9TH ANNUAL CHAIR SUMMIT
Master Class for Neuroscience Professional Development

September 16 – 17, 2016 | The Biltmore Hotel | Miami, FL

Sponsored by CME Outfitters
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Disclosures

- **Stock Shareholder:** Orexigen Therapeutics, Inc.
Describe the impact of comorbid depression and chronic illness
Learning Objective 2

Apply the principles of collaborative care to the treatment of depression
People with chronic medical conditions are more expensive to treat and manifest a variety of other problems i.e. depression, anxiety, substance use disorder and other behavioral disorders.

Does the MH/SU disorder cause a more severe medical condition, or does the severe medical condition cause the MH/SU disorder?

MH = mental health, SU = substance use
Depression is Common Among People Who Have Chronic Illnesses

- Cancer
- Coronary heart disease
- Diabetes
- Epilepsy
- Multiple sclerosis
- Stroke
- Alzheimer’s disease
- HIV/AIDS
- Parkinson’s disease
- Systemic lupus erythematosus

People With Depression are at Higher Risk for Other Medical Conditions

- Cardiovascular disease
- Diabetes
- Stroke
- Alzheimer’s disease
- Osteoporosis

Physiological Changes Seen in Depression Play a Role in Increasing the Risk of Physical Illness

- Increased inflammation
- Control of heart rate and blood circulation
- Abnormalities in stress hormones
- Metabolic changes

Heart Disease

- Studies of the relationship between depression and prognosis of coronary artery disease (CAD), in people without preexisting CAD.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Follow-up (years)</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallstrom et al(^{12})</td>
<td>38-54</td>
<td>12</td>
<td>Severity of depression, predicted angina only</td>
</tr>
<tr>
<td>Appels and Mulder(^{13})</td>
<td>39-65</td>
<td>4.5</td>
<td>RR=2.28 for nonfatal MI; no association with fatal MI</td>
</tr>
<tr>
<td>Anda et al(^{14})</td>
<td>45-77</td>
<td>12.4</td>
<td>RR=1.5 for depressive affect</td>
</tr>
<tr>
<td>Aromaa et al(^{15})</td>
<td>40-64</td>
<td>6.6</td>
<td>RR=3.36</td>
</tr>
<tr>
<td>Wassertheil-Smolier et al(^{16})</td>
<td>≥60</td>
<td>4.5</td>
<td>Deaths: RR=1.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MI or stroke: RR=1.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MI: RR=1.14, but not significant*</td>
</tr>
<tr>
<td>Barefoot and Schroll(^{17})</td>
<td>50</td>
<td>24</td>
<td>Death: RR=1.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MI: RR=1.71</td>
</tr>
<tr>
<td>Pratt et al(^{18})</td>
<td>&gt;18</td>
<td>13</td>
<td>MI: RR=4.54 for major depressive episode</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MI: RR=2.07 for dysphoria</td>
</tr>
<tr>
<td>Ford et al(^{19})</td>
<td>26±2</td>
<td>37</td>
<td>MI or CAD: RR=2.12</td>
</tr>
<tr>
<td>Mendes de Leon et al(^{20})</td>
<td>65-99</td>
<td>9</td>
<td>Mortality: RR=1.03</td>
</tr>
</tbody>
</table>

*Adjusted for multiple factors (varies between studies, in general age, conventional cardiovascular risk factors, such as smoking, cholesterol, weight, or body mass index, and physical conditions at entry of the study).

MI = myocardial infarction; RR = relative risk

Heart Disease (cont’d)

- Studies of the relationship between depression and prognosis in coronary artery disease (CAD), in people with preexisting CAD.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-up (months)</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stern et al⁴</td>
<td>68</td>
<td>12</td>
<td>7.5 (OR)</td>
</tr>
<tr>
<td>Schleifer et al³⁴</td>
<td>282</td>
<td>6</td>
<td>3.1</td>
</tr>
<tr>
<td>Ahern et al³⁵</td>
<td>265</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>Ladwig et al³⁶</td>
<td>552</td>
<td>6</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>Frasure-Smith et al³⁶</td>
<td>222</td>
<td>6</td>
<td>3.1</td>
</tr>
<tr>
<td>Frasure-Smith et al³⁸</td>
<td>218</td>
<td>18</td>
<td>6.64</td>
</tr>
<tr>
<td>Frasure-Smith et al³⁹</td>
<td>896</td>
<td>12</td>
<td>3.66</td>
</tr>
<tr>
<td>Kaufman et al³³</td>
<td>361</td>
<td>12</td>
<td>2.33</td>
</tr>
</tbody>
</table>

RR = adjusted relative risk ratio for mortality after myocardial infarction with versus without depression; OR = odds ratio.
Mental stress, which can be provoked by a number of strategies, such as asking an individual to speak publicly, do mental arithmetic, etc, has been shown to provoke ischemia that can be reliably measured.

Patients with established CAD and depressive symptoms showed more ischemia during mental stress testing.

LOD: A Vascular Phenomenon

- Vascular changes on CT and MRI led to a review of previous work and to new studies
- Vascular risk factors and Late Onset Depression (LOD)
- Stroke and depression

LOD = late-onset depression
Vascular Depression as a Clinical Subtype of Major Depression

- MRI-defined vascular depression
- Clinically defined vascular depression
- “Vascular depression” hypothesis
- Structural neuroimaging and mood disorders

Criteria for “Vascular Depression”

- Presence of major depression
- Specific characteristics of depression
- Older age of onset or change in character of symptoms if early onset
- Presence of non-CNS vascular disease
- Documentation of brain damage: neuroimaging findings, neurological findings, neuropsychological findings

Evidence from the Cardiovascular Health Study

- 3657 subjects at five sites
- Detailed interview
- Standardized assessments
- MRI scans with lesion grading and count
- Modified version of the CES-D

CES-D = Center for Epidemiological Studies of Depression Scale
Cardiovascular Health Study: Lesions and Depression

- Severe white matter grade
- Number of small basal ganglia lesions
- Effect of basal ganglia lesions remains highly significant controlling for white matter severity and all of the non-MRI variables

Orbital Frontal Cortex

- 88 elderly depressives and 47 controls
- A statistical parametric map was formed from a two-group t-test to test for differences in lesion density between depressed patients and control subjects
- Additional testing was performed to evaluate whether there were regions that correlated with the severity of depression using the Hamilton Depression Rating Scale

Consequences of Depression in Patients With Vascular Lesions

- Refractory to medication monotherapy
- Longer time to recovery
  - months not weeks
- Cognitive decline and vascular dementia
- Stroke

Lesions and History of Suicide Attempts

- 19 patients with suicide attempt history
  - age- and gender-matched with 19 patients without such a history
- Fazekas ratings for PVH, DWMH, and SGH
- PVH: $p = 0.030$, $t = 2.348$
- DWMH: $p = 0.207$, $t = 1.310$
- SGH: $p = 0.037$, $t = 2.256$

PVH, periventricular hyperintensities, DWMH, deep white matter hyperintensities, SGH, subcortical gray matter hyperintensities.
Lesions and Treatment Response

- Remitted patients (n = 71) had fewer lesions in the left white matter (2.1 ml) vs nonremitted patients (n = 65) – (3.1 ml; p < .04)
- Remitted patients also had fewer lesions in the right white matter – similar magnitude to left

Lesion Change and Treatment Response

- Remitted patients (n = 66) had a smaller change (0.22) than nonremitted patients (n = 39) over a 2-year period (0.45) ($p = .04$) in both left and right white matter

- Similar changes for caudate and gray matter

Leukoencephalopathy and Cognition

- Resembles subcortical dementia
- Subtle changes related to severity
- Psychomotor speed
- Recent memory

Gray Matter Lesions and Dementia: Results

- Controlling for age, gender, baseline MMSE, and age of onset, the volume of SCG significantly predicted development of later dementia

- Log-rank test \( p \) value = .002

MMSE, Mini-Mental State Examination; SCG, subcortical gray matter
Lesions and Mortality

<table>
<thead>
<tr>
<th>Severity of Lesion</th>
<th>None to Mild</th>
<th>Moderate to Severe</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWMH</td>
<td>5.1%</td>
<td>21%</td>
<td>.003</td>
</tr>
</tbody>
</table>

MRI lesion severity and **mortality** in geriatric depression.

Treatment Options

● Nonpharmacologic
  - Behavioral intervention
  - Stress management
  - Exercise training

● Pharmacologic
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin reuptake inhibitors (SSRIs)
Drug-Drug Interaction

- Protein binding: warfarin, etc.
- CYP 2D6 interaction
- CYP 3A4 interaction
- 2C9/C19 interaction

Drug-Disease Interaction

- Liver disease
- Renal failure
- Medication-induced depression (e.g., reserpine)

Pharmacologic Therapy: Cardiac Effects

- **SSRIs**
  - No evidence of orthostatic hypotension
  - No evidence of pro/antiarrhythmic properties
  - Modest decrease in heart rate
  - No influence on BP, PR, QRS, or QTc

Summary

- Depression—the result of vascular disease?
- Depression—increases risk of vascular disease?
- Depression—affecting prognosis?
- Treatment of depression in context of vascular disease
Individuals with medical conditions and co-occurring MH/SU disorders are often never diagnosed and treated for their MH/SU conditions.
Three Minimally Overlapping Systems

- Mental Health
- Medical
- Substance abuse
Different

- People
- Payment
- Places
- Programs
- Policies
Cost

- Costs more to treat comorbid conditions
- $1085 versus $397 per member per month
- Economic Impact of Integrated Medical-Behavioral Healthcare

MH/SU Population Size and Spend

14% of population

30% of spend

MH/SU Doubles or Triples Expenditure

- Cancer
- Heart failure
- COPD
- Chronic Pain

- Asthma
- Stroke
- Diabetes
- Osteoporosis

Value Opportunity by Integrated Treatment

- 162 billion USD annually
- Big ticket areas
  - Arthritis
  - Asthma
  - Cancer
  - Heart failure

Integrated Medicine and Behavioral Health Care Programs Five Principles

- **Patient-Centered Team Care**
  - Primary care and behavioral health providers collaborate using shared care plans

- **Population-Based Care**
  - Care team shares a defined group of patients tracked in a registry

- **Measurement-Based Treatment to Target**

- **Evidence-Based Care**

- **Accountable Care**
  - Providers are accountable and reimbursed for quality of care and clinical outcomes

Half of the patients randomly assigned to receive the care normally available in their primary care clinic, including medications and/or referral to specialty mental health. The others were randomly assigned to Collaborative Care.

Collaborative Care more than doubled the effectiveness of depression treatment for older adults in primary care settings. At 12 months, about half of the patients receiving Collaborative Care reported at least a 50 percent reduction in depressive symptoms, compared with only 19 percent of those in usual care.

Pathways

- 329 patients with diabetes mellitus and comorbid major depression and/or dysthymia. Intervention Patients were randomly assigned to the Pathways case management intervention (n = 164) or usual care (n = 165).

- Intervention patients showed greater improvement in depression severity over time ($z = 2.84, p = .004$), a higher rating of patient-rated global improvement at 6 months.

Meta-analyses

- 37 studies
- 12,355 patients
- Depression outcomes better with intervention at 6 months

Collaborative Care for Depression

- Random-effects meta-analysis of longer-term outcome of collaborative care for depression.

Seven studies were included with a total of 2105 participants.

Collaborative care was superior to care as usual, with a small effect size (SMD = 0.35, 95% CI 0.14-0.56) for all anxiety disorders combined and a moderate effect size (SMD = 0.59, 95% CI 0.41-0.78) in a subgroup analysis (five studies) on patients with panic disorder.

Three Systems

- Fragmented and unintegrated
- Insufficient and relatively untrained workforce
- Payment systems that do not incentivize
Directions

- Value based models can promote integration
- Workforce training and expansion
- Integrated care models
Call To Action

- Patients with chronic medical illness should be assessed for substance abuse and mental health problems