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

Thursday, February 6, 2014
Ft Lauderdale, Florida

Educational Partner:
Session 6: 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. Dr Culpepper has conducted federally funded studies of depression and anxiety disorders, diabetes, otitis media, and school based and community interventions to improve pregnancy outcomes and prevent teen pregnancies. He served as president of the North American Primary Care Research Group (NAPCRG), chaired or served as a member of research grant review committees for five NIH and other federal agencies, and has served on six federal expert panels for consensus committees or evidence based centers. He is a member of the Depression and Bipolar Support Alliance and the Anxiety Disorders Association of America scientific advisory boards. Dr Culpepper serves as the editor of The Primary Care Companion for CNS Disorders and past family medicine editor of UpToDate. He received the NAPCRG-STFM 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.

Bradley N. Gaynes, MD, MPH
Professor of Psychiatry
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University of North Carolina School of Medicine
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Dr Bradley Gaynes is a professor of psychiatry at the University of North Carolina and the associate chair of research training and education. Dr Gaynes works at the crossroads between clinical trials research and mental health services research, focusing his clinical and research efforts on mental health primary care integration and health care delivery in real world nonpsychiatric settings. His primary research interests involve assessing and managing depressive illness in primary care settings, HIV settings, and obstetrical/gynecological settings.
Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Dr Culpepper participates in Advisory Boards for AstraZeneca, Forest Laboratories; H. Lundbeck A/S; Merck & Co., Inc.; Sunovion Pharmaceuticals Inc., Takeda Pharmaceuticals Inc. Dr Culpepper also serves as consultant for My Mood Monitor (M3).

Dr Gaynes has no financial relationships to disclose.

Education Partner Financial Disclosure Statement
The content collaborators at Spire Learning have reported the following:
Kashemi Rorie, PhD, Clinical Director, served as a clinical content planner as the Educational Partner for this activity and has disclosed no relevant financial relationships.

Christine Kocienda, Program Director, served as faculty planner as the Educational Partner for this activity.
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Suggested Reading List
SESSION 6
4–5:15pm

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

SPEAKERS
Larry Culpepper, MD, MPH
Bradley N. Gaynes, MD, MPH

Presenters Disclosure Information

The following relationships exist related to this presentation:

► Larry Culpepper, MD, MPH, has disclosed the following financial relationships: Advisory Board for AstraZeneca, Forest Laboratories, H. Lundbeck A/S, Merck & Co. Sunovion Pharmaceuticals, Taeka Pharmaceuticals; Consultant and Stockholder for My Mood Monitor (M3)
► Bradley N. Gaynes, MD, MPH, has disclosed that he does not have any relevant financial relationships specific to the subject matter of the content of this activity

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.

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

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• 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

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

<table>
<thead>
<tr>
<th>% age 18+ with MDE receiving treatment in the past year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. average</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Private Medicaid</td>
</tr>
<tr>
<td>Private Uninsured</td>
</tr>
<tr>
<td>Medicare**</td>
</tr>
<tr>
<td>Medicare** Uninsured</td>
</tr>
<tr>
<td>Uninsured</td>
</tr>
</tbody>
</table>

*Major depressive episode is defined as a period of at least 2 weeks during which 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

Adjusted for age, sex, race/ethnicity, family composition

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

Optimal vs Suboptimal Care

- PCPs and PCMHs are increasingly responsible for treatment (direct, with team, or through referral) of common psychiatric conditions
- Chronic medical outcomes improved through care management strategies that integrate depression care with care of other disease is one proven strategy

Episodes of Poverty Have Cumulative Risk of Subsequent Major Depression

- Relative Risk of Depression
  - DSM-III-R MDD
    - High Depressive Symptoms
      - Relative Risk
        - 1
        - 1.75
        - 4.02
      - Number of Times Income less than 200% Poverty 1965-1983
        - 0
        - 1
        - 2
        - 3

Implications

- Will take a decade or more to work through all of the system reconfigurations required to optimize care
  - EMR adoption, eg, meaningful use
  - Shift of behavioral health workforce (eg, psychologists/psychiatric social workers) from solo/small cash-based practices to employed positions with teams
PCMH: Integration of Care Strategy

<table>
<thead>
<tr>
<th>Tools &amp; Objectives</th>
<th>Process</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify goals/targets</td>
<td>Collaborate to formulate specific measurable targets (eg, BP, PHQ-9, HbA1c, walk # steps)</td>
<td>Patient, 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 review, formulate treatment adjustment recommendations to PCP</td>
<td>Care-by-case training, accountability for improving outcomes</td>
</tr>
<tr>
<td>Care coordination</td>
<td>Communicate and coordinate (eg, thru 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>Intervention</td>
<td>Usual Care</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>3.37 (2.92-3.89)</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

<table>
<thead>
<tr>
<th>QIDS-SR24 item</th>
<th>n</th>
<th>Symptom at baseline (%)</th>
<th>Persistent baseline symptoms (%)</th>
<th>Symptom at baseline and at remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradyness</td>
<td>233</td>
<td>20.0</td>
<td>19.8</td>
<td>13.1</td>
</tr>
<tr>
<td>Increased weight</td>
<td>233</td>
<td>28.0</td>
<td>20.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Agitation</td>
<td>233</td>
<td>18.9</td>
<td>14.3</td>
<td>9.9</td>
</tr>
<tr>
<td>Fatigue/</td>
<td>233</td>
<td>36.1</td>
<td>15.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Early morning</td>
<td>233</td>
<td>50.0</td>
<td>34.2</td>
<td>25.8</td>
</tr>
<tr>
<td>Appetite</td>
<td>233</td>
<td>26.7</td>
<td>32.0</td>
<td>16.6</td>
</tr>
<tr>
<td>Sleep onset</td>
<td>233</td>
<td>78.4</td>
<td>50.8</td>
<td>32.0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>233</td>
<td>19.5</td>
<td>10.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Guilt</td>
<td>233</td>
<td>65.5</td>
<td>81.9</td>
<td>52.8</td>
</tr>
<tr>
<td>Concentration/decision making</td>
<td>233</td>
<td>53.3</td>
<td>22.0</td>
<td>24.9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>233</td>
<td>92.0</td>
<td>88.9</td>
<td>8.9</td>
</tr>
<tr>
<td>Anxiety</td>
<td>233</td>
<td>92.8</td>
<td>93.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Feeling</td>
<td>233</td>
<td>37.8</td>
<td>37.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Slowed speech</td>
<td>233</td>
<td>76.2</td>
<td>65.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>233</td>
<td>68.0</td>
<td>64.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Suicide risk</td>
<td>233</td>
<td>91.6</td>
<td>2.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Prevalence of Residual Symptoms by Type in MDD


Basic Tools and Resources for Depression Care in the PCMH

**Tools**
- **Screening /case finding & severity measures**
  - QIDS or PHQ-9
  - CDI 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
- PCP/Psychiatry Collaboration
  - Access to Treatment Options
  - Individualized

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

- 47 yo 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…”

- Problem list includes
  - Diabetes, poorly controlled (HgbA1c = 11.0)
  - Hypertension, poorly controlled (145/105)
  - BMI 32
  - Hx hysterectomy
  - Major depression 5 years ago, refused treatment

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**QIDS-SR Positive Responses**

QIDS Score = 21 (Severe MDE)

- I take at least 30 minutes to fall asleep, more than half the time
- I wake up at least once a night, but I go back to sleep easily
- 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
- I have lost 2 pounds or more
- I feel sad more than half the time

- 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 I have interest in only 1 or 2 of my formerly pursued activities
- I get tired more easily than usual
- I find that my thinking is slowed down or my voice sounds dull or flat

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**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

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**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

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**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

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**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?

Neurotransmitters Regulate Different Aspects of Mood, Cognition, and Behavior

Beyond the Cell Surface: Neurotrophic Actions of Antidepressants

Antidepressant Treatments Inhibit 5-HT and/or NE Reuptake or Breakdown

- Decrease in synaptic levels
- Action on postsynaptic targets
- Increase in synaptic density
- \( \text{NMDA} \)
- \( \text{dopaminergic} \)
- \( \text{serotonergic} \)
- \( \text{catecholaminergic} \)
- \( \text{NMDA} \)
- \( \text{dopaminergic} \)
- \( \text{serotonergic} \)
- \( \text{catecholaminergic} \)

\( \text{DAM} \), \( \text{dopaminergic} \); \( \text{SAM} \), \( \text{serotonergic} \); \( \text{CAM} \), \( \text{catecholaminergic} \);
\( \text{NMDA} \), \( \text{N}-\text{methyl-D-aspartic acid} \);
\( \text{ACCh} \), \( \text{acetylcholine} \);
\( \text{PKA} \), \( \text{protein kinase A} \);
\( \text{CREB} \), \( \text{cAMP response element-binding protein} \);
\( \text{BDNF} \), \( \text{brain-derived neurotrophic factor} \).

Antidepressant Drugs: Unmet Needs Circa 2014

- Limited efficacy (50-60% ITT response rates; ~10-20% advantage vs PBO)
- 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 Mechanism(s) 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

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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 = 10 (Mild)

- 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 11 Psychiatric Reassessment

- QIDS = 10
- Still concerned about job functioning
- Feels sleep has improved significantly
  - “I’m not tired during the day like I was, I’m sleeping better”
- Feels she is engaging more and more successfully with family
- Has 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

QIDS = 5

- 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

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

Strategies for Achieving Remission

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

Treatment Resistance

- Up to one-half of "treatment resistant" depressions are improperly dosed or nonadherent
- In non-treatment resistant MDD, only 30-40% remit with the first treatment
- 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
- Treatment resistance may increase with greater chronicity

Consequences of Not Reaching Remission

- Affects disease course
  - Higher risk of relapse
  - More rapid relapse
  - Increased rate of recurrence
  - Shorter course of well intervals
  - Fewer symptom-free weeks
  - Increased risk of suicide

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

1Kupfer DJ et al. Arch Gen Psychiatry. 2003;60(10):999-1010.
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

Proportion of Patients With and Without Residual Symptoms: Relapse After Remission

New Treatment Options

- Levomilnacipram
- Vortioxetine
- L-methylfolate

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

- 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

Levomilnacipram

- Enantiomer of milnacipram, has potent, selective and specific NE and 5-HT reuptake inhibition
- Preference for the NE transporter inhibition (compared to SNRIs) may convey greater benefits in improving symptoms associated with dysfunction of this system including alertness, attention, fatigue, and comorbid pain
  - Also demonstrates increased serotonin, norepinephrine and dopamine in the prefrontal cortex
- Sustained release form allows once-daily dosing
L-Methylfolate

- 70% of depressed patients have a genetic variant of the methylenetetrahydrofolate reductase (MTHFR) enzyme that decreases conversion of dietary or synthetic folic acid to L-methylfolate
- L-methylfolate is a cofactor in the production of monoamines serotonin, dopamine, and norepinephrine
- 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
- MDD care integrated with other chronic disease care
- Collaboration with Psychiatry critical to success

- Active management critical
- Residual symptoms, including cognition, are important contributors to continued functional impairment even with “remission”
- New treatment options with enhanced impact on monoamines may help respond to residual symptoms while minimizing side effects

Question & Answer