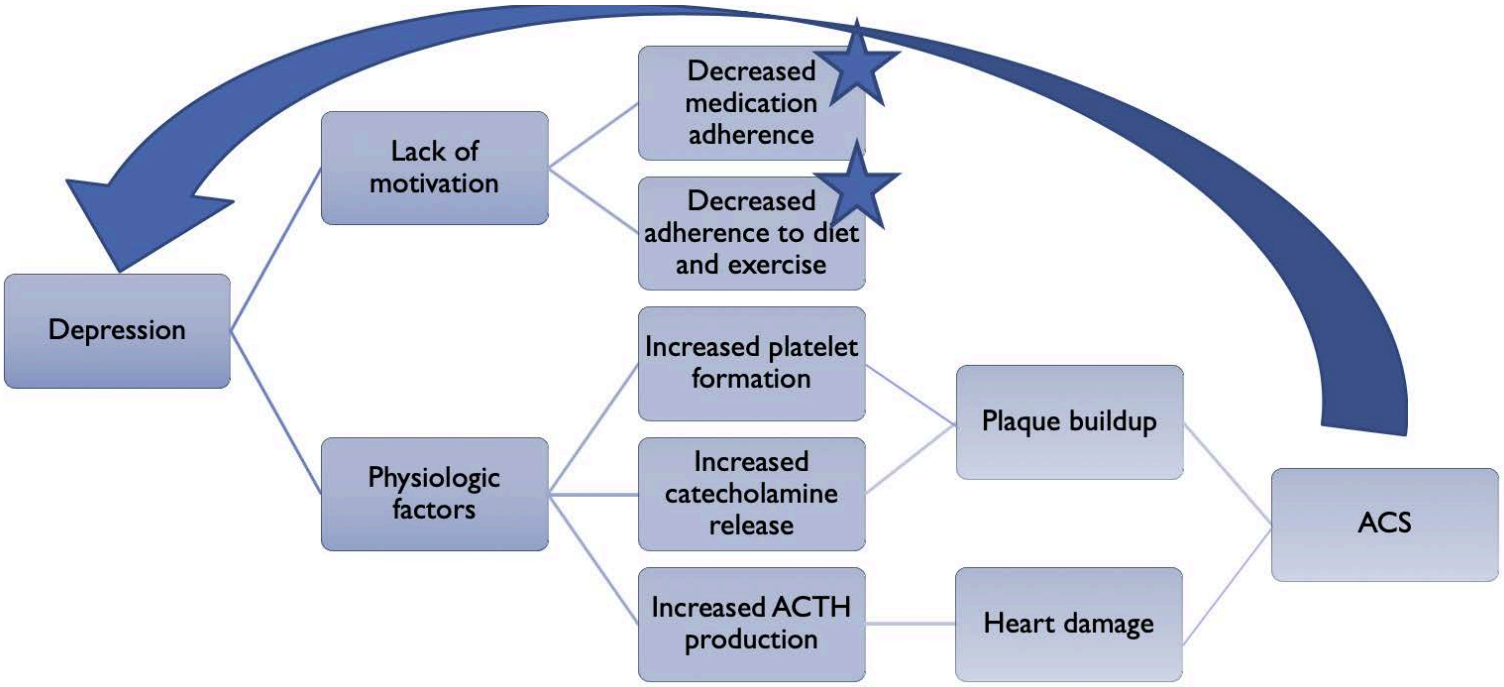


b. Standard of Care:[3]
    i. Pharmacotherapy
        1. STEMI and NSTEMI:
            a. Beta blocker
            b. Angiotensin converting enzyme inhibitor
            c. Calcium channel blocker
            d. Nitrates (eg. nitroglycerin)
            e. Aspirin
            f. P2Y12 Inhibitors (ie. clopidogrel, prasugrel, ticagrelor)
    ii. Non-pharmacotherapy
        1. Healthy Diet
        2. Moderate exercise as tolerated
        3. Cardiac rehabilitation programs
c. Complications:
    i. Recurrent MI
    ii. Heart Failure
    iii. Arrhythmias
    iv. Post-ACS Depression

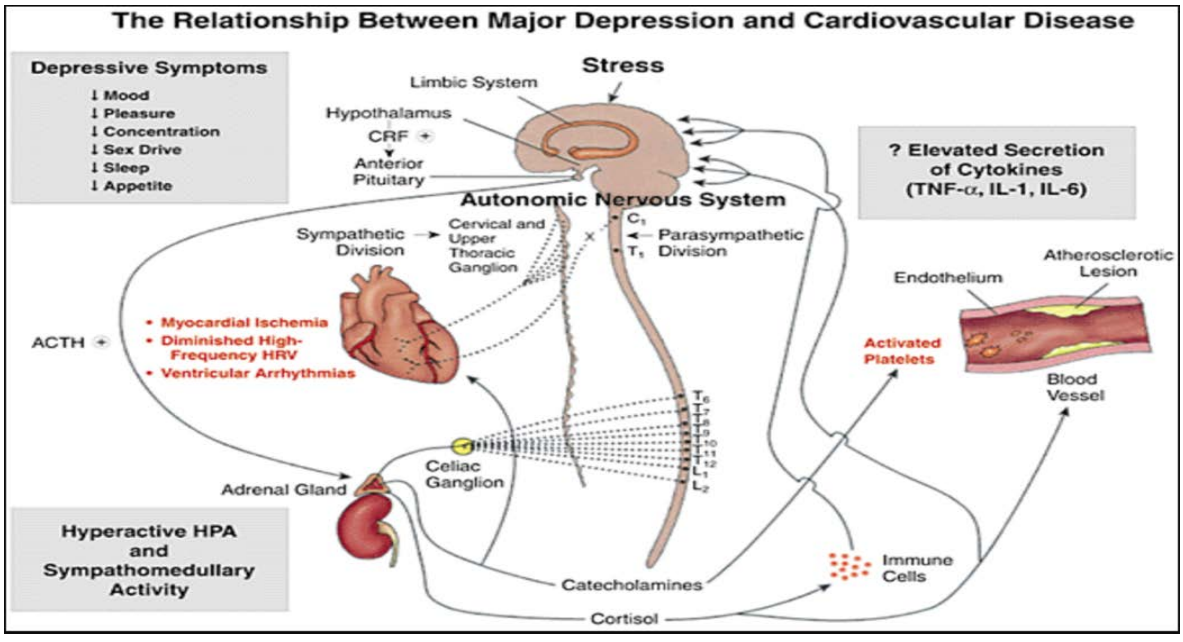
2. Post-ACS Depression
    a. Background:
        i. Incidence/Prevalence[,4,5,6]
            1. Depression in non-cardiac patients occurs at a rate of 6.4%.
            2. Studies have varied in the true prevalence of post-ACS depression
                a. Results depend on having clinically significant symptoms of depression or meeting full criteria for Major Depressive Disorder (MDD)
                b. Rates of MDD have been found anywhere from 17-27%
                c. All depressive symptoms ranged from 31-45%
            3. Recent study demonstrated 6-month prevalence of depression in post-ACS patients to be ~44% which is the highest for any psychiatric disorder[6]
        ii. Possible reasons for an increased MDD prevalence[5,7]
            1. Worsening health and overall well-being
            2. Stress from recent traumatic experience including the cardiovascular event and/or hospital stay
            3. Fear of recurrence
            4. Decreased motivation and activity levels compared to pre-MI
                a. Less adherent to clinical management and treatments including follow-up appointments, lifestyle modifications, and medications
            5. Increased risk if lack of social, mental, or physical support

iii. Relationship Between MDD and Cardiovascular Health[7]





Picture 2.



b. Standard of Care[8,9]:
    i. Pharmacotherapy
        1. Antidepressants
            a. The American Psychiatric Association Guidelines on treating MDD recommend customizing a patient's treatment plan based on patient preferences and comorbidities
            b. Selective serotonin reuptake inhibitors (SSRIs) are often utilized first due to a better safety profile than other available agents in both the general population and cardiac patients, including post-ACS patients.
            c. Other classes of antidepressants, with the exception of mirtazapine (MIND-IT), carry an increased risk for cardiovascular events and are often avoided post-ACS.

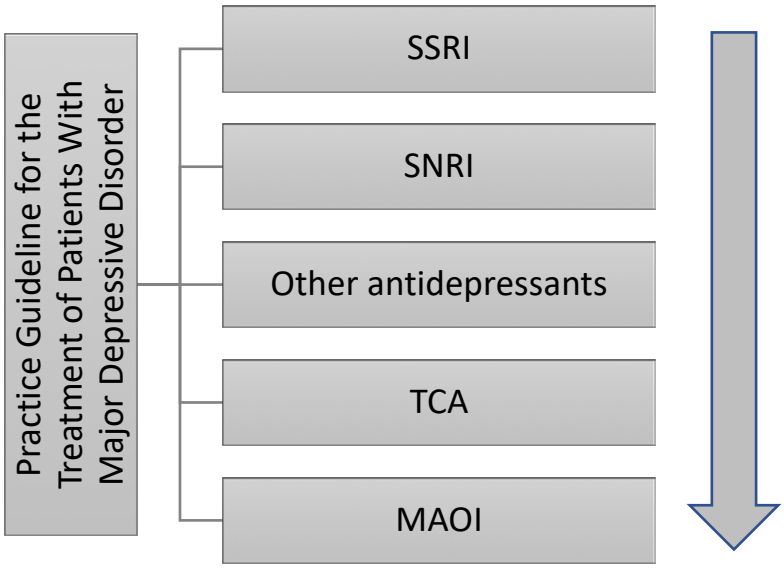


Table 1: Antidepressant Classes[8]

Class	Medications
Monoamine Oxidase Inhibitors (MAOIs)	Tranylcypromine (Parnate), phenelzine (Nardil),
Tricyclic Antidepressants (TCAs)	Imipramine (Tofranil), nortriptyline (Pamelor), amitriptyline, doxepin, desipramine
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	Venlafaxine (Effexor), desvenlafaxine (Pristiq), duloxetine (Cymbalta), levomilnacipran (Fetzima)
Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram (Celexa), sertraline (Zoloft), paroxetine (Paxil), fluoxetine (Prozac), escitalopram (Lexapro)
Other Antidepressants	Bupropion, nefazodone, trazodone, mirtazapine

Table 2: SSRI Class Review[9,10]					
SSRI	Medications	MOA	CYPs	Drug Interactions	ADE
	Citalopram	Block serotonin receptors in the synapse causing for decreased serotonin reabsorption	+ 2C19, 2D6	MAOI, flecainide, propafenone, metoprolol, warfarin, clopidogrel	Increased risk of bleeding Impotence Serotonin syndrome Palpitations Prolonged QTc (Citalopram, Escitalopram) Chest pain (Paroxetine)
	Fluoxetine		++ 2C19 +++ 2D6	Tamoxifen, MAOI, flecainide, propafenone, warfarin, clopidogrel	
	Sertraline		++ 2D6, 2C19	MAOI, warfarin, clopidogrel	
	Paroxetine		+ 2C19, 3A4 +++ 2D6	Tamoxifen, MAOI, flecainide, propafenone, metoprolol, warfarin, clopidogrel	
	Escitalopram		++ 2D6	MAOI, flecainide, propafenone, metoprolol, warfarin, clopidogrel	

ii. Non-Pharmacotherapy
    1. Interpersonal Psychotherapy (IPT)
    2. Electroconvulsive therapy (ECT)

c. Complications[11,12]

Table 3: Frasure-Smith et al. (1993)	
Population	222 patients mostly men with recent MI
Intervention	Utilizing the National Institute of Mental Health Diagnostic Interview Schedule (DIS), 35 patients were diagnosed with MDD: 17 were treated (14 with therapy and 3 with antidepressants)
Outcome	Mortality rates increased significantly in patients with depression (17% vs 3%, P=0.0006) Depression proved a significant predictor of mortality despite controlling for LVEF dysfunction and previous MI history (HR=5.74, P=0.006)

Table 4: Smolderen et al. (2017)	
Population	4,062 patients with acute MI. 759 were diagnosed with depression via a PHQ-9 score $\geq$10
Intervention	231/759 (30.4%) of patients were treated for depression while the remaining 528/729 (69.6%) of patients remained untreated
Outcome	1-year mortality rates of treated patients did not differ from patients without depression whereas untreated patients had a significantly higher rate of mortality (10.8% vs 6.1%, P < 0.0001)

3. Controversy[13-20]
    a. Are SSRIs safe in patients with a cardiac history?
        i. This was the main question for a long time as minimal studies had looked into cardiac safety of antidepressants. However, safety of SSRIs in post-ACS patients has now been well proven through a meta-analysis and more recent studies.
    b. Given that we now know SSRIs are safe in patients with a cardiac history, which one is the safest?
        i. Without comparative head-to-head trials that have looked into safety and efficacy of SSRIs in post-ACS patients, the controversy becomes whether one SSRI is preferred over any other.

4. Evidence:

Sertraline Treatment of Major Depression in Patients With Acute MI or Unstable Angina[14]

JAMA 2002;288(6):701–709

STUDY OVERVIEW	
Funding	• Pfizer
Objectives	• **Primary objective:** Change from baseline left ventricular ejection fraction (LVEF) • **Secondary objective:** Cardiovascular markers, Hamilton Depression Rating Scale (HAMD-17) and Clinical Global Impression Improvement scale (CGI-I) • **Safety objective:** Incidence of cardiac adverse events
METHODS	
Design	• Multi-center, randomized, double-blinded, placebo-controlled trial conducted from April 1997 to April 2001 • 40 centers were used including outpatient cardiology and psychiatry clinics in the US, Canada, Europe, and Australia • Patients were randomized into two groups in a 1:1 ratio: • Flexible dose sertraline 50-200mg vs placebo • All patients underwent a 2 week placebo period before the trial started to make sure all patients were adequately met criteria for MDD according to the DSM-IV criteria • Patients took 50mg/day of sertraline for first 6 weeks and at that point, clinical response was assessed and dose could be increased
Inclusion criteria	• Patients ≥ 18 years old • Acute MI or hospitalized for unstable angina in the past 30 days • Currently meeting DSM-IV criteria for MDD
Exclusion criteria	• Uncontrolled hypertension defined as SBP >180mmHg or DBP >100mmHg • Cardiac surgery in the next 6 months • ACS occurrence after recent CABG (<3 months) • ACS of non-atherosclerotic etiology • Resting HR <40 bpm or <50 bpm and symptomatic • Severe life-threatening illness that could interfere with recovery from ACS • Persistent laboratory abnormalities • Severe renal or hepatic dysfunction • Women of childbearing potential not using adequate contraception • Concurrent use of class I antiarrhythmic medications, use of methyldopa, clonidine, or reserpine, use of antidepressants, anticonvulsants, or regular benzodiazepine use • Initiation of psychotherapy in the past 3 months

Enrollment	• A total of 369 patients were randomized into treatment groups
	• Enrollment for each arm of the study was as followed:
	  • Sertraline total enrollment (N=186)
	  • Placebo total enrollment (N=183)

Baseline Characteristics	**Demographic and Characteristics of Included Patients (Table 1):**

	Sertraline	Placebo
Mean age (yrs)	56.8	57.6
Women (%)	37	36
Race (%)		
White	74	79
Black	12	14
Hispanic	14	7
Cardiac risk factors (%)		
Smoker	27	28
Hypertension	61	69
Diabetes	31	30
Hyperlipidemia	70	67
BMI ≥ 30	36	30

	Cardiovascular history Congestive heart failure Prior CABG Prior MI	 12 43 43	 16 42 41
	LVEF (%)	54	52
	HAMD-17	19.6	19.6
	Prior episodes of MDD (%) None 1 ≥ 2	 48 20 32	 51 21 29

Statistical analysis

- Mixed-model repeated measures analysis of covariance was used to assess the changes in the CGO-I and HAMD score
- Cochran-Mantel-Haenszel methods were used to compare responders and remitters in the treatment groups
- Adverse events were assessed by the clinical events committee as all physicians were blinded
- A 2-way analysis of variance was used to compare continuous variables between treatment groups at baseline

R E S U L T S

Primary outcome

	Sertraline		Placebo		P value
	Baseline	Week 16	Baseline	Week 16	-
LVEF total (avg %)	54	54	52	53	NR
LVEF ≤ 30 (avg %)	20	20	24	24	NR
>5 point decrease in LVEF (%)	-	4.4	-	4.0	NR

NR = none reported

- Reported non-significant difference in primary endpoints from baseline to week 16 between sertraline and placebo though no P-values given

Secondary outcomes

	Sertraline		Placebo		P value
	Baseline	Week 16	Baseline	Week 16	-
SBP (mmHg)	124	127	126	130	NR
DBP (mmHg)	74	76	74	77	NR
Heart rate (bpm)	65	64	65	66	NR
QRS duration (ms)	97	98	98	98	NR
QTc >450 ms (%)	19	12	19	13	NR

- Reported non-significant between group differences in secondary endpoints from baseline though no P-values given

	Sertraline	Placebo	P value
All patients CGI-I score (mean) HAMD-17 score (mean change)	(N=186) 2.57 -8.4	(N=183) 2.75 -7.6	 0.049 0.14
All recurrent MDD CGI-I score (mean) HAMD-17 score (mean change)	(N=96) 2.49 -9.8	(N=90) 2.80 -7.6	 0.02 0.009
More severe (2 prior episodes and HAMD ≥18) CGI-I score (mean) HAMD-17 score (mean change)	(N=50) 2.41 -12.3	(N=40) 2.98 -8.9	 0.002 0.01

Safety

	Total		Severe	
Adverse Event (%)	Sertraline	Placebo	Sertraline	Placebo
Total CV events	52.7	59.0	14.5	22.4
Nausea	19.9	10.9	1.6	0.5
Diarrhea	18.8	7.7	1.6	0.5
Insomnia	18.8	18.8	2.7	3.3
Dyspnea	13.4	19.7	1.6	2.2
Fatigue	14.5	13.7	1.1	1.1
Pain	10.2	11.5	1.1	1.6
Headache	20.4	16.4	2.7	2.2
Dizziness	15.6	12.0	2.2	0

Adverse Event (%)	Sertraline	Placebo	RR
Death	2	5	0.39 (0.08-1.39)
MI	5	7	0.70 (0.23-2.16)
Heart Failure	5	7	0.70 (0.23-2.16)
Stroke	2	2	0.98 (0.14-6.93)
Angina	26	30	0.85 (0.53-1.38)
Composite	32	41	0.77 (0.51-1.16)

AUTHOR CONCLUSIONS

"[S]ertraline appears to be a safe and, in patients with recurrent major depression, effective treatment in the setting of ACS."

CRITIQUE

Study strengths

- Design (multi-centered, randomized, double-blinded, placebo controlled)
- Assessed efficacy as well as cardiovascular and non-cardiovascular safety
- Utilized appropriate tapering regimens off sertraline

Study limitations

- No uniform clinical response assessment prior to dose titration
- Excluded many patients with more severe disease who may have benefitted from the decreased mortality risk that comes with treating depression post MI
- No P-values reported for primary outcome
- Blood pressure control better than average cardiac patients
- Did not meet power

Take home points

- No increase in LVEF or incidence of cardiac adverse effects (cardiac mortality, MI, HF, stroke, angina) in patients taking sertraline compared to placebo
- Trend towards decreased cardiac adverse effects in patients taking sertraline
- Demonstrated similar efficacy as placebo however study not powered to detect difference and other additional studies have proven efficacy (see below)

McFarlane et al. (2001)[15]	Mohapatra et al. (2005)[16]
38 post-ACS patients, randomized, placebo-controlled Primary outcome: Rate of recovery of SDNN and change in depression score (IDD) Results: • Significant decrease in IDD score in the sertraline group (P<0.05) • Increase in SDNN in sertraline group vs decrease in placebo group (P<0.05) • No major cardiac adverse effects reported	50 post-ACS patients, randomized, placebo-controlled Primary outcome: Change in depression score (HAMD17) Results: • Significant decrease in HAMD scores in sertraline group (P=0.007) • 18.2% vs 66.7% of patients in the sertraline vs placebo group had recurrent MI (no P-value)

Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome: A Randomized Clinical Trial[17]

JAMA. 2018;320(4):350-357. doi:10.1001/jama.2018.9422

STUDY OVERVIEW			
Funding	• National Research Foundation of Korea and National Institute for Health Research Biomedical Research Centre at South London		
Objectives	• **Primary objective**: to determine the long-term effect escitalopram has on major adverse cardiac events (MACE) including all-cause mortality, cardiac death, MI, and PCI in patients with a recent ACS • **Secondary objectives**: All-cause mortality, cardiac death, MI, and PCI individually		
METHODS			
Design	• Randomized, double-blinded, placebo-controlled, single-centered trial conducted from May 2007 to March 2013 with final follow-up through June 2017 • Long-term follow up to the previous 24-week study (EsDEPACS) • All patients were followed for 5-11 years until death or June 2017 • Examinations were scheduled at baseline and at weeks 4,8, 12, 16, 20,and 24 there after		
Inclusion criteria	• Patients ≥ 18 years old • Confirmed ACS in the past 2 weeks • DSM-IV criteria for major or minor depressive disorder • BDI score > 10		
Exclusion criteria	• ACS occurrence while hospitalized for another reason • ACS occurrence after recent CABG (<3 months) • Uncontrolled hypertension defined as SBP >180mmHg or DBP >100mmHg • Resting heart rate <40/min • Severe life-threatening illness that could interfere with recovery from ACS • Persistent laboratory abnormalities including thyroid tests, CBCs, LFTs or renal function tests • Pregnancy • Use of class 1 antiarrhythmics, reserpine, guanethidine, clonidine, methyldopa, lithium, anticonvulsants, antipsychotics, or antidepressants • History of dementia, Parkinson's, psychosis, bipolar disorder or substance abuse disorder		

Enrollment	• A total of 300 patients were randomized into treatment groups
	• Enrollment for each arm of the study was as followed:
	  • Escitalopram 5 or 10mg total enrollment (N=149)
	  • Placebo total enrollment (N=151)
	• All enrolled patients completed the study		

Baseline Characteristics	**Demographic and Characteristics of Included Patients (Table 1):**		
		Escitalopram	**Placebo**
	Mean age (yrs)	60.0	60.1

	Men (%)	59.1	61.6
	Unmarried (%)	12.1	19.2
	Beck Depression Inventory Score • Mean • Median	 18.8 16	 19.2 17
	DSM-IV diagnosis of MDD (%)	57.0	55.6
	Cardiovascular risk factors (%) • Hypertension • Diabetes Mellitus • Obesity • Smoker • Previous ACS • Family history of ACS	 60.4 29.5 39.6 28.9 5.4 6.0	 62.3 27.2 43.0 27.8 7.3 5.3
Statistical analysis	• Baseline characteristics and clinical characteristics were analyzed via t-tests and X^2 tests • Kaplan-Meyer and cox regression statistics were used to assess and compare time to first Major adverse cardiovascular event (MACE) event • Post-hoc analyses were utilized to evaluate treatment effects and remission • All statistical tests were two sided with an a=0.05 • Sensitivity analyses were used to account for patients taking antidepressants at 1 year and to restrict analysis to those with impaired LVEF		
RESULTS			
Primary outcome	• Mean follow time in the included population was 8.1 years • 53.6% vs 40.9% experienced MACE in placebo and escitalopram groups respectively (P=0.03); NNT= 8 • In patients with LVEF <55%, MACE occurred in 72.7% (24/33) with placebo vs 67.6% (23/34) with escitalopram (P=.12)		
Secondary outcomes	• Incidence of MI was 15.2% vs 8.7% in the escitalopram and placebo groups respectively (P=0.04); NNT= 16 • No significant differences noted in for all-cause mortality, cardiac death, or PCI (P=0.43, 0.48 and 0.07 respectively) • Post-hoc analysis of remission rates demonstrated significant increase in remission of depression for patients in the escitalopram group vs patients in the placebo group (52.3% vs 34.9%, P<0.001)		
AUTHOR CONCLUSIONS			
"In this median 8.1-year follow-up of a randomized 24-week clinical trial of treatment for depression in patients with recent ACS, MACE incidence was significantly lower in patients receiving escitalopram than those receiving placebo."			
CRITIQUE			
Strengths	• First randomized long-term outcomes study with single interventional medication • Primary outcome was a composite of major adverse cardiac events • Large sample size • Assessed remission rates via post-hoc analysis • Included patients with minor depression as well as those with major depression • Patient retention		
Limitations	• Single center • Single ethnic population and low generalizability		
Take home points	• Patients taking escitalopram have a lower long-term risk of MACE (including all-cause mortality, cardiac death, MI, and PCI) and long-term risk of MI compared to placebo • Consistent efficacy shown for treatment of depression both short-term and long-term		

Effects of Citalopram and Interpersonal Psychotherapy on Depression in Patients With Coronary Artery Disease: The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) Trial[18]

JAMA 2007;297(4):367–377

<table>
<tr><th colspan="6">STUDY OVERVIEW</th></tr>
<tr><td>Funding</td><td colspan="5">• Canadian Institutes of Health Research (CIHR) Clinical Trials Program grant, the Fondation du Centre Hospitalier de l’Universite´ de Montre´ al, and the Fondation de l’Institut de Cardiologie de Montre´ al</td></tr>
<tr><td>Objectives</td><td colspan="5">• Primary objective: Short term efficacy of citalopram in patients with coronary artery disease
• Safety objective: Incidence of adverse events</td></tr>
<tr><th colspan="6">METHODS</th></tr>
<tr><td>Design</td><td colspan="5">• Multicenter, randomized, placebo-controlled, parallel-group trial conducted from May 2002 to March 2006 with final follow-up through March 2017
• Patients underwent two separate randomization in a 1:1 ratio into the following groups
  • IPT weekly sessions + clinical management vs clinical management alone
  • Citalopram 20 to 40mg vs matching placebo
• Patient’s dual randomization created 4 distinct groups</td></tr>
<tr><td>Inclusion criteria</td><td colspan="5">• Patients ≥ 18 years old
• History of CAD based on chart evidence of previous MI or revascularization
• DSM-IV criteria for major depression for at least 4 weeks duration
• Baseline HAMD-17 score of ≥ 20</td></tr>
<tr><td>Exclusion criteria</td><td colspan="5">• History of bipolar disorder with psychotic features
• Substance abuse or dependency within the last 12 months
• Current use of antidepressants, anticonvulsants, or lithium
• Previous lack of response to citalopram or history of early discontinuation (< 8weeks)
• Current psychotherapy
• MMSE score <24
• CABG planned to occur within 4 months</td></tr>
<tr><td>Enrollment</td><td colspan="5">• A total of 284 patients were randomized into treatment groups
• Enrollment for each arm of the study was as followed:
  • Interpersonal psychotherapy (IPT) weekly sessions + clinical management (CM) + citalopram (N=67)
  • IPT weekly sessions + clinical management + placebo (N=75)
  • Clinical management + Citalopram 20 to 40mg (N=75)
  • Clinical management + placebo (N=67)</td></tr>
<tr><td rowspan="8">Baseline Characteristics</td><td colspan="5"><u>Demographic and Characteristics of Included Patients (Table 1):</u></td></tr>
<tr><td></td><td>IPT + Citalopram</td><td>IPT + Placebo</td><td>CM + Citalopram</td><td>CM + Placebo</td></tr>
<tr><td>Mean age (yrs)</td><td>58.6</td><td>59.4</td><td>57.3</td><td>57.3</td></tr>
<tr><td>Women (%)</td><td>38.8</td><td>24.0</td><td>9.3</td><td>28.4</td></tr>
<tr><td>Cardiac risk factors (%)
  Smoker
  History of treatment for HTN
  BMI ≥ 30
  Diabetes medications</td><td>
19.4
70.1
39.4
17.9</td><td>
23.0
64.0
46.7
22.7</td><td>
22.7
66.7
53.3
24.0</td><td>
29.9
74.6
33.8
25.4</td></tr>
<tr><td>Cardiac history (%)
  History of MI
  History of CABG
  Time since recent cardiac event</td><td>
59.7
43.3

19.7</td><td>
72.0
42.7

24.0</td><td>
65.3
49.3

33.8</td><td>
61.2
46.3

28.8</td></tr>
</table>

	< 6 months 6 months – 2 years > 2 years	36.4 43.9	29.3 46.7	25.7 40.5	31.8 39.4
	HAMD-24 score	28.8	30.0	29.6	30.3
	BDI-II score	30.2	29.4	30.4	31.3
	Duration of depression (%) 4 weeks to < 6 months 6 months – 2 years > 2 years	 40.3 38.8 20.9	 41.3 37.3 21.3	26.7 44.0 29.3	 38.8 44.8 16.4
	Recurrent Depression (%)	49.3	56.0	45.3	40.3
	IPT = interpersonal psychotherapy, CM = clinical management, HTN = hypertension, CABG = coronary artery bypass graft				
Statistical analysis	• Intention-to-treat analysis • Last-observation-carried-forward principle applied for missing data • Primary efficacy was analyzed using a 2 x 2 analysis of covariance • Parallel analysis was used to assess time to treatment effect • Logistic regression was used to compare remission and response rates to other trials				

Primary outcome	• Citalopram decreased both the HAMD-24 and BDI-II score significantly compared to placebo
	  • -14.9 vs -11.6 respectively (P=0.005)
	  • -14.7 vs -11.1 respectively (P=0.005)
	• Citalopram also showed a significantly decrease in HAMD-17 score compared to placebo
	  • -10.7 vs -8.5 respectively (P=0.02)				

Safety

Type of Event	**IPT + Citalopram**	**IPT + Placebo**	**CM + Citalopram**	**CM + Placebo**
MI (n)	0	2	0	0
Congestive heart failure (n)	1	1	1	1
Worsening angina (n)	2	1	0	0
Stroke (n)	1	0	0	0
Total cardiovascular adverse events (%)	7.5	5.3	1.3	3.0
Total non-cardiovascular events (%)	11.9	5.3	5.3	10.4

Type of Event	**Citalopram**	**Placebo**	**P Value**
SBP (mmHg) Baseline Week 12	 127.3 127.7	 128.3 127.9	0.80
DBP (mmHg) Baseline Week 12	 75.5 75.8	 76.1 75.0	0.29
QRS interval (ms) Baseline Week 12	 96.7 95.7	 96.5 96.6	0.15
QT interval (ms) Baseline	405.9 412.4	410.8 411.2	0.34

	Week 12			
	QTc interval (ms) Baseline Week 12	 416.3 418.1	 416.4 415.1	 0.18

AUTHOR CONCLUSIONS
"We found a clinically meaningful antidepressant effect of citalopram in comparison with placebo but no demonstrable benefit of the psychotherapeutic intervention, IPT, over clinical management alone. Citalopram (or sertraline, as previously shown in the SADHART trial) plus clinical management should be considered for the initial acute-phase treatment for major depression in patients with CAD."

CRITIQUE	
Study strengths	• Design (multi-centered, randomized, double-blinded, placebo controlled) with intention to treat analysis • Assessed efficacy as well as cardiovascular and non-cardiovascular safety • Compared standard pharmacologic and non-pharmacologic treatments with multiple intervention groups to assess which combination is most effective • No funding bias
Study limitations	• Mismatched baseline characteristics including gender • Inaccurate data representation in article vs table • Cardiac safety reported as a secondary outcome • Safety data reported ambiguously • No P-values reported for safety outcome
Take away points	• Significantly reduced symptoms of depression as seen by the HAMD and BDI scores • No significant increase in QTc or increased risk of cardiac complications including MI, CHF, angina, and stroke compared to placebo • No significance can be determined from safety outcomes

Efficacy and Safety of Fluoxetine in the Treatment of Patients With Major Depression After First Myocardial Infarction: Findings From a Double-Blind, Placebo-Controlled Trial[19]

Psychosomatic Medicine 2000;62:783–789

STUDY OVERVIEW	
Funding	• Eli Lilly, the Dutch Prevention Fund, and Maastricht University Hospital Research Fund
Objectives	• **Primary objective:** Efficacy of fluoxetine in post-MI depression using the Hamilton Depression Rating Scale (HAMD17) and the Hostility Scale of the 90-item Symptom Check List (SCL-90) • **Safety objective:** incidence of adverse events and cardiovascular events
METHODS	

Design	• Mutlicenter, randomized, double-blinded, placebo-controlled trial conducted from May 1994 to December 1997
	• Patients were randomized receive the following:
	  • Fluoxetine 20mg
	  • Placebo
	• Fluoxetine dose could be increased to 40mg by week 3 and 60mg by week 6 at prescriber's discretion
	• Study was conducted for an initial 9 weeks. However, if patients chose to continue then the trial extended an additional 16 weeks for a total of 25 weeks

Inclusion criteria	• Patients 18 – 75 years old • Clinical picture typical of MI • ECG changes specific for MI • Maximum plasma concentration of ASAT of 2x ULN • HAMD-17 score > 17 and clinical diagnosis of depression using DSM-III criteria

<table>
<tr><td>Exclusion criteria</td><td>

Presence of psychotic symptoms
History of a secondary psychiatric diagnosis or history of mania
Current pregnancy or lactation
Life-threatening physical illness
Concurrent use of psychotropic drugs with the exception of oxazepam
Liver or severe kidney dysfunction (CrCl <10 ml/min)

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<tr><td>Enrollment</td><td>

A total of 68 patients were randomized into treatment groups
14 patients dropped out at a later stage in the process leaving 54 total patients included
Enrollment for each arm of the study was as followed:

Fluoxetine total enrollment (N=27)
Placebo total enrollment (N=27)

31patients (57%) enrolled were diagnosed with MDD 3 months post MI

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<tr><td>Baseline Characteristics</td><td>
<u>Demographic and Characteristics of Included Patients (Table 1):</u>
<table>
<tr><th></th><th>Fluoxetine</th><th>Placebo</th><th>P Value</th></tr>
<tr><td>Mean age (yrs)</td><td>54.1</td><td>58.7</td><td>0.11</td></tr>
<tr><td>Men (%)</td><td>77.7</td><td>62.9</td><td>0.23</td></tr>
<tr><td>HAM D-17 Score</td><td>22.0</td><td>21.2</td><td>0.46</td></tr>
<tr><td>Hostility Score</td><td>10.7</td><td>9.5</td><td>0.30</td></tr>
<tr><td>LVEF (%)</td><td>51.3</td><td>50.7</td><td>0.85</td></tr>
<tr><td>HR (bpm)</td><td>67.8</td><td>65.8</td><td>0.76</td></tr>
<tr><td>QTc (ms)</td><td>417</td><td>414</td><td>0.72</td></tr>
<tr><td>SBP (mmHg)</td><td>127</td><td>130</td><td>0.33</td></tr>
<tr><td>DBP (mmHg)</td><td>85.6</td><td>81.9</td><td>0.44</td></tr>
</table>
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<tr><td>Statistical analysis</td><td>

Needed sample size of 54 patients to meet power of 0.95 using a one-tailed t-test
T tests were used to analyze efficacy data on an intention to treat basis
The “last observation carried forward technique” was used for patients who did not complete the 9 or 25 weeks of treatment
One tailed test were utilized for primary efficacy variables (HAMD-17 and SCL-90)
Regression analyses were used for safety data only including patients who data was available for at the 6 and 25 week endpoint

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<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Primary outcome</td><td>

No significant difference between fluoxetine and placebo on HAMD-17 scores at baseline and at 9 vs 25 weeks (P=0.06 and 0.08 respectively)
SCL-90 hostility score was not significantly decreased in the fluoxetine group at the end of the 9 weeks compared to the placebo group (-2.61 vs -1.18; P=0.08)
At 25 weeks, SCL-90 hostility score was significantly decreased in the fluoxetine group vs placebo group (-2.44 vs -0.07; P =0.02)

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<tr><td>Safety</td><td>

15 patients in the fluoxetine group experienced a decreased in QRS interval compared to 9 patients in the placebo group who experienced an increase (P=0.03)
22% of patients in the placebo group vs 3.7% patient in the fluoxetine group were re-hospitalized (P=0.13)

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<tr><td colspan="2">AUTHOR CONCLUSIONS</td></tr>
<tr><td colspan="2">“[T]he results suggest that fluoxetine can be safely used in patients with major depression starting 3 months after MI. Although the overall difference between treatment with fluoxetine and placebo was not statistically significant, there was a clear trend favoring fluoxetine in this relatively small sample.”</td></tr>
<tr><td colspan="2">CRITIQUE</td></tr>
<tr><td>Study strengths</td><td>

Design (randomized, double-blinded, placebo controlled, multi-centered) with intention to treat analysis
Analyzed safety and efficacy at 9 and 25 weeks
Met power for primary outcome
Included minor depression

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<tr><td>Study limitations</td><td>

Small sample size
Mismatched baseline characteristics in regard to gender and age though non-significant

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</table>

	• Cardiac safety was a secondary outcome • One tailed t-test for primary outcome
Take away points	• Statistically similar safety profile between fluoxetine and placebo with a trend towards decreased re-hospitalizations in the fluoxetine group • Need more robust data with two-tailed analysis to identify differences in primary and secondary outcomes

5. Further Evidence[20]

Table 5: Roose et al (1998)	
Population	81 outpatients meeting DSM IV criteria for depression and diagnosis with IHD
Intervention/ Comparator	Paroxetine 20 or 30mg/ Nortriptyline dosed to target level 50-150ng/mL
Outcome	No significant difference in reduction of depression symptoms Nortriptyline significantly increased HR by 11% compared to baseline (P<0.01) Cardiac adverse effects occurred in 18% of nortriptyline patients vs 2% of paroxetine (P<0.03)

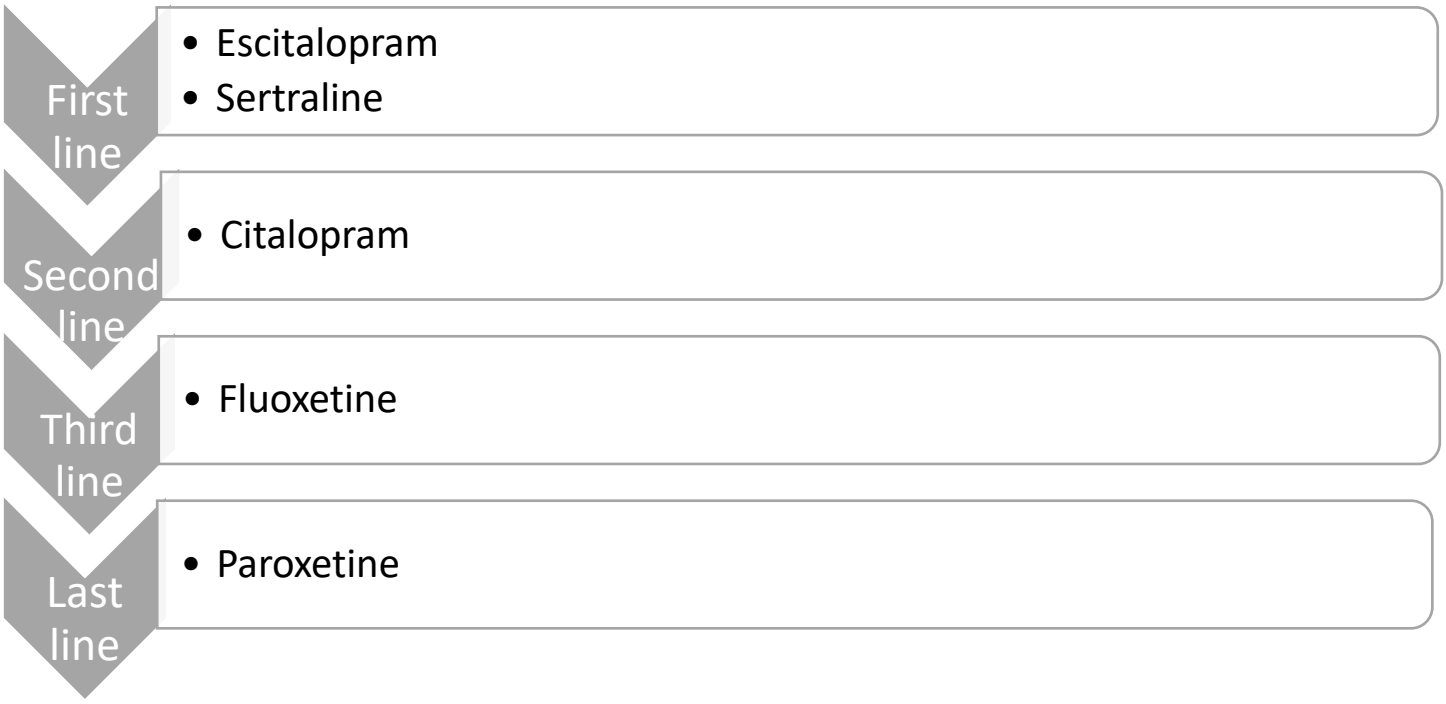
6. Conclusion[14-21]
   a. Escitalopram has two robust studies, that despite being single-center, have demonstrated short-term and long-term cardiac safety in post-ACS patients.
   b. Sertraline was not powered to determine efficacy in SADHART but multiple other studies have confirmed both its safety and efficacy.
   c. Citalopram has a greater incidence and magnitude for QTc prolongation than other SSRIs, including escitalopram, and should be used cautiously in patients with increased risk of arrhythmias or high baseline QTc.
   d. Fluoxetine did not increase cardiac adverse events, and even showed a trend towards decreased re-hospitalizations in post-ACS patients in a small, randomized placebo control trial. However. more robust studies with a larger sample size are needed to better assess safety and efficacy.
   e. Paroxetine has not been studied as extensively as other SSRIs in post-ACS patients. However, one study in patients with ischemic heart disease (IHD) that excluded patients with recent history of ACS has shown that it has a better cardiac safety profile than TCAs.

Overview of Strength of Evidence Regarding Safety and Efficacy of SSRIs in post-ACS patients

SSRI	Safety	Efficacy	Strength of Evidence*
Escitalopram	+++	+++	Strong
Sertraline	++	++	Strong
Citalopram	++	++	Intermediate
Fluoxetine	++	+	Weak
Paroxetine	-	-	No Evidence

*Strength of evidence based on quantity of studies and quality of data as assessed by JADAD scoring

7. Recommendation



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