Cardiovascular Benefits of Antidepressants Post-ACS

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No conflicts of interest to disclose

Objectives
1. Discuss the pathophysiology, presentation, and treatment of ACS and depression
2. Describe the correlation between ACS and new-onset depression
3. Analyze the effect of antidepressants on cardiovascular outcomes for the treatment of post-ACS depression

Abbreviations
- 5-HT = Serotonin
- ACS = Acute coronary syndrome
- BDI = Beck Depression Inventory
- BZD = Benzodiazepine
- CABG = Coronary artery bypass grafting
- CBT = Cognitive-behavioral therapy
- CI = Confidence interval
- DA = Dopamine
- EPS = Extrapyramidal symptoms
- HDRS = Hamilton Depression Rating Scale
- HR = Hazard ratio, heart rate
- HT = Serotonin
- ICD-10 = 10th Revision of the International Classification of Disease
- MI = Myocardial infection
- NE = Norepinephrine
- PCI = Percutaneous coronary intervention
- SIADH = Syndrome of inappropriate antidiuretic hormone secretion
- SNRI = Selective serotonin reuptake inhibitor
- SSRI = Serotonin-norepinephrine reuptake inhibitor
- TCA = Tricyclic antidepressant
- TSH = Triiodothyronine

Objectives
1. Discuss the pathophysiology, presentation, and treatment of ACS and depression
2. Describe the correlation between ACS and new-onset depression
3. Analyze the effect of antidepressants on cardiovascular outcomes for the treatment of post-ACS depression

Do antidepressants improve cardiovascular outcomes when used in the treatment of depression post-ACS?

- Yes
- No
- Maybe

Acute Coronary Syndrome (ACS)
Reduced blood flow (coronary atherosclerosis)
- Leads to imbalance between O_2 supply and demand
Myocyte necrosis and release of biochemical markers into bloodstream
- Cardiac troponins I and T

Polling Question
Acute Coronary Syndrome (ACS)
Reduced blood flow (coronary atherosclerosis)
- Leads to imbalance between O_2 supply and demand
Myocyte necrosis and release of biochemical markers into bloodstream
- Cardiac troponins I and T
ACS Presentation

**SIGNS AND SYMPTOMS**
- Chest pain ≥ 10 minutes
- Discomfort, pressure, squeezing
- Dyspnea
- Diaphoresis
- Syncope
- Palpitations

**RISK FACTORS**
- Age (M > 45 yo, F > 55 yo)
- Family history
- Smoking
- Hypertension
- Diabetes
- Chronic angina
- Known coronary artery disease
- Sedentary lifestyle, lack of exercise

ACS Treatment

**Acute:** MONA + GAP-BA
- Morphine, Oxygen, Nitroglycerin, Aspirin
- GP IIb/IIIa receptor antagonists, Anticoagulants, P2Y<sub>12</sub> inhibitors, Beta blockers, ACE inhibitors
- PCI or fibrinolytic therapy for STEMI

**Long-term management**
- Aspirin, P2Y<sub>12</sub> inhibitor, nitroglycerin, beta blocker, ACE Inhibitor, aldosterone antagonist, statin

Post-ACS Depression

- ~20% patients with coronary heart disease
- 2- to 2.5-fold increased risk for all-cause mortality, CV mortality, and CV events
- Characteristics:
  - Poorer quality of life post-MI
  - Longer hospital stays
  - Greater cardiac-related readmissions post-MI
  - Incomplete recovery, greater disease progression
  - Nonadherence
  - Increased use of urgent and unscheduled care

Depression Pathophysiology

No known reliable biological markers

"Biogenic Amine Hypothesis"
- Results from lack of one or more: 5-HT, NE, and DA
- Dysregulation of both NE and 5-HT leading to alterations in NE and 5-HT receptors

Depression Rating Scales

**Hamilton Depression Rating Scale (HAM-D, HDRS)**
- 17-item, clinician-rated, 15- to 20-minute interview and score results
- 0-7 = Normal, 8-13 = mild depression, 14-18 = moderate depression, 19-22 = severe depression, ≥ 23 = very severe depression

**The Beck Depression Inventory (BDI)**
- 21-item, self-report, 10 minutes to complete
- 0-9 = minimal depression, 10-18 = mild depression, 19-29 = moderate depression, 30-63 = severe depression

**Others**

Depression Diagnosis

One of following:
- Depressed mood
- Markedly diminished interest/pleasure in most activities
- And 5 of the following:
  - Appetite changes
  - Sleep changes
  - Psychomotor changes
  - Fatigue/energy
  - Feelings of worthlessness, inappropriate guilt
  - Poor concentration, indecisive
  - Suicidal thoughts, plans, or attempts
Polling question:
Which antidepressant would you choose?

Antidepressants

**MAOIs**
- • Isocarboxazid, phenelzine, selegiline, tranylcypromine
- • Orthostatic hypotension, hypertensive crisis

**TCAs**
- • Amitryptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine
- • Increase HR, orthostatic hypotension, prolong cardiac conduction, trigger ventricular arrhythmias

**SSRIs**
- • Fluoxetine, sertraline, paroxetine, (es)citalopram, vilazodone, vortioxetine
- • Most efficacious for treating depression in coronary disease patients

**SNRIs**
- • Duloxetine, levomilnacipran, (des)venlafaxine
- • Not well studied in ACS patients
- • Can increase BP and HR

**Others**
- • Bupropion, mirtazapine, trazodone, nefazodone

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SSRI Mechanism of Action

SSRI Pharmacokinetics

Cytochrome (CYP) P450 Enzyme Inhibitory Potential

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>CYP Enzymes</th>
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</thead>
<tbody>
<tr>
<td>Thioridazine, haloperidol, clozapine</td>
<td>Warfarin, omeprazole, phenytoin, NSAIDs, BDZs, Ca2+ blockers</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Haloperidol, Ca2+ blockers</td>
</tr>
<tr>
<td>Sertaline</td>
<td>Haloperidol, Ca2+ blockers</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Haloperidol, Ca2+ blockers</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Citalopram</th>
<th>Escitalopram</th>
<th>Fluoxetine</th>
<th>Paroxetine</th>
<th>Sertaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titration increment (mg)</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

SSRI Dosing

Time course for antidepressant response:
- • Synaptic effects: within minutes to hours
- • Side effects: within hours to days
- • Therapeutic effects: 4-6 weeks

SSRI Adverse Events

Worsening suicidality
- EPS: dystonic reactions, akathisia
- Abnormal bleeding
- Altered appetite/weight
- Serotonin Syndrome
- Hyponatremia/SAADH
- Teratogenicity?
- SSRI withdrawal with abrupt discontinuation
Barriers to Treatment of Depression
- Failure to recognize symptoms
- Fears associated stigma
- Limited access to treatment
- Poor compliance
- Insufficient time to spend on differential diagnosis
- Inadequate dosing or length of treatment

Characteristics of Depression Post-ACS
Timing of depression and later CV morbidity
- Stronger association with mortality and recurrent CV events in patients with new-onset depression

Depression symptomatology
- Somatic symptoms (pessimism, fatigue) “cardiotoxic”
- Cognitive (social withdrawal, work difficulty) and appetitive (loss of appetite, weight loss) not predictive CV events

Limited responsiveness to treatment

Clinical Question
Can antidepressants provide cardiovascular benefit to patients being treated for depression post-ACS?

Study I - Berkman et al. (2003)
"Effects of Treating Depression and Low Perceived Social Support on Clinical Events After Myocardial Infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial"

Objective
- Determine whether morbidity and recurrent infarction are reduced by treatment of depression and LPSS with CBT supplemented with SSRI therapy post-MI

Study Design
- Multicenter, randomized clinical trial
- 2481 patients from 8 clinical centers (USA)

Intervention
- LPSS = low perceived social support
- CBT = cognitive behavior therapy
- HRSD = Hamilton Rating Scale for Depression
- BDI = Beck Depression Inventory

Inclusion:
- Acute MI, met criteria for major or minor depression and/or low social support, enrolled w/in 28 days of acute event

Exclusion:
- Acute MI following PCI or CABG, taking antidepressant medication, noncardiac conditions likely to be fatal within 1 year, too ill to participate, major psychiatric comorbidity, imminent risk for suicide

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Usual Care</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61 (12.5)</td>
<td>61 (12.6)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>BDI score (depressed), mean (SD)</td>
<td>18.0 (7.4)</td>
<td>17.7 (6.1)</td>
</tr>
<tr>
<td>HRSD score (depressed), mean (SD)</td>
<td>17.8 (4.6)</td>
<td>17.7 (6.4)</td>
</tr>
</tbody>
</table>

Primary Outcome: Death or recurrent MI
- 300 participants (24.1%) in usual care group vs 299 participants (24.2%) in intervention group
- HR 1.01, 95% CI (0.86-1.18), P = .94
Study II - Taylor et al. (2005)

**Objective**
- Determine effects of using antidepressants on morbidity and mortality in patients who participated in the ENRICHD trial
- Observational secondary analysis of the ENRICHD trial
- 73.9% of patients who had depression with or without low social support

**Study Design**
- Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction
- Arch Gen Psychiatry. 2005 Jul;62(7):792

**Strengths**
- Large and diverse patient population
- Long follow-up time (29 months)

**Limitations**
- Observational, not designed to evaluate use of antidepressants
- Half of patients also received CBT

**Implications**
- Use of SSRIs might reduce subsequent CV morbidity and mortality
- Further evaluation with a controlled trial is needed

**Study III - Melle et al. (2007)**

**Inclusion:**
- Definite MI, "current depressive episode according to ICD-10"

**Exclusion:**
- Occurrence of MI while patient hospitalized for another reason, already receiving psychiatric treatment for depression, any disease likely to influence short-term survival
- 23% (45/196) patients in intervention group not lost to follow-up did not receive antidepressant treatment

**Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=209)</th>
<th>Usual Care (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>58.8 (11.9)</td>
<td>57.5 (10.6)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>BDI score, mean (SD)</td>
<td>11.9 (7.2)</td>
<td>11.7 (8.4)</td>
</tr>
</tbody>
</table>

**Objective**
- Determine if antidepressant treatment for depression post MI improves long-term depression status and CV prognosis
- Multicenter, randomized controlled trial, Zelen design (The Netherlands)
- 2177 MI patients evaluated ICD-10 depression and randomized to intervention (n=196) or care as usual (n=122)

**Intervention**
- First choice: mirtazapine (double blind placebo controlled)
- Refusal or insufficient treatment 8 weeks: citalopram (open)
- Third, tailored treatment

**Primary Outcome:**
- Recurrent MI or death from any cause
- 21.5% (96/446) of patients who did NOT take antidepressants vs 26.0% (361/1388) of patients who did NOT take antidepressants during follow up

**Implications**
- Depressed patients reporting SSRI use post MI had relative risk of death or recurrent MI of 0.57 (95% CI, 0.38-0.84)

**Study III - Melle et al. (2007)**

**ICD-10 depression (intervention vs usual care):**
- 30.5% vs 32.1% (P=0.68)
- No significant differences with respect to depressive symptoms, health complaints, disability, and quality of life

**Total event rate at 18 months (intervention vs usual care):**
- Includes cardiac death, recurrent MI, revascularization, heart failure, MI, ventricular arrhythmia
- 14% vs 13% (P=0.76)
Study III- Melle et al. (2007)

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Effectiveness study design and flexibility in treatment</td>
<td>• Short follow-up duration (18 months)</td>
<td>• Would effective treatment of depression result in better cardiac outcomes?</td>
</tr>
<tr>
<td>• Thorough assessment of baseline characteristics</td>
<td>• Composite MACE incidence low (13.4%)</td>
<td></td>
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<tr>
<td></td>
<td>• No differences in depression</td>
<td></td>
</tr>
</tbody>
</table>


Study IV- Kim et al. (2018)

Study Design
• Randomized, double-blind, placebo-controlled trial
• 100 patients with recent ACS and depression (South Korea)

Objective
• Investigate the effect on long-term major adverse cardiac events (MACE) of escitalopram treatment of depression in patients with recent ACS

Study IV- Kim et al. (2018)

Inclusion:
◦ 18-85 yo, confirmed ACS, ability to complete study questionnaires, BDI>10, major or minor depressive disorder (DSM-IV)

Exclusion:
◦ Occurrence of ACS while hospitalized for another reason, ACS w/in 3 mo of CABG, uncontrolled HTN, HR <40 bpm, clinically significant laboratory abnormalities, concomitant use of certain medications, neuropsychiatric illness, pregnancy

Patient Characteristics

<table>
<thead>
<tr>
<th>Escitalopram (n = 149)</th>
<th>Placebo (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.0 (11.2)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>59.1</td>
</tr>
<tr>
<td>BDI score, mean (SD)</td>
<td>18.8 (8.3)</td>
</tr>
<tr>
<td>BDI score, median (IQR)</td>
<td>16 (13-22)</td>
</tr>
<tr>
<td>DSM-IV diagnosis of major depression (%)</td>
<td>57.0</td>
</tr>
<tr>
<td>Previous depression (%)</td>
<td>4.6</td>
</tr>
<tr>
<td>NYHA class &gt;1 (%)</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Primary Outcome
• MACE (composite of all-cause mortality, MI, and PCI)
• MACE occurred in 61 patients (40.9%) receiving escitalopram and 81 (53.6%) receiving placebo
• HR, 0.69, 95% CI, 0.49-0.96, P = .03

Secondary Outcomes
• All-cause mortality: 10.8% vs 16.6% (HR, 0.59; P = .04)
• Cardiac death: 4.7% vs 10.6% (HR, 0.39; P = .04)
• MI: 9.7% vs 13.2% (HR, 0.68; P = .04)
• PCI: 10.8% vs 20.6% (HR, 0.39; P = .04)

Implications
• Similar results in post-stroke depression cohort
• Further research needed to assess the generalizability of these findings


Study IV- Kim et al. (2018)

Do antidepressants improve cardiovascular outcomes when used in the treatment of depression post-ACS?

- Yes
- No
- Maybe
Conclusions

Comorbid depression is commonly observed in patients post-ACS. Depression in patients post-ACS is associated with increased risk for CV events and death. SSRIs have been shown to be safe and effective in post-ACS patients for the treatment of depression. Further research is needed to determine whether antidepressants provide CV benefits to patients being treated for depression post-ACS.

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Resources


Questions?