Major Depression in the Primary Care Setting: Clinical Updates on Novel Strategies for Relapse Prevention and Sustained Recovery

Wednesday, June 4, 2014
Philadelphia, Pennsylvania
Session 4: Major Depression in the Primary Care Setting:
Clinical Updates on Novel Strategies for Relapse Prevention and Sustained Recovery

Learning Objectives
1. Identify residual symptoms of major depressive disorder (MDD) and evaluate their impact on symptomatic remission and recovery.
2. Review recent clinical updates on traditional and newer pharmacotherapies for MDD and their benefits/limitations in symptomatic remission and recovery.
3. Examine the role of serotonin in the pathogenesis of MDD, including the significance of molecular targets in mitigating residual symptoms of depression.

Faculty

Larry Culpepper, MD, MPH
Professor of Family Medicine
Boston University School of Medicine
Staff Physician
Boston Medical Center
Boston, Massachusetts

Dr Larry Culpepper is professor of family medicine and founding chairman of the Department of Family Medicine at Boston University School of Medicine. He has conducted federally funded studies on depression and anxiety disorders; diabetes; otitis media; and school- and community-based interventions to improve pregnancy outcomes and prevent teen pregnancies.

Dr Culpepper has served as president of the North American Primary Care Research Group (NAPCRG); chaired or been a member of five research grant review committees, among them the National Institutes of Health and other federal agencies; and has served on six federal expert panels for consensus committees or evidence-based centers.

Dr Culpepper is a member of the Depression and Bipolar Support Alliance, the Anxiety Disorders Association of America, and the Depression and Bipolar Support Alliance (DBSAA) Scientific Advisory Board. He was editor of The Primary Care Companion for CNS Disorders and past family medicine editor of UpToDate. Dr Culpepper received the NAPCRG-STFM (Society of Teachers of Family Medicine) Career Research Award in 1997, was elected to the Institute of Medicine in 1998, and received the NAPCRG Maurice Wood Lifetime Research Award in 2010.

Michael E. Thase, MD
Professor of Psychiatry
Perelman School of Medicine
University of Pennsylvania
Philadelphia VA Medical Center
Philadelphia, Pennsylvania

Dr Michael Thase is professor of psychiatry and director of the Mood and Anxiety Disorders Program at the Perelman School of Medicine at the University of Pennsylvania. He received his medical degree from the Ohio State University College of Medicine, followed by a residency and fellowship at the Western Psychiatric Institute and Clinic in Pittsburgh.
Dr Thase is a distinguished fellow of the American Psychiatric Association (APA), a founding fellow of the Academy of Cognitive Therapy, a member of the board of directors of the American Society of Clinical Psychopharmacology, and vice chairman of the Scientific Advisory Board of the National Depression and Bipolar Support Alliance. He has received numerous honors in the field of psychiatry, including the APA’s Marie Eldredge Award. He is also a member of many professional and scientific societies, including the American Medical Association, the American College of Psychiatrists, the American College of Neuropsychopharmacology, and the Society for Psychotherapy Research.

Dr Thase has authored or co-authored more than 500 scientific articles and book chapters, as well as 15 books. His published articles have been featured in various journals, including Archives of General Psychiatry, the American Journal of Psychiatry, and the British Journal of Psychiatry. He is editor-in-chief of Psychopharmacology Bulletin. A consultant and lecturer, Dr Thase remains active in the community by giving numerous presentations and seminars at state and community hospitals and at the Office of Education and Regional Programming at University of Pittsburgh.

Faculty Financial Disclosure Statements

The presenting faculty reports the following:

Dr Culpepper serves as advisor to AstraZeneca Pharmaceuticals LP; Forest Laboratories, Inc.; H. Lundbeck A/S; Merck & Co., Inc.; Sunovion Pharmaceuticals Inc.; and Takeda Pharmaceuticals U.S.A., Inc.; and is a consultant for and stockholder in My Mood Monitor (M3)

Dr Thase is an advisor and consultant to Alkermes; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Eli Lilly and Company; Forest Laboratories, Inc.; Gerson Lehman Group; GlaxoSmithKline; Guidepoint Global LLC; H. Lundbeck A/S; Janssen Pharmaceuticals, Inc.; MedAvante, Inc.; Merck & Co., Inc.; Neuronetics, Inc.; Ortho-McNeil Pharmaceutical, Inc.; Otsuka America Pharmaceutical; Pfizer Inc.; Roche; Shire US Inc.; Sunovion Pharmaceuticals Inc.; Takeda Pharmaceuticals U.S.A., Inc.; and Transcept Pharmaceuticals, Inc.; receives grant support from Eli Lilly and Company, Otsuka America Pharmaceutical, and Forest Pharmaceuticals, Inc.; as well as honoraria from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company; Eli Lilly and Company, Pfizer Inc., and Merck & Co., Inc. He also possesses equity holdings in MedAvante, Inc., and receives royalties from the American Psychiatric Foundation, Guilford Publications, Herald House, and W. W. Norton & Company, Inc. Dr Thase’s spouse/partner is employed at Peloton Advantage, which does business with Pfizer/Wyeth.

Education Partner Financial Disclosure Statement

The content collaborators at Spire Learning have reported the following:

Kashemi Rorie, PhD, clinical director, and Christine Kocienda, program director, have no financial relationships to disclose. Ms. Kocienda’s spouse/partner is a shareholder in Johnson & Johnson and Procter and Gamble.

Suggested Reading List


Celada P, Bortolozzi A, Artigas F. Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: rationale and current status of research. CNS Drugs. 2013;27(9):703-716.


SESSION 4
1:15–2:30pm
Major Depression in the Primary Care Setting: Clinical Updates on Novel Strategies for Relapse Prevention and Sustained Recovery
SPEAKERS
Larry Culpepper, MD, MPH
Michael Thase, MD

Presenter Disclosure Information
Off-Label/Investigational Discussion
► In accordance with PMICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives
• IDENTIFY residual symptoms of MDD and EVALUATE their impact on symptomatic remission and recovery
• REVIEW recent clinical updates on traditional and newer pharmacotherapies for MDD and their benefits/limitations in symptomatic remission and recovery
• EXAMINE the role of serotonin in the pathogenesis of MDD, including the significance of molecular targets in mitigating residual symptoms of depression

Major Depression in the Primary Care Setting:
Clinical Updates on Novel Strategies for Relapse Prevention and Sustained Recovery
Larry Culpepper, MD, MPH (Co-Chair)
Boston University School of Medicine
Boston, MA

Michael Thase, MD (Co-Chair)
University of Pennsylvania
Philadelphia, PA

Drivers of Change at the Primary Care-Psychiatry Interface
External
• Affordable Care Act: increasing access to patients previously uninsured, including those with psychiatric disorders
• Mental Health Parity: increasing funding for behavioral health care

New Frameworks for Care
• PCMHs and ACOs – integrate medical and mental health care – multidisciplinary teams (PCP, care managers, behavioral health staff) – interdisciplinary collaboration between Primary Care and Psychiatry – Panel management
Adults With Major Depressive Episode (MDE) Who Received Treatment, 2009

% age 18+ with MDE receiving treatment in the past year*

<table>
<thead>
<tr>
<th></th>
<th>U.S. average</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>Private</th>
<th>Medicaid</th>
<th>Medicare**</th>
<th>Uninsured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>64</td>
<td>69</td>
<td>53</td>
<td>49</td>
<td>65</td>
<td>79</td>
<td>72</td>
</tr>
</tbody>
</table>

*Major depressive episode is defined as a period of at least 2 weeks when a person experienced a depressed mood ** or loss of interest or pleasure in daily activities and had a majority of the symptoms for depression. **Medicare includes other insurance such as military and veterans health care.


Prevalence of Depression and Anxiety By Income

- Major depression increases within 1 year of:
  - increased financial strain (OR = 1.47)
  - increased deprivation (OR = 1.19)
- Low SES even more strongly associated with maintenance of depression than onset

Implications

- Shift from rewarding productivity (# of services) to value added as measured in improved health status
  - Quality measures of individual patients, PCP panel, and population enrolled with the PCMH or ACO
- Shared savings from reduction of poor disease outcomes
  - Reduce high-cost hospital and diagnostic utilization
  - Increased expense at the PCMH and ambulatory level

Episodes of Poverty Have Cumulative Risk of Subsequent Major Depression

<table>
<thead>
<tr>
<th>Relative Risk of Depression in 1994</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-III-R MDD</td>
</tr>
<tr>
<td>High Depressive Symptoms</td>
</tr>
<tr>
<td>Number of Times Income less than 200% Poverty 1965-1983</td>
</tr>
<tr>
<td>0 1 2 3</td>
</tr>
<tr>
<td>1 1 1.72 3.24</td>
</tr>
<tr>
<td>0 1 2 3</td>
</tr>
<tr>
<td>1 1.75 4.02 4.56</td>
</tr>
</tbody>
</table>


PCMH: Integration of Care Strategy

<table>
<thead>
<tr>
<th>Tasks &amp; Objectives</th>
<th>Process</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify goals/target</td>
<td>Collaborate to formulate specific measurable targets (eg, BP, PHQ-9, HbA1c, walk # stops)</td>
<td>Patients, PCPs, care managers</td>
</tr>
<tr>
<td>Support self-care</td>
<td>Motivate, problem-solve to promote self-monitoring, adherence to medications, lifestyle change</td>
<td>Patient, care manager</td>
</tr>
<tr>
<td>Monitor progress</td>
<td>Systematic, proactive tracking, population-based</td>
<td>Patient, care manager, multidisciplinary consultant</td>
</tr>
<tr>
<td>Treat-to-target case reviews</td>
<td>Weekly multidisciplinary case load review, formulate treatment adjustment recommendations to PCP Case-by-case training</td>
<td>Treat to target physician consultants, care manager</td>
</tr>
<tr>
<td>Care coordination</td>
<td>Communicate and coordinate (eg, EMR, telephone, or in person)</td>
<td>Care manager</td>
</tr>
</tbody>
</table>

Integrated Care: Major Effect on Treatment Adjustments

<table>
<thead>
<tr>
<th>Rate (95% CI)</th>
<th>Relative Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>3.37 (2.92-3.89)</td>
</tr>
<tr>
<td>Insulin</td>
<td>3.26 (2.43-4.36)</td>
</tr>
<tr>
<td>Oral hypoglycemic</td>
<td>0.62 (0.44-0.88)</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>2.33 (1.86-2.92)</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>0.81 (0.64-1.03)</td>
</tr>
</tbody>
</table>


Residual Symptoms After Remission From Depression With Citalopram: STAR*D

Most Frequent Residual Symptoms Not Present at Baseline but at Remission:
- Mid-nocturnal insomnia (24%)
- Increased weight (16%)
- Hypersomnia (14%)
- Decreased weight (11%)
- Early morning insomnia (10%)

Basic Tools and Resources for Depression Care in the PCMH

**Tools**
- Screening /case finding & severity measures
  - QIDS or PHQ-9
  - CIDI 3.0 (Bipolar Disease)
  - PC-PTSD/PCL (PTSD)
- Function measures
  - Sheehan Disability Scale
  - MGH Cognitive and Physical Functioning Questionnaire
- Quality of life scale
  - Q-LES-Q

**Resources**
- Guideline-based acute and chronic care management strategies
- Evidence-Based Guideline
- Consider comorbidities, side effects, and residual symptoms
- PC/Psychiatry Collaboration
- Access to Treatment Options
  - Individualized

QIDS, Quick Inventory of Depressive Symptomatology; PHQ, Patient Health Questionnaire; CIDI, Composite International Diagnostic Interview; PC-PTSD, Primary Care Posttraumatic Stress Disorder; PCL, Posttraumatic Stress Disorder Checklist-Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire


Prevalence of Residual Symptoms by Type in MDD

Basic Tools and Resources for Depression Care in the PCMH

Mrs. Carroll: “It’s back and I can’t think straight...I’m worried about my job.”

- 47 y/o married female accountant reporting
  - Profound sadness
  - Loss of enjoyment
  - Increasing inability to sleep
  - Loss of appetite
  - Profound sense that she is letting her family down: “My daughter really needs my help with her 3 year old, and I just can’t do it. I get irritated at both of them about things I used to enjoy...”
Mrs. Carroll: “It’s back and I can’t think straight...I’m worried about my job.”

- Problem list includes
  - Diabetes, poorly controlled (HgA1c = 11.0)
  - Hypertension, poorly controlled (145/105)
  - BMI 32
  - Hx hysterectomy
  - Major depression 5 years ago, refused treatment

QIDS-SR Positive Responses (sample items)

QIDS Score = 21 (Severe MDE)

- I take at least 30 minutes to fall asleep, more than half the time
- I awaken at least one hour before I need to, and can’t go back to sleep
- I sleep no longer than 7-8 hours/night, without napping during the day
- I eat somewhat less often or lesser amounts of food than usual

- Most of the time, I struggle to focus my attention or to make decisions
- I largely believe that I cause problems for others
- I feel that life is empty or wonder if it’s worth living
- I find that my thinking is slowed down or my voice sounds dull or flat

Further Evaluation of Major Depressive Episode

Rule Out Other Causes
- CIDI 3.0 (Bipolar) – Negative responses to initial questions
- No recent major losses
- Not likely due to medication (atenolol, hydrophilic beta blocker, doesn’t pass blood-brain barrier)
- No problem alcohol or substance use

Evaluate Past History, Comorbidities, and Suicidality
- Not currently suicidal
- Comorbidities
  - Sleep impairment
  - No pain
  - Quite anxious, not a problem before current episode
- Prior episode
  - 5 years ago
  - Untreated
  - ~3 months duration
  - Mild

Patient Priorities, Goals, Concerns

Most troublesome symptoms
- Difficulty concentrating
- Lack of enjoyment and irritability with daughter and granddaughter

Functional impairment
- Most worried about inability to concentrate and perform at work as accountant
- Decreased energy and engagement with family
- Has stopped going to church and book group
- Did not do fall garden cleanup
- Not sexually active, long-term relationship issues

Treatment Preference: Willing and interested in taking medication, does not feel she has time, energy or ability to concentrate and engage in therapy

Treatment Initiation: Generic SSRI

- Escitalopram 5 mg
- Increasing to 10 mg in 1 week
  - due to concern about anxiety level
- Sleep hygiene counseling
- Exercise prescribed

Next Contact

- Phone call in 1-3 days by office staff
- 3 questions
  - Did you get prescription filled?
  - Did you take first dose?
  - Any questions for us?

- Takes 3-4 minutes
- Nonadherence particularly a concern with anxious patients
Next Contact: 10 Day Staff Phone Call
- Advanced dose at 6 days
- Minimal improvement (QIDS = 19)
- No reported improvement in sleep, concentration, irritability
- Side effects tolerable
  - Some increase in anxiety
  - Nausea moderate for two days, none now
- Irregular exercise
- Continue 10 mg dose of escitalopram, encouraged to exercise

3 Week Visit With PCP
- QIDS = 18
- Insomnia continues, not sexually active, no change in weight
- No functional improvement, feels minimally better
- Continued concern about work performance, concentration, irritability, lack of engagement with family or friends
- No change in DM or HTN status
- Increase dose to 20 mg of escitalopram

Phone Call at 5 Weeks
- QIDS = 17
- Frustrated with lack of improvement
- Agrees to consult with collaborating psychiatrist
- Switched to duloxetine 60 mg dose

Psychiatric Consultation at 8 Weeks
Evaluation
- Reassess and confirm MDD diagnosis
- Little improvement with medication switch
- Reports some increased agitation with new medication
- Identify early childhood trauma with physically abusive alcoholic father (no sexual trauma)
- Insomnia of considerable concern to patient, feels PCP has not really responded to it

Treatment Adjustment
- Patient refuses CBT but will consider in future
- Medication adjustment?
- Sleep: trazodone or nonbenzodiazepine, doxepin?

Antidepressant Drugs: Unmet Needs Circa 2014
- Limited efficacy (50-60% intention-to-treat response rates; ~ 10-20% advantage vs placebo)
- Intolerable side effects for 10%
- Inconsistent effects on key symptoms (insomnia, anxiety)
- Relatively slow onset of action
- Better alternatives for nonresponders

Addressing Unmet Needs: Do Antidepressant Mechanisms of Action Matter?
- Most antidepressants, including all SSRIs & SNRIs, primarily initiate action by inhibiting serotonin (5-HT) reuptake
- Although some depressed people respond better to switching to a second reuptake inhibitor, results of STAR*D suggested diminishing returns following multiple switches

Unmet Needs: Alternate Targets

- For depressed patients who do not respond to SSRIs & SNRIs, antidepressant action might be improved by:
  - targeting different receptors within the 5-HT or NE systems
  - OR
  - targeting completely different neurotransmitter systems

Mrs. Carroll: Treatment Adjustment Options

- Continue current treatment for another few weeks
- Refer for CBT
- Dose increase (anxiety concern)
- Atypical antipsychotic (not acceptable to patient due to potential side effects and her diabetes)
- Other augmentation
  - Bupropion
  - Thyroid
  - L-methylfolate
  - Modafinil/stimulant
  - Mood stabilizer

Week 11 QIDS-SR Positive Responses

QIDS Score = 12 (Mild-Moderate)

- I take at least 30 minutes to fall asleep, less than half the time
- I have a restless, light sleep with a few brief awakenings each night
- I feel sad less than half the time
- I eat somewhat less often or lesser amounts of food than usual
- Most of the time, I struggle to focus my attention or to make decisions
- I find that my thinking is slowed down or my voice sounds dull or flat
- I am more self-blaming than usual
- I notice that I am less interested in people or activities

Week 14 PCP Reassessment

QIDS = 9

- I take at least 30 minutes to fall asleep, less than half the time
- Most of the time, I struggle to focus my attention or to make decisions
- I find that my thinking is slowed down or my voice sounds dull or flat
- I am more self-blaming than usual

Other Assessment

- Still difficulty concentrating and focusing at accounting job
- 1 pound weight gain in past month
- DM and HTN improved
  - Improved adherence to testing
  - Reports increased medication adherence
  - BP 130/90

Week 11 Psychiatrist Reassessment

- QIDS = 12
- Still concerned about job functioning
- Sleep has improved significantly
  - “I’m not tired during the day like I was, I’m sleeping better”
- Engaging more and more successfully with family
- Started going to church again
- Plans to go to book group next week
- Continue therapy with no adjustment
- Discussed exercise again

Week 14 PCP Reassessment

- Patient requests help with cognitive symptoms
- PCP decides to phone consult psychiatrist
Remission: Goal of Treatment

- Full remission of symptoms
  - No longer meets criteria for major depression
  - Displays minimal or no symptoms
- Return of pre-morbid psychosocial functioning
- No longer meets diagnostic criteria
- Often measured as
  - PHQ-9 of 4 or less or
  - QIDS of 5 or less

Consequences of Not Reaching Remission

**Affects disease course**
- Higher risk of relapse1,3
- More rapid relapse
- Increased rate of recurrence
- Shorter well intervals
- Fewer symptom-free weeks2
- Increased risk of suicide4

**Affects direct & indirect costs**
- Medical, psychiatric, emergency care
- More psychiatric hospitalizations
- More benefits received through welfare or disability insurance1
- Association with work impairment4

3Duley SC, Psychopathology. 1994;110(5-61.

Common Residual Symptoms

**Serotonin-related**
- Anxiety
- Inhibited communication
- Dysfunctional attitude
- High neuroticism
- Social maladjustment
- Insomnia
- Psychotic and somatic anxiety
- Guilt & lowered self-esteem
- Hopelessness
- Impaired work and interests
- Psychosocial disability
- Sexual symptoms
- Anhedonia
- Lack of motivation

**Norepinephrine-related**
- Excessive reactivity to social stress
- Fatigue
- Interpersonal friction
- Irritability

Residual Symptoms Increase Risk of Relapse After Remission

![Graph showing the increase in risk of relapse after remission.](image)

P<0.001

Treatment Resistance

- Up to one-half of “treatment resistant” depressions are improperly dosed or nonadherent
- Treatment resistance may increase with greater chronicity
- Up to 20% of patients with MDD do not remit after 3 aggressive treatment trials
- Depression-targeted psychotherapies may work even if medications have failed

Strategies for Achieving Full Remission

- Selection of Antidepressant
- Longer trials, higher dosages
- Monitoring outcome to optimize Rx
- Switch to another antidepressant
- Augmentation strategies
- Combination antidepressants
- Antidepressants + Psychotherapy

Shelton RC et al. CNS Drugs. 2010;24(2):131-141.

New Treatment Options

- Levomilnacipran
- Vortioxetine
- L-methylfolate

Levomilnacipran

- Enantiomer of milnacipran
- Potent, NE and 5-HT reuptake inhibition
- Preference for NE transporter inhibition (compared to other SNRIs) may lead to greater improvement in symptoms associated with dysfunction of this system including alertness, attention, fatigue, and comorbid pain
- Demonstrates increased serotonin, norepinephrine and dopamine in the prefrontal cortex
- Sustained release form allows once-daily dosing

Translation From Targets to Clinical Effects: A Hypothesis Regarding Effects of Vortioxetine

L-Methylfolate

- L-methylfolate is a cofactor in the production of monoamines serotonin, dopamine, and norepinephrine
- 70% of depressed patients have a genetic variant of the methylenetetrahydrofolate reductase (MTHFR) enzyme
  - Decreases conversion of dietary or synthetic folic acid to L-methylfolate
- L-methylfolate supplementation may improve response to antidepressants among those who do not respond adequately
- L-methylfolate in studies enhances
  - antidepressant response and clinical and social recovery
  - more rapid improvement
  - fewer therapy discontinuations
  - same rate of adverse effects as SSRI or SNRI monotherapy

Mrs. Carroll

- Switched to vortioxetine
  - cognition improves
  - weight stable at 3 and 6 month f/up
- DM and HTN further improved
- Transition to maintenance therapy
- Reeducated about importance of continued treatment at established dose in preventing relapse or recurrence

Concluding Remarks

- Changes underway in primary care and relationships with psychiatry and other specialties
- PCMH/team concept critical to supporting expanded primary care role including with psychiatric conditions
- Collaboration with Psychiatry critical to success
- MDD care integrated with other chronic disease care
- Active management critical
- Residual symptoms, including cognition, are important contributors to functional impairment even with "remission"
- New treatment options with enhanced impact on monoamines may treat residual symptoms while minimizing side effects
Questions

Residual Symptoms in Depression

- More common in more severely ill patients
- Strong predictors of early relapse
- Associated with work impairment and increased risk for suicide