Considerations in Managing Major Depressive Disorder in Patients With Comorbid Cardiovascular Disease
This presentation was developed with the support of Otsuka Pharmaceutical Development & Commercialization, Inc., (OPDC) and Lundbeck, LLC

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Key Objectives

- Describe the bidirectional association between major depressive disorder and cardiovascular disease
- Review pathophysiology that may underlie the complex relationship between cardiovascular disease and depression
- Discuss considerations for pharmacological treatment of depression that avoid exacerbation of cardiovascular symptoms
- Discuss nonpharmacological considerations for patients with depression and comorbid cardiovascular disease
Bidirectional Relationship Between Major Depressive Disorder (MDD) and Cardiovascular Disease (CVD)
Depression and Cardiovascular Disease: A Bidirectional, Multifaceted Relationship

Depression doubles the risk of developing new cardiovascular disease\(^1\) and may be associated with greater cardiac complications\(^2\)

Depression is 3 times more frequent in patients after an acute MI than in the general community and may be associated with worse prognosis\(^3\)

MI, myocardial infarction.

Depression Is Highly Prevalent in Patients With Cardiovascular Disease

After acute myocardial infarction, two-thirds of patients reported mild depression

Approximately 15% of patients with CVD had MDD (2 to 3 times higher than the general population)

40% of patients with severe chronic heart failure (NYHA class IV) were depressed

27% of patients undergoing coronary artery bypass graft surgery had depression afterwards

CVD, cardiovascular disease; MDD, major depressive disorder; NYHA, New York Heart Association.
Patients With Major Depressive Disorder Demonstrated Reduced Cardiac Resilience

Decreased heart rate variability (HRV)
- Marker of autonomic inflexibility, inability to respond to change, and ill health\(^1\)
- May be a trait marker for depression\(^2\)
- May link cardiovascular disease, depression, and sudden cardiac death\(^2\)

Patients with depression with comorbid cardiovascular disease displayed lower HRV than patients who were not depressed\(^1\)

Unmedicated patients with major depressive disorder and no cardiovascular disease displayed lower HRV than healthy, age-matched controls\(^1\)

Low HRV predicts
- Future adverse cardiovascular events\(^2\)
- Inflammatory-mediated atherosclerosis\(^1\)
- Death after myocardial infarction\(^2\)

Depression and Cardiovascular Disease Comorbidity Is Associated With Poor Outcomes

After myocardial infarction, patients with depression had

- More medical comorbidities and cardiac complications\(^1\)
- 3-fold increase in mortality\(^2\)
- 41% higher 1-year health costs\(^1\)

Patients with acute coronary syndrome and history of depression reported\(^1\)

- Triple the physical limitations
- Almost triple the risk of diminished health-related quality of life
- Twice the rate of angina

Patients with chronic heart disease and depression reported\(^1\)

- Depression as the most important correlate of diminished quality of life
- More days in bed due to illness
- More ambulatory and emergency room visits
- Increased functional disability

Depression Is a Predictor of Mortality in Patients With Established Coronary Heart Disease

In patients with established CHD, depression was predictive of all-cause mortality and cardiac-related mortality

<table>
<thead>
<tr>
<th>Studies analyzed</th>
<th>Outcome(s) assessed</th>
<th>OR relative risk (95% CI) of CHD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Melle et al, 2004</td>
<td>All-cause mortality</td>
<td></td>
<td>&lt;0.00001</td>
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<td>Cardiac mortality</td>
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<td>Cardiovascular events</td>
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<td>Barth et al, 2004</td>
<td>All-cause mortality</td>
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<td>Nicholson et al, 2006</td>
<td>All-cause mortality</td>
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<td>&lt;0.00001</td>
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<td>Meijer et al, 2011</td>
<td>All-cause mortality</td>
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<td>Cardiac mortality</td>
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<td>Meijer et al, 2013</td>
<td>All-cause mortality</td>
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<td>Cardiovascular events</td>
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Following a meta-analysis of 53 studies, an AHA expert panel recommended that depression be elevated to the status of a risk factor for poor prognosis in patients with ACS

ACS, acute coronary syndrome; AHA, American Heart Association; CHD, coronary heart disease; CI, confidence interval; NR, not reported; OR, odds ratio.

Pathophysiology Underlying Major Depressive Disorder and Cardiovascular Disease
Psychosocial Factors May Negatively Affect Select Biological Mechanisms

**Mood state** (e.g., depression, anxiety) can lead to increased:
- Inflammation
- Platelet function
- Autonomic nervous system dysregulation
- Hypothalamic pituitary adrenal axis dysregulation

**Acute stress** (e.g., traumatic life event) can lead to increased:
- Sympathetic nervous system function
- Hypothalamic pituitary adrenal axis activity
- Blood pressure
- Heart rate
- Interleukin-6 level

**Chronic stress** (e.g., work stress, marital strain, life adversity) can lead to increased:
- Sympathetic nervous system function
- Hypothalamic pituitary adrenal axis activity
- Ambulatory blood pressure
- Heart rate
- Inflammation

Complex Relationship Between Depression and Cardiovascular Disease

Psychosocial stress can lead to chronic inflammation throughout the body, contributing to both depression\(^2\) and cardiovascular disease\(^3\)

Biological mechanisms influence both depression and cardiovascular disease\(^1\)
- inflammation, autonomic nervous system, platelet receptors, coagulopathic factors, endothelial function, neurohormonal factors, and genetic linkages such as serotonin transporter mechanism

Depression may lead to behavioral factors that facilitate development of cardiovascular disease\(^4\)
- weight gain, inactivity, poor nutrition

Perceived loss (eg, perception of lost independence or physical health) can lead to a depressed state\(^1\)

Inflammation Plays a Key Role in Both Depression and Cardiovascular Disease

Patients with depression display higher levels of the inflammatory cytokines IL-6 and TNF-α.

Relative risk of recurrent myocardial infarction or coronary death is elevated in patients with higher baseline levels of C-reactive protein.

CRP, C-reactive protein; IL-6, interleukin 6; MDD, major depressive disorder; TNF-α, tumor necrosis factor alpha.

*P<0.05 vs <0.12 mg/dL CRP.

Microbiota-Gut-Brain Axis May Link Depression and Comorbidities¹,²

The gut microbiome is influenced by diet, may be associated with the pathogenesis of MDD and other conditions, and may contribute to drug metabolism and interindivdual variability in treatment efficacy and side effects²

Dysbiosis
(microbial imbalance in the gastrointestinal tract)

Eubiosis
(Healthy balance of microflora in the gastrointestinal tract)

CNS, central nervous system; IBS, irritable bowel syndrome MDD, major depressive disorder.

Considerations for Management of Depression in Patients With Comorbid Cardiovascular Disease
Routine Depression Screening Is Recommended for Patients With Coronary Heart Disease

The AHA and APA suggest screening for depressive symptoms in patients with CHD to identify patients who may require further assessment and treatment.

1. Screen with PHQ-2
   If yes to either question
   2. Screen with PHQ-9
      If necessary, evaluate for acute suicidality and respond accordingly

- Minimal symptoms, short duration
  Provide support and education follow-up

- Mild to moderate, uncomplicated
  Refer for clinical evaluation by mental health specialist

- Major depression
  Determine appropriate treatment and carefully monitor for adherence, drug efficacy, and safety

AHA, American Heart Association; APA, American Psychiatric Association; CHD, coronary heart disease; PHQ, Patient Health Questionnaire.

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Optimal Treatment for Depression May Involve a Combination of Approaches

Although antidepressants are the cornerstone of treatment for depression, a combination of treatments may yield optimal outcomes

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Psychotherapy</th>
<th>Other</th>
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<tbody>
<tr>
<td>• Antidepressants</td>
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<td>• Atypical antipsychotics</td>
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<td>• Lithium</td>
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<td>• Thyroid medication</td>
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<td>• L-methylfolate</td>
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<td>• Psychostimulants</td>
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<td>• Sedative-hypnotic medications</td>
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<td>• CBT</td>
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<td>• Group therapy</td>
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<td>• Problem-solving therapy</td>
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<td>• Electroconvulsive therapy</td>
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<td>• TMS</td>
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<td>• VNS</td>
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<td>• Light therapy</td>
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<tr>
<td>• Promotion of healthy behaviors</td>
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<td>- Sleep hygiene</td>
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<td>- Decreased caffeine, tobacco, and alcohol</td>
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<td>- Increased exercise</td>
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<td>- Weight loss</td>
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<td>- Meditation</td>
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CBT, cognitive-behavioral therapy; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.

Antidepressants Have Been Associated With Weight Gain and Metabolic Abnormalities

- Weight gain is a common side effect of acute and long-term antidepressant use\(^1\)
  - TCAs and MAOIs are more likely to cause weight gain than SSRIs
- Antidepressant use may be associated with\(^2\)
  - Metabolic syndrome
  - Metabolic syndrome components

HDL, high-density lipoprotein; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

\(^{*}P < 0.01\) vs patients not using antidepressants. \(\dagger P < 0.05\).

Cardiovascular Side Effects of Antidepressants

Examples of cardiovascular side effects of antidepressants\textsuperscript{1,2}

- Lengthening of cardiac myocyte action potentials
- Increases in heart rate
- Increases in blood pressure
- Orthostatic hypertension
- Arrhythmias
- Tachycardia
- Hypertensive crisis

Tricyclic antidepressants and monoamine oxidase inhibitors are contraindicated in many patients with comorbid cardiac conditions because they may cause cardiotoxic side effects\textsuperscript{3}

Determining optimal therapy for patients with chronic heart failure may be challenging. For example, when the QTc interval is borderline, the physician may choose to examine the potential for improved quality of life against potential arrhythmic risk\textsuperscript{1}

SSRI Treatment Can Improve Global Functioning in Patients With MDD and Are Generally Safe in the Cardiac Setting

Treatment with an SSRI significantly improved CGI-I score vs placebo in patients with recurrent depression with recent MI or unstable angina (SADHART trial)\(^1\)

![Graph showing CGI-I responders](chart)

LVEF, left ventricular ejection function; MDD, major depressive disorder; MI, myocardial infarction; PR interval, time from the onset of the P wave to the start of the QRS complex; QRS complex, the portion of the electrocardiogram comprising the Q, R, and S waves, together representing ventricular depolarization; QTc interval, corrected measure of the time between the start of the Q wave and the end of the T wave; SSRI, selective serotonin reuptake inhibitor.

\(*P<0.01\) vs placebo.


CGI-I, Clinical Global Impression Improvement scale; LVEF, left ventricular ejection function; MDD, major depressive disorder; MI, myocardial infarction; PR interval, time from the onset of the P wave to the start of the QRS complex; QRS complex, the portion of the electrocardiogram comprising the Q, R, and S waves, together representing ventricular depolarization; QTc interval, corrected measure of the time between the start of the Q wave and the end of the T wave; SSRI, selective serotonin reuptake inhibitor.

No significant difference between groups in measures of cardiovascular safety

- LVEF
- Heart rate
- Blood pressure
- PR interval
- QRS duration
- QTc interval
- Measure of autonomic balance
- Ventricular tachycardia
- Laboratory indices

*P<0.01 vs placebo.

Inflammation May Influence Effectiveness of Antidepressant Treatment

CRP levels have been differentially related to antidepressant treatment outcomes in patients with MDD

Data are consistent with a previous assessment of patients with depression in which
- Patients with CRP <1 mg/L had greater reduction in depression severity with an SSRI (compared with a TCA)
- Patients with CRP ≥1 mg/L had better response to a TCA (compared with an SSRI)

CO-MED, Combining Medications to Enhance Depressions Outcome; CRP, C-reactive protein; MDD, major depressive disorder; NDRI, norepinephrine-dopamine reuptake inhibitor; QIDS-SR, Quick Inventory of Depressive Symptomatology Self-Report; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

*P≤0.05 for SSRI CRP <1 vs ≥1 mg/L.

Adjunctive atypical antipsychotics may improve rate of remission

### Studies analyzed

<table>
<thead>
<tr>
<th>Studies analyzed*</th>
<th>Odds ratio, 95% CI</th>
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<tbody>
<tr>
<td>Shelton et al. 2001</td>
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<td>Shelton et al. 2005</td>
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<td>Marcus et al. 2008</td>
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*Meta-analysis of 16 trials in patients with treatment-resistant major depressive disorder (N=3484 patients).


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**Individual patient characteristics and relative risk of side effects should inform optimal treatment choice.**

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Cl, confidence interval.
Nonpharmacological Considerations for Depression and Cardiovascular Disease
Many Guidelines Recommend Nonpharmacological Interventions for MDD and CV Risk Reduction

In addition to recommending pharmacological therapy, treatment guidelines for MDD\(^1\) and reduction of CV risk\(^2\) promote healthy behaviors:

- Healthy weight
- Physical activity
- Good nutrition
- Psychosocial interventions
- Cessation of smoking or substance use
- Establish a therapeutic alliance

CV, cardiovascular; MDD, major depressive disorder.

Weight Management May Help Optimize MDD Treatment and Reduce Cardiovascular Risk

Patients with MDD and elevated BMI demonstrated a reduced rate of response with antidepressants\(^1\)

For all patients, including those with mental illness, as little as 5% weight loss may significantly decrease risk factors of cardiometabolic disease, including\(^2\):

- Glucose
- Glycemic control
- Triglycerides
- HDL cholesterol
- Blood pressure

BMI, body mass index; HAM-D, Hamilton Rating Scale for Depression; HDL, high-density lipoprotein; MDD, major depressive disorder.

Physical Activity May Improve Depression and Cardiovascular Health

Patients with inadequate response to SSRI who added exercise demonstrated improved rates of remission after 12 weeks\(^1\)

In patients with recent AMI, exercise reduced rate of mortality and subsequent nonfatal AMI over 4 years\(^2\)

AMI, acute myocardial infarction; SSRI, selective serotonin reuptake inhibitor.

*\(P<0.05\) vs low add-on exercise.

In female patients hospitalized for coronary disease, adding a psychosocial intervention to treatment regimen was associated with a reduction in all-cause mortality.

*Women (N=237) were consecutively hospitalized at a university hospital in Stockholm, Sweden, for acute myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention. Patients were not screened at enrollment for depression. †Intervention provided education about the heart, achieving a healthy lifestyle, improving mastery of marital stress, coping with illness, counteracting anxiety and depression, improving social relationships, and relaxation.

Healthy Lifestyle Modifications May Improve Overall Wellness

Intensive lifestyle modifications* improved cardiovascular risk factors, as well as ratings of depression, physical health, and mental health, over a 1-year period.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients with cardiovascular disease (N=35)</th>
<th>Patients with elevated risk factors (N=37)</th>
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</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>-5.4%</td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>-5.2%</td>
<td>-14.2%</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
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<td>-11%</td>
</tr>
<tr>
<td>Depression scale (CES-D)</td>
<td>-17.1%</td>
<td>-46.4%</td>
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<tr>
<td>Physical health composite</td>
<td>17.7</td>
<td>17.3</td>
</tr>
<tr>
<td>Mental health composite</td>
<td>11.3</td>
<td>36.8</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; CES-D, Center for Epidemiologic Studies Depression Scale. *Program includes eating a low-fat vegetarian diet, participating in 1 hour of stress management per day, performing 3 hours of aerobic exercise each week, and attending weekly group support sessions for 1 year. Participants must have a diagnosis of cardiovascular disease or two or more cardiovascular risk factors and were not screened for depression before enrollment.

Summary

Major depressive disorder (MDD) and cardiovascular disease are highly comorbid and share a complex, multifactorial, and bidirectional relationship

Psychosocial, biological, and behavioral mechanisms may underlie the shared pathophysiology between MDD and cardiovascular disease

Individual patient characteristics and possible adverse effects are factors in treatment choice for patients with comorbid MDD and cardiovascular disease

Nonpharmacological strategies, such as increasing physical activity, may confer benefit in patients with comorbid MDD and cardiovascular disease
Discussion
Thank You