Assessing and Managing Pain and Major Depression With Medical Comorbidities

This activity is supported by an educational grant from Lilly. For further information concerning Lilly grant funding, visit www.lillygrantoffice.com.

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Dr. Jackson is a consultant for Pamlab and has received honoraria from and is a member of the speakers/advisory boards for DepoMed, Eli Lilly, Pamlab, and Sunovion.
Objectives

- Assess and monitor major depression and pain in patients with medical conditions
- Develop a safe and effective treatment plan for major depression and pain in patients with medical conditions
Remission is the Goal of Treatment

Response = 50% decrease in baseline depression scores

Remission = being virtually asymptomatic:

- HDRS score ≤7 for at least 2 consecutive weeks
- QIDS-SR score ≤5
- PHQ-9 score <5

<table>
<thead>
<tr>
<th>Measure</th>
<th>Time to Complete (min)</th>
<th>Patient/ Clinician Rated</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-item Patient Health Questionnaire (PHQ-9)</td>
<td>&lt;3</td>
<td>Patient</td>
</tr>
<tr>
<td>17-item Hamilton Depression Rating Scale (HDRS-17)</td>
<td>30</td>
<td>Patient or clinician</td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>5–10</td>
<td>Patient</td>
</tr>
<tr>
<td>Montgomery-Asberg Depression Rating Scale (MADRS)</td>
<td>10–15</td>
<td>Patient or clinician</td>
</tr>
<tr>
<td>Quick-Inventory of Depression Symptomatology—Self Report (QIDS-SR)</td>
<td>5–10</td>
<td>Patient or clinician</td>
</tr>
<tr>
<td>Toronto 7-item Hamilton Depression Rating Scale (HDRS-7)</td>
<td>NA</td>
<td>Clinician</td>
</tr>
<tr>
<td>Sheehan Disability Scale (SDS)</td>
<td>1–2</td>
<td>Patient or clinician</td>
</tr>
</tbody>
</table>

Adapted with permission from McIntyre RS. *J Clin Psychiatry.* 2010;71(suppl 1):17.
Measurement-Based Care in MDD Leads to Better Outcomes Vs Usual Care

Change in IDS-C$_{30}$ Scores From Baseline to 1 Year With Algorithm-Guided Treatment Vs Treatment as Usual, Categorized by Depression Severity

The Importance of Attaining and Maintaining Remission

- Partial remission is still associated with significant and persisting functional impairment
- Improvements in depression symptom severity are directly correlated with improvements in functional impairment
- Patients who achieve complete remission are 3x more likely to achieve normal functioning than those with partial remission
- Adding exercise to any treatment regimen can significantly improve remission rates

In depression, inflammatory cytokines are released, activating the HPA system and releasing adrenocorticotrophic hormone (ACTH) and cortisol.

Chronic HPA system activation in depressed patients suppresses the production of inflammatory cytokines, affecting ACTH, cortisol, and TNF-α levels.

When patients with depression achieve remission, HPA activity normalizes.

- Patients had a significant reduction of ACTH and cortisol response compared with nonremitters (p=.04).
- Change in TNF-α levels was associated with ACTH response.
Residual Anxiety May Increase the Risk of Relapse in MDD Patients


![2-Year Depression-Free Survival Rates for Patients With MDD and Low Vs High Anxiety Levels](chart)

- **Placebo Group**
  - Anxiety Score = 0: 60%
  - Anxiety Score = 3: 28%

- **Pharmacotherapy Group**
  - Anxiety Score = 0: 79%
  - Anxiety Score = 3: 56%

Among patients with depression who relapsed, 90% had mild-to-moderate physical symptoms. Relapse resulted from a clear worsening of mild residual symptoms.

Physical symptoms were measured by HDRS-17 item #13 (score 8–12).

Physical Symptoms of Depression are Less Responsive to Treatment Than Other Symptoms

Patients were randomly assigned to treatment in a primary care office and interviewed at 1, 3, 6, and 9 months.

Patients With Depression Have a Predominance of Physical Symptoms

Other reported rates:

- **76%** of patients with depression or anxiety also made somatic presentations\(^3\)
- **69%** of primary care patients with depression also had pain\(^4\)
- **43%** of patients with depression also had chronic painful physical conditions\(^5\)
- **66%** of patients with MDD had chronic pain\(^6\)

Comorbidity of Pain and Depression

- 50% of chronic pain patients have depression\(^1\)
- Pain is equally comorbid with anxiety and depression\(^2\)
- 70%–90% of patients with irritable bowel syndrome have depression\(^3\)

Impact of Pain Comorbidity

- Negatively impacts the recognition of depression
- Increases severity of depressive and anxiety symptoms
- Increases impairment of psychosocial functioning
- Decreases responsiveness to antidepressant treatment
- Decreases remission rates
- Increases risk for relapse/recurrence of depressive episode

Higher Levels of Pain (not somatization) Lengthens the Time to Remission in MDD

Median Time to Remission for Patients With Chronic Depression

<table>
<thead>
<tr>
<th>Time, Weeks</th>
<th>Without Pain (n=136)</th>
<th>With Pain (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
<td>17</td>
</tr>
</tbody>
</table>

# Depression of Chronic Pain: A Subset?

<table>
<thead>
<tr>
<th>Common Symptoms</th>
<th>Uncommon Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Low energy</td>
<td>- Loneliness</td>
</tr>
<tr>
<td>- Disturbed sleep</td>
<td>- Guilt</td>
</tr>
<tr>
<td>- Worry</td>
<td></td>
</tr>
</tbody>
</table>
Emotional and Painful Physical Symptoms: A Shared Neurochemical Link in Depression?

- Dysregulation of serotonin (5-HT) and norepinephrine (NE) in the brain are strongly associated with depression.
- Because of the same imbalance of 5-HT and NE in the spinal cord, the brain may perceive an amplified pain signal.
- Imbalances of both 5-HT and NE may explain the presence of the emotional and physical symptoms of depression.

Neurobiology of Pain

Genetic Vulnerability

Stress

“Network” Level:
Dysregulation of Neural Circuitry
- Functional changes
- Structural changes

Neuroendocrine, Autonomic, and Immune Dysregulation

Cellular and Subcellular Level
Impact on:
- Intracellular signaling
- Gene transcription
- Neurotrophic support

Neuropsychiatric symptoms:
- Emotional
- Cognitive
- Behavioral
- Physical

Systemic manifestations

Epigenetic modulation

Adapted with permission from Maletic V, et al. *Front Biosci*. 2009;14:5291–5338.
Do Anxiety, Depression, and Sleep Problems Predict the Development of Pain?

- 15-month prospective study of 3171 adults aged 25–65 years
- 324 developed chronic widespread pain

HAD = Hospital Anxiety and Depression Scale

Emotions and Stress May Modulate Amygdala Response to Pain (hypothesised model)


**Negative Emotion**  
(chronic stress)  
*Increases* amygdala activity

**Positive Emotion**  
(music, pleasant odors, etc)  
*Inhibits* amygdala activity

ACC  
Thalamus  
Amygdala

Pain
“The sorrow that has no vent in tears may make other organs weep.”
Pain Becomes More Common in Both Sexes as People Get Older


Prevalence of Chronic Painful Physical Conditions (CPPCs) by Age Group and Gender

*P* < .0001 between age groups (15–24 year-old and 25–44 year-old groups vs 45–64 year-old and ≥65-year-old groups) and between genders.
Peripheral and dorsal horn neuron sensitization may generate a disruption of corticolimbic processing of pain in vulnerable individuals\(^1–^3\)

Functional and structural changes in the brain may result in descending pain facilitation and inadequate descending inhibition\(^2–^4\)

Neuroendocrine, neuroimmune, and sympathetic dysregulation may further impact nociception and spinal pain signaling\(^5\)

“Pain is a more terrible lord of mankind than even disease itself.”
Chronic Back Pain (CBP) is Associated With Gray Matter Loss in Dorsolateral PFC and Thalamus

- Patients with CBP had 5%–11% less neocortical gray matter volume than controls, equivalent to 10–20 years of normal aging.\(^1\)
- Executive working memory areas have a role in pain inhibition.\(^2\)

**Voxel-Based Morphometry\(^1\)**

Areas in red indicate a composite of regions where gray matter density was reduced in patients with CBP compared with controls

A slice of the right anterior thalamus at the peak of decreased thalamic gray matter

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Domains of Chronic Pain

Quality of Life
- Physical functioning
- Ability to perform activities of daily living
- Work
- Recreation

Psychological Morbidity
- Depression
- Anxiety, anger
- Sleep disturbances
- Loss of self-esteem

Social Consequences
- Marital/family relations
- Intimacy/sexual activity
- Social isolation

Socioeconomic Consequences
- Healthcare costs
- Disability
- Lost workdays
Algorithm for the Assessment of Chronic Pain

**First Step**
- Pain screeners and visual analog scales

**Determine Mechanism of Pain**
- History and physical examination
- Pain evaluation and description
- Functional and social assessment tools

**Neuropathic**
- (burning, stabbing, shooting)
  - Peripheral nervous system conditions (complex regional pain syndrome, phantom pain, metabolic)
  - Central nervous system conditions (Parkinson’s disease, multiple sclerosis, myelopathies, stroke)
  - Fibromyalgia

**Musculoskeletal**
- (aching, stiffness, soreness)
  - Fibromyalgia
  - Myofascial pain syndrome
  - Trauma

**Inflammatory**
- (aching, swelling, erythema, heat)
  - Arthropathies (rheumatoid arthritis, ankylosing spondylitis)
  - Infection
  - Postoperative pain
  - Tissue injury

**Mechanical Compression**
- (aching, soreness, stiffness)
  - Low back pain
  - Musculoskeletal pain
  - Visceral pain
  - Muscle, tendon, ligament pain

**Mixed**
- (combination of pain patterns)
  - Various conditions

**Examples of possible conditions**

Bidirectional Relationship: Pain Predicts Depression and Anxiety

Prevalence of the Most Common Clinical Syndromes in the Study Population

- **Depressive Disorder**
  - Group 1: Control (n=50) - 4%
  - Group II: Chronic pain in 1 region (n=50) - 20%
  - Group III: Chronic pain in multiple regions (n=50) - 32%

- **Generalized Anxiety Disorder**
  - Group 1: Control (n=50) - 14%
  - Group II: Chronic pain in 1 region (n=50) - 30%
  - Group III: Chronic pain in multiple regions (n=50) - 54%

*P < .05 vs Group 1

Pain and Depression: A Vicious Cycle

- Presence of pain diminishes recognition and treatment of depressive symptoms

- Pain worsens depression outcomes:
  - ↓ QOL
  - ↓ Work function
  - ↑ Health care utilization
  - ↑ Relapse

- Depression worsens pain outcomes:
  - ↑ Pain complaints
  - ↑ Impairment

“Pain is perfect misery, the worst of all evils; and excessive, overturns all patience.”
Standard Pharmacologic Treatment Options for MDD

- TCAs (amitriptyline, nortriptyline)
- MAOIs (phenelzine, selegiline)
- SSRIs (fluoxetine, paroxetine)
- SNRIs (venlafaxine, duloxetine)
- NRIs (bupropion)
- Olanzapine/fluoxetine combination
- 5-HT$_{1A}$ antagonists (vilazodone)
- 5-HT$_2$ antagonists (trazodone)
- Noradrenergic antagonist (mirtazapine)
Other Pharmacologic Treatment Options for MDD

- Antipsychotics
- Buspirone
- L-methylfolate
- Inositol
- Lamotrigine
- Lithium
- Omega-3 fatty acids
- Pindolol
- Psychostimulant (e.g., modafinil)
- S-adenosyl methionine (SAM-e)
- St. John’s wort
- Testosterone
- Thyroid

* Some agents are not FDA approved for the treatment of MDD. Providers should be aware of efficacy, safety, tolerability, and adverse events of off-label medications. Please see prescribing information for further information.
Nonpharmacologic Treatment Options for MDD

- Exercise
- Acupuncture
- Deep brain stimulation (DBS)
- Electroconvulsive therapy (ECT)
- Light therapy
- Psychosurgery
- Psychotherapy
- Transcranial magnetic stimulation (TMS)
- Vagus nerve stimulation (VNS)
STAR*D: Current Antidepressant Treatments May Be Inadequate

Cumulative Proportion of Participants Without Relapse

Patients Without Relapse During Follow-Up
Per Treatment Step

Causes of nonremission in major depressive disorder:

- Failure to establish the diagnosis
- Absence of measurement-based care
- Complex illness presentations
- Absence of early improvement

Those who required more treatment steps had higher relapse rates.

More Antidepressant Bang (efficacy), but for More Buck (adverse events) With SNRIs


Pooled Discontinuation Rates (Due to Intolerance) for Patients With Depression and SSRI Resistance Who Switched to an SSRI Vs a Non-SSRI (N=1,496)

Next-Step Medication

Non-SSRIs=bupropion, mirtazapine, venlafaxine.

Considerations When Switching Antidepressants

- Efficacy
  - For depressive symptoms
  - For other conditions (eg, pain)

- Tolerability

- Patient preference

- Treatment history

- Risk of withdrawal symptoms

- Potential loss of partial therapeutic benefit
Are We Reassessing Too Late?

- Early improvement at 2 weeks predicts response
- Lack of improvement in the first 2 weeks of treatment may indicate changes in management should be considered

Therapeutic Options for Chronic Pain Management

- Pharmacotherapy
- Rehabilitative approaches
- Psychological interventions
- Anesthesiological approaches
- Neurostimulatory techniques
- Surgery
- Complementary/alternative approaches
- Lifestyle changes
Pharmacologic Agents Affect Pain Differently

- Peripheral Sensitization
  - Local Anesthetics
  - Topical Analgesics
  - Anticonvulsants
  - TCAs
  - Opioids

- Central Sensitization
  - Anticonvulsants
  - Opioids
  - NMDA-Receptor Antagonists
  - TCAs/SNRIs

- Descending Modulation
  - Anticonvulsants
  - Opioids
  - TCAs/SNRIs

Opioids: A Balancing Act

- Pharmacologic Effects
- Efficacy
- Routes of Administration

- Adverse Events
- Abuse and Misuse
- Legal and Regulatory
Opioid Therapy: Monitoring Outcomes

Monitoring the 4 A’s

- **Analgesia** (pain relief)
- **Activities** of daily living (psychosocial functioning)
- **Adverse** effects (side effects)
- **Aberrant** drug taking (addiction-related outcomes)

Effectiveness of Standard Antidepressant Agents on Pain

Of 100 patients with neuropathic pain who are given antidepressants:

- 30 patients will achieve $\geq 50\%$ pain relief
- 30 patients will have minor adverse effects
- 4 patients will discontinue treatment due to major adverse effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>50% Relief (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical facial pain</td>
<td>2.8</td>
</tr>
<tr>
<td>Central pain</td>
<td>1.7</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>3.0</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>2.3</td>
</tr>
<tr>
<td>Minor adverse effects</td>
<td>3.7</td>
</tr>
<tr>
<td>Major adverse effects</td>
<td>22</td>
</tr>
</tbody>
</table>

Dual Neurotransmitter Antidepressants (SNRIs)

**Previous Model**

Analgesic properties secondary to affective properties

**Current Model**

Analgesic properties secondary to enhanced neurotransmitter activity in descending corticobulbar pathways (which inhibit pain signals)

- Serotonin
- Norepinephrine
SNRIs Reduce Painful Symptoms

Patients With Depression Who Switched to an SNRI (n=368) and Its Impact on Painful Physical Symptoms

<table>
<thead>
<tr>
<th>Depressed Patients, %</th>
<th>Significant Pain at Baseline</th>
<th>No Significant Pain at Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61.0</td>
<td>29.7</td>
</tr>
<tr>
<td>Direct switch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start-taper switch</td>
<td>65.4</td>
<td>34.75</td>
</tr>
</tbody>
</table>

Chronic Pain Management: Anesthetic Approaches

- Neuraxial drug administration
- Opioids, local anesthetics, and/or clonidine* via continuous epidural or intrathecal infusion
- Neural blockade
- Temporary block
- Neurolytic block

* Not FDA approved for pain management. Providers should be aware of efficacy, safety, tolerability, and adverse events of off-label medications. Please see prescribing Information for further information.
Cognitive-Behavioral Management of Chronic Pain

Pilot Study of 6 Weekly 90-Minute Group Sessions Based on CBT Attention Management Manual

Data for individuals completing 6-month follow-up.

Mind-Body Intervention for Older Adults With Chronic Pain

Randomized Trial of 6-Week Online Interventions Focusing on Self-Care and Mind-Body Exercises

<table>
<thead>
<tr>
<th>Measure</th>
<th>Comparison group (n=37)</th>
<th>Intervention group (n=41)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (CES-D)</td>
<td>0.37</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Anxiety (STAI)</td>
<td>-1.50</td>
<td>-0.64</td>
<td></td>
</tr>
<tr>
<td>Pain Interference (BPI)</td>
<td>-0.88</td>
<td>-1.21</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

BPI = Brief Pain Inventory, CES-D = Center for Epidemiologic Studies Short Depression Scale, SATI = State Trait Anxiety Inventory form. No significant between-group differences for any measure.

Exercise: An Effective Treatment for Pain

24-Month Randomized Trial of Diet and Exercise Vs Patient Education for Knee Pain/Osteoarthritis (N=389)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Improvement, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advice Leaflet</td>
<td>30</td>
</tr>
<tr>
<td>Diet Only</td>
<td>35</td>
</tr>
<tr>
<td>Exercise Only</td>
<td>47*</td>
</tr>
<tr>
<td>Diet + Exercise</td>
<td>43*</td>
</tr>
</tbody>
</table>

30% Reduction in Pain Score

*P<.05 vs non-exercise groups (overall, those with knee exercise were more likely to experience a ≥30% reduction in pain P=.022).

Data from Jenkinson CM, et.al. BMJ. 2009;339:b3170.
Case Study

JB is a 52yo caucasian female
- Diagnosed with depression 3 months ago
- Started on sertraline 25 mg/d; titrated to 50 mg/d at 2 weeks, then to 100 mg/d at 6 weeks

Symptoms
- Depressed mood
- Poor sleep
- Daytime fatigue
- Anhedonia
- Sexual dysfunction
- Weight gain
- Mild anxiety
- No suicidal thoughts

“I just don’t feel well anymore. I don’t sleep right, and I just don’t have any zip.”
### Patient History

<table>
<thead>
<tr>
<th>PMH</th>
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<tbody>
<tr>
<td>- Obesity</td>
</tr>
<tr>
<td>- Hypothyroidism</td>
</tr>
<tr>
<td>- G2P2 (postpartum depression with child 2; treated successfully with sertraline)</td>
</tr>
<tr>
<td>- Osteoarthritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
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<tbody>
<tr>
<td>- Sertraline 100 mg/d</td>
</tr>
<tr>
<td>- Levothyroxine 50 mcg/d</td>
</tr>
<tr>
<td>- Diclofenac 75 mg/bid</td>
</tr>
<tr>
<td>- Multivitamin qd</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- BMI = 32 kg/m2</td>
</tr>
<tr>
<td>- BP = 126/75</td>
</tr>
<tr>
<td>- CMP = within normal limits</td>
</tr>
<tr>
<td>- TSH = 4.3 (on 50 mcg/d)</td>
</tr>
<tr>
<td>- ESR = 3</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Assessment Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>- PHQ-9 = 14</td>
</tr>
<tr>
<td>- GAD-7 = 4</td>
</tr>
<tr>
<td>- MDQ = (-)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>6 weeks</th>
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</thead>
<tbody>
<tr>
<td>- PHQ-9 = 10</td>
</tr>
</tbody>
</table>
What is the Next Step in JB’s Treatment?

▪ Implement cognitive-behavioral counseling?
▪ Add a nutraceutical supplement (eg, L-methylfolate)
▪ Prescribe physical therapy and exercise
▪ Increase the dosage of sertraline
▪ Switch to another antidepressant with a different mechanism of action (eg, an SNRI)
▪ Add an atypical antipsychotic
Thank You