Carefully Listening for Patient Cues: Designing Collective and Collaborative Care in Major Depressive Disorder

Vladimir Maletic, MD, MS
Clinical Professor of Psychiatry and Behavioral Science
University of South Carolina School of Medicine
Greenville, South Carolina

This activity is supported by an educational grant from Otsuka America Pharmaceutical, Inc.
Faculty Disclosure

Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – The off-label use of adjunctive lithium, triiodothyronine, S-adenosylmethionine, creatine, omega-3, scopolamine, and agomelatine for the treatment of major depressive disorder/treatment-resistant depression will be discussed.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.
Learning Objectives

• Discuss the clinical consequences associated with major depressive disorder (MDD) and the therapeutic challenges associated with traditional antidepressants
• Describe the difference between partial responders, non-responders, and treatment-resistant depression (TRD)
• Thoroughly appraise the current and evolving therapies for the treatment of patients with MDD based on their mechanism of action, clinical strengths and opportunities that they offer as optimal pharmacologic options for individualized patient treatment
• Develop strategies for addressing and overcoming inadequate response to antidepressants and TRD with agents approved as adjuvant therapy to traditional antidepressants while mitigating adverse effects
Major Depressive Disorder: *Introduction*

- MDD appears to be a clinically and biologically heterogeneous condition associated with emotional, physical, and cognitive symptoms
- Current descriptive nomenclature does not allow us to deduce specific treatment strategies that could be more effective for MDD subtypes
- Mood disorders are associated with changes in endocrine, immune, and autonomic function
- Remission and functional recovery are the optimal outcomes in the treatment of MDD

MDD = major depressive disorder.

Shortcomings of Current Major Depressive Disorder Treatments
Response to treatment occurs when there is a clinically meaningful degree of symptom reduction, typically defined as ≥ 50% reduction in pretreatment symptom severity. Partial Response ≥ 25% improvement from baseline. Non-Response < 25% improvement from baseline. Remission occurs when the symptoms of the MDE are absent or close to it. Recovery may not be clinically distinguishable from remission but is implied after an extended asymptomatic period (≥ 2 months). A relapse is defined as the return of the initial MDE following remission, while recurrence is defined as the development of a new MDE following the onset of recovery.

MDE = major depressive episode.
MDD is one of the most common mental health disorders in the United States, with a lifetime prevalence* of 16.2%.

...which is equivalent to 32–35 million US adults.

In fact, MDD accounted for more than $100 billion of lost workplace productivity in the United States in 2010.

Disability-Adjusted Life Years (DALYs)

STAR*D: Unresolved Symptoms following Antidepressant Treatment

Percent  

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27

Depressive Symptoms (QIDS-SR score) after up to 12 Weeks of Antidepressant Treatment

Remission ~33%
Mild Symptoms ~28%
Moderate Symptoms ~23%
Severe Symptoms ~12%
Very Severe Symptoms ~4%

39%

N=2876.
Remission Rates Decreased While Discontinuation Due to Side Effects Increased with Each Additional Change in Therapy

SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; T₃ = triiodothyronine.


Rates of remission and discontinuation due to intolerable side effects at each step exit in the STAR*D trial

Each step of therapy included options to switch or augment.

Options included various SSRIs, SNRIs, lithium, T₃, and cognitive therapy.

What Does Failure to Remit Look Like in Those Who Respond to an Antidepressant?

Proportion of responders who had symptoms at baseline that persisted at exit*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midnocturnal Insomnia</td>
<td>81.6</td>
</tr>
<tr>
<td>Sad Mood</td>
<td>70.8</td>
</tr>
<tr>
<td>Concentration/Decision Making</td>
<td>70.6</td>
</tr>
<tr>
<td>Energy</td>
<td>64.6</td>
</tr>
<tr>
<td>Restlessness</td>
<td>63</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>60.4</td>
</tr>
<tr>
<td>Sleep Onset Insomnia</td>
<td>57.5</td>
</tr>
<tr>
<td>General Interest</td>
<td>55</td>
</tr>
<tr>
<td>Early-morning Insomnia</td>
<td>49</td>
</tr>
<tr>
<td>Negative Self-view</td>
<td>38.9</td>
</tr>
<tr>
<td>Slowed Down</td>
<td>35.6</td>
</tr>
<tr>
<td>Increased Weight</td>
<td>35.5</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>31</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>27.8</td>
</tr>
<tr>
<td>Decreased Weight</td>
<td>25.1</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>17.1</td>
</tr>
</tbody>
</table>

*Percentages are reported as the remaining percent of those with each symptom at baseline that continued to have the symptom at exit. Response was defined as ≥ 50% reduction in QIDS-SR16. Presence of symptoms was indicated by a QIDS-SR16 domain score ≥ 1.

Remitters, Responders, and Non-Responders Have Very Different Functional Outcomes

<table>
<thead>
<tr>
<th>Variablea</th>
<th>Remitter (N=451)</th>
<th>Partial Responder (N=317)</th>
<th>Non-Responder (N=337)</th>
<th>95% CI for Difference in Means PR vs R</th>
<th>PR vs NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS-A</td>
<td>5.99 (3.26)</td>
<td>10.31 (3.24)</td>
<td>12.86 (3.74)</td>
<td>-3.73, 4.91</td>
<td>-3.18, -1.92</td>
</tr>
<tr>
<td>SF36 items</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health summary measure (SF36 physical component score)</td>
<td>51.81 (7.26)</td>
<td>46.50 (8.76)</td>
<td>43.21 (9.41)</td>
<td>-6.77, -3.87</td>
<td>1.74, 4.83</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>52.34 (6.40)</td>
<td>47.02 (9.38)</td>
<td>42.41 (10.53)</td>
<td>-6.82, -3.82</td>
<td>3.01, 6.21</td>
</tr>
<tr>
<td>Role physical</td>
<td>47.34 (7.89)</td>
<td>38.44 (8.78)</td>
<td>34.31 (9.51)</td>
<td>-10.39, -7.41</td>
<td>2.53, 5.72</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>51.98 (9.67)</td>
<td>44.34 (9.90)</td>
<td>39.46 (10.57)</td>
<td>-9.37, -5.92</td>
<td>3.04, 6.72</td>
</tr>
<tr>
<td>General health</td>
<td>45.82 (8.57)</td>
<td>37.03 (6.98)</td>
<td>32.90 (7.64)</td>
<td>-10.15, -7.44</td>
<td>2.68, 5.56</td>
</tr>
<tr>
<td>Mental health summary measure (SF36 mental component score)</td>
<td>43.94 (8.67)</td>
<td>30.63 (7.40)</td>
<td>23.70 (8.45)</td>
<td>-14.73, -11.88</td>
<td>5.41, 8.45</td>
</tr>
<tr>
<td>Vitality</td>
<td>51.08 (7.61)</td>
<td>40.04 (6.76)</td>
<td>33.71 (7.23)</td>
<td>-12.29, -9.79</td>
<td>5.00, 7.67</td>
</tr>
<tr>
<td>Social functioning</td>
<td>45.24 (7.93)</td>
<td>34.52 (7.34)</td>
<td>29.06 (8.46)</td>
<td>-12.09, -9.36</td>
<td>4.00, 6.91</td>
</tr>
<tr>
<td>Role emotional</td>
<td>43.64 (9.06)</td>
<td>32.31 (8.15)</td>
<td>26.34 (9.78)</td>
<td>-12.88, -9.77</td>
<td>4.31, 7.63</td>
</tr>
<tr>
<td>Mental health</td>
<td>45.95 (8.04)</td>
<td>33.48 (7.39)</td>
<td>26.09 (8.26)</td>
<td>-13.84, -11.11</td>
<td>5.93, 8.84</td>
</tr>
<tr>
<td>SSI-item 7</td>
<td>2.00 (0.93)</td>
<td>2.98 (1.04)</td>
<td>3.56 (1.11)</td>
<td>0.79, 1.17</td>
<td>-0.79, -0.37</td>
</tr>
<tr>
<td>No. HCP visits between baseline and 3 months</td>
<td>5.25 (4.69)</td>
<td>6.18 (6.18)</td>
<td>6.41 (6.25)</td>
<td>-0.06, 1.93</td>
<td>-1.30, 0.84</td>
</tr>
<tr>
<td>Occupational outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paid work, n (%)</td>
<td>274 (60.08)</td>
<td>159 (50.2)</td>
<td>139 (41.2)</td>
<td>-0.18, -0.04</td>
<td>0.01, 0.16</td>
</tr>
<tr>
<td>% with paid work at baseline who had paid work at 3 months</td>
<td>259 (95.2)</td>
<td>146 (96.1)</td>
<td>131 (92.3)</td>
<td>-0.04, 0.05</td>
<td>-0.02, 0.09</td>
</tr>
<tr>
<td>% who missed paid work between baseline and 3 months, of those in paid work at baseline</td>
<td>52 (19.0)</td>
<td>67 (42.1)</td>
<td>66 (47.5)</td>
<td>0.14, 0.32</td>
<td>-0.17, 0.06</td>
</tr>
</tbody>
</table>

aMean (SD) unless otherwise stated.

HADS-A = Hospital Anxiety and Depression Scale, Anxiety Subscale; HCP = health care professional; NR = non-responders; PR = partial responders; R = remitters; SF-36 = 36-item Short Form Health Survey; SSI = Somatic Symptom Inventory.

## Tools to Improve Screening, Diagnosis, and Monitoring of Major Depressive Disorder

<table>
<thead>
<tr>
<th>Screening Tools</th>
<th>Diagnostic Tools</th>
<th>Monitoring Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9, PHQ-2</td>
<td>PHQ-9</td>
<td>PHQ-9</td>
</tr>
<tr>
<td>QIDS/SR</td>
<td>MINI</td>
<td>QIDS/SR</td>
</tr>
<tr>
<td>BDI-II</td>
<td>MDQ</td>
<td>BDI-II</td>
</tr>
<tr>
<td>CES-D</td>
<td>CIDI</td>
<td>CUDOS</td>
</tr>
<tr>
<td>HADS</td>
<td>HADS</td>
<td>HADS</td>
</tr>
<tr>
<td>Zung SDS</td>
<td>Zung SDS</td>
<td>IDS</td>
</tr>
<tr>
<td>MDQ</td>
<td>SCID-5-RV</td>
<td>MADRS</td>
</tr>
<tr>
<td>CIDI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies Depression Scale; CIDI = WHO Composite International Diagnostic Interview; CUDOS = Clinically Useful Depression Outcome Scale; HADS = Hospital Anxiety and Depression Scale; IDS = Inventory of Depressive Symptomatology; MADRS = Montgomery–Åsberg Depression Rating Scale; MDQ = Mood Disorder Questionnaire; MINI = Mini-International Neuropsychiatric Interview; PHQ-2 = Patient Health Questionnaire 2-item; PHQ-9 = Patient Health Questionnaire 9-item; QIDS = Quick Inventory of Depressive Symptomatology (clinician and self-report); SCID-5-RV = Structured Clinical Interview for DSM-5 Disorders-Revised; Zung SDS = Zung Self-Rating Depression Scale.
The PHQ-9 Can Be Used to Monitor Depressive Symptoms

<table>
<thead>
<tr>
<th>PHQ-9 Score</th>
<th>Mean Disability Days</th>
<th>Symptom-Related Difficulty (%)</th>
<th>Mean Physician Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4</td>
<td>2.4</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>5–9</td>
<td>6.7</td>
<td>10.2</td>
<td>1.8</td>
</tr>
<tr>
<td>10–14</td>
<td>11.4</td>
<td>24.4</td>
<td>2.0</td>
</tr>
<tr>
<td>15–19</td>
<td>16.6</td>
<td>45.1</td>
<td>2.4</td>
</tr>
<tr>
<td>20–27</td>
<td>28.1</td>
<td>57.1</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Disability days refers to number of days in past 3 months that their symptoms interfered with their usual activities.

<table>
<thead>
<tr>
<th>Initial Episode in Teenage Years</th>
<th>Greater Risk of Hospitalization</th>
<th>Presence of Psychotic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset and offset of depressive episodes</td>
<td>Greater risk of suicide attempts</td>
<td>Family history of bipolar disorders</td>
</tr>
<tr>
<td>Greater episode frequency</td>
<td>Greater risk of comorbid substance use disorders, anxiety disorders, and eating disorders</td>
<td>More mixed symptoms</td>
</tr>
<tr>
<td>Antidepressant misadventures (poor response, syndromal shifts, induction of mood lability or rapid cycling)</td>
<td>Greater likelihood of seasonal pattern of depressive episodes</td>
<td>Higher rates of substance use</td>
</tr>
</tbody>
</table>

Practical Take-Away

- Even patients who are responding to antidepressants continue to suffer from symptoms that interfere with functioning
Factors Associated with Reduced Response and Increased Relapse in Major Depressive Disorder Treatments
Lucy

• 32-year-old married female
• She has been referred by her primary care physician for treatment of depression, which started 6 months ago; treated with an appropriate dose of an SSRI ever since
• Lucy reports feeling sad and tired most of the days. She is waking up often during the night
• Anhedonia; loss of interest for work and hobbies. Some social withdrawal
• Lucy has to “make” herself go to work
• She and her husband have had marital problems in the past. Currently, they feel estranged and are considering separation
• Patient is concerned about the weight that she has recently gained
• Initial anxiety has improved, but she still reports some irritability
Factors Associated with Treatment Resistance in Major Depressive Disorder

- Recurrent episodes vs single episode: $P=0.009$, Odds Ratio 1.5
- Melancholic features: $P=0.018$, Odds Ratio 1.5
- No. of hospitalizations > 1: $P=0.003$, Odds Ratio 1.6
- Nonresponse to first AD treatment lifetime: $P=0.019$, Odds Ratio 1.6
- Severe intensity vs moderate intensity: $P=0.001$, Odds Ratio 1.7
- Personality disorder (DSM-IV criteria): $P=0.049$, Odds Ratio 1.7
- Age at onset before 18 y: $P=0.009$, Odds Ratio 2
- Social phobia: $P=0.008$, Odds Ratio 2.1
- Current suicidal risk: $P<0.001$, Odds Ratio 2.2
- Comorbid anxiety disorder: $P<0.001$, Odds Ratio 2.6
- Comorbid panic disorder: $P<0.001$, Odds Ratio 3.2

N=702.
AD = antidepressant.
Adverse Effects and Adherence in Major Depressive Disorder

Survey of N=350 people with mild to severe depression.

Frequency of Antidepressant Adverse Effects Reported as “Extremely Difficult to Live With”

Nonadherence (22%)
- Trouble remembering to take medication (43%)
- Gained a lot of weight (27%)
- Couldn’t have an orgasm (20%)
- Lost my sex drive (20%)
Dyadic Discord is Associated with Lack of Remission in Major Depressive Disorder

• Comparing exit rates of remission for patients with and without dyadic discord at baseline
• Remission was defined as an IDS-SR30 score of ≤ 14 at study exit
• “Dyadic discord” if their MAS scores were above 2.36. This score, is 1.28 SD above the mean of a normative sample

CBASP = cognitive behavioral analysis system of psychotherapy; IDS-SR30 = Inventory of Depressive Symptomatology, Self-Report; MAS = Marital Adjustment Scale.
Childhood Maltreatment Predicts Poor Response to Treatment

A meta-analysis of 10 studies (3098 individuals) retrospectively reported childhood maltreatment predicted poorer response to psychotherapy, antidepressants, and combined therapy.


History of maltreatment was associated with an elevated risk of developing recurrent and persistent depressive episodes (odds ratio=2.27, 95% confidence interval [CI]=1.80–2.87).
BMI Impacts Antidepressant Response

- Response to antidepressant treatment according to weight status
- Mean HAM-D rating scores and SEMs for 5 weeks after hospitalization

BMI = body mass index; HAM-D = Hamilton Rating Scale for Depression.
Increased Inflammation May Contribute to Treatment Resistance

Clinical phenotypes most strongly associated with CRP were not feeling calm, psychomotor retardation, middle insomnia, not being able to work, BMI, state anxiety, and feeling unloved as a child or wishing for a different childhood.

F=3.57, P=.015; F=2.67, P=.048. *P<.05, **P<.01 significant pairwise difference.

CRP = C-reactive protein.
Practical Take-Away

• Troubled primary relationships, history of early life adversity, medical conditions/inflammation, chronic stress, significant delay of treatment, and substance use may all diminish response to antidepressant treatment.
Common Augmentation, Combination, and Switch Strategies
Early Symptom Improvement in Major Depressive Disorder Treatment Non-Responders

RE Model, MADRS Change from Baseline at 2 Weeks

19 RCTs investigating 13 pharmacologic interventions and 12 RCTs investigating ECT and rTMS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Favors Intervention</th>
<th>Favors Placebo/Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>-14.0 (-19.9, -8.0)</td>
<td></td>
</tr>
<tr>
<td>ECT</td>
<td>-4.6 (-11.2, 2.1)</td>
<td></td>
</tr>
<tr>
<td>rTMS (80%-120%)</td>
<td>-4.2 (-6.4, -1.8)</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>-1.0 (-12.2, 10.3)</td>
<td></td>
</tr>
<tr>
<td>OFC 1/5</td>
<td>-1.5 (-12.1, 9.4)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>-1.5 (-11.7, 8.8)</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>-3.5 (-13.7, 6.8)</td>
<td></td>
</tr>
<tr>
<td>OFC</td>
<td>-5.6 (-15.7, 4.7)</td>
<td></td>
</tr>
<tr>
<td>Risperidone (aug)</td>
<td>-10.3 (-19.3, -1.2)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole (aug)</td>
<td>-3.0 (-6.5, 0.4)</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (mono)</td>
<td>-1.3 (-9.9, 7.4)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine 300 mg (mono)</td>
<td>-2.9 (-8.9, 3.1)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine 150 mg (aug)</td>
<td>-2.4 (-8.4, 3.6)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine 800 mg (aug)</td>
<td>-6.7 (-23.6, 10.1)</td>
<td></td>
</tr>
<tr>
<td>Lithium (aug)</td>
<td>-2.0 (-14.0, 10.1)</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine (aug)</td>
<td>-0.8 (-10.0, 8.4)</td>
<td></td>
</tr>
</tbody>
</table>

aug = augmentation; ECT = electroconvulsive therapy; RE = random effects; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; mono = monotherapy; OFC = olanzapine/fluoxetine combination.

## Efficacy of Interventions in Major Depressive Disorder Treatment Non-Responders

### Response Rate Compared to Placebo at 6 Weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Favors Placebo/Sham</th>
<th>Favors Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTMS (80%–120%)</td>
<td>8.01 (1.16, 56.98)</td>
<td></td>
</tr>
<tr>
<td>T₃</td>
<td>0.08 (0.00, 3.96)</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>0.09 (0.00, 4.56)</td>
<td></td>
</tr>
<tr>
<td>Buspirone</td>
<td>0.07 (0.00, 3.83)</td>
<td></td>
</tr>
<tr>
<td>Sodium Valproate</td>
<td>0.09 (0.00, 4.63)</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.05 (0.00, 2.48)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>0.11 (0.00, 5.67)</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0.08 (0.00, 3.94)</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>2.17 (0.19, 24.98)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole (aug)</td>
<td>2.09 (0.51, 8.41)</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (mono)</td>
<td>0.10 (0.00, 2.22)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine 300 mg (mono)</td>
<td>0.87 (0.04, 12.49)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine 300 mg (aug)</td>
<td>1.42 (0.16, 9.59)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine 150 mg (aug)</td>
<td>1.36 (0.13, 13.32)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine 800 mg (aug)</td>
<td>21.65 (0.34, 2312.02)</td>
<td></td>
</tr>
<tr>
<td>Lithium (aug)</td>
<td>1.01 (0.09, 7.70)</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine (aug)</td>
<td>0.67 (0.04, 11.42)</td>
<td></td>
</tr>
</tbody>
</table>
Switching to a New Antidepressant after Non-Response to Initial Treatment

### Standardized Mean Differences

<table>
<thead>
<tr>
<th>Study / First Author</th>
<th>Standardized Mean Difference</th>
<th>Standard Error</th>
<th>Variance</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Z Value</th>
<th>P Value</th>
<th>Sample Size (n)</th>
<th>Standardized Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferreri 2001</td>
<td>0.245</td>
<td>0.239</td>
<td>0.057</td>
<td>-0.223</td>
<td>0.713</td>
<td>1.025</td>
<td>.305</td>
<td>33</td>
<td>0.223 (0.057 - 0.383) (1.025)</td>
</tr>
<tr>
<td>Shelton 2005</td>
<td>0.127</td>
<td>0.148</td>
<td>0.022</td>
<td>-0.162</td>
<td>0.416</td>
<td>0.862</td>
<td>.389</td>
<td>142</td>
<td>0.162 (0.022 - 0.302) (0.862)</td>
</tr>
<tr>
<td>Corya 2006</td>
<td>-0.229</td>
<td>0.184</td>
<td>0.034</td>
<td>-0.589</td>
<td>0.132</td>
<td>-1.244</td>
<td>.213</td>
<td>60</td>
<td>-0.589 (0.034 - 0.132) (-1.244)</td>
</tr>
<tr>
<td>Souery 2011</td>
<td>-0.948</td>
<td>0.289</td>
<td>0.083</td>
<td>-1.513</td>
<td>-0.382</td>
<td>-3.285</td>
<td>.001</td>
<td>20</td>
<td>-1.513 (0.083 - 0.382) (-3.285)</td>
</tr>
<tr>
<td>Combined estimate</td>
<td>-0.165</td>
<td>0.219</td>
<td>0.048</td>
<td>-0.594</td>
<td>0.264</td>
<td>-0.756</td>
<td>.450</td>
<td></td>
<td>-0.594 (0.048 - 0.264) (-0.756)</td>
</tr>
</tbody>
</table>

### Remission

<table>
<thead>
<tr>
<th>Study / First Author</th>
<th>Odds Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Z Value</th>
<th>P Value</th>
<th>Remission (n) / Total (n)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferreri 2001</td>
<td>2.531</td>
<td>0.856</td>
<td>7.484</td>
<td>1.678</td>
<td>.093</td>
<td>12 / 33</td>
<td>0.856 (2.531 - 7.484) (1.678)</td>
</tr>
<tr>
<td>Shelton 2005</td>
<td>0.721</td>
<td>0.328</td>
<td>1.586</td>
<td>-0.813</td>
<td>.416</td>
<td>19 / 142</td>
<td>0.328 (0.721 - 1.586) (-0.813)</td>
</tr>
<tr>
<td>Corya 2006</td>
<td>0.708</td>
<td>0.283</td>
<td>1.770</td>
<td>-0.739</td>
<td>.460</td>
<td>10 / 60</td>
<td>0.283 (0.708 - 1.770) (-0.739)</td>
</tr>
<tr>
<td>Souery 2011</td>
<td>0.126</td>
<td>0.007</td>
<td>2.351</td>
<td>-1.388</td>
<td>.165</td>
<td>0 / 20</td>
<td>0.007 (0.126 - 2.351) (-1.388)</td>
</tr>
<tr>
<td>Combined estimate</td>
<td>0.899</td>
<td>0.410</td>
<td>1.968</td>
<td>-0.267</td>
<td>.789</td>
<td></td>
<td>0.410 (0.899 - 1.968) (-0.267)</td>
</tr>
</tbody>
</table>

Nonresponse (< 30% improvement) of every participant to a first treatment period of at least 2 weeks at standard or higher doses.
Antidepressant Augmentation vs Switching after Suboptimal SSRI Response (non-remission)

RR = risk ratio.
Switching Within vs Across Class vs Continuing Original Antidepressant

**STAR*D Remission after Switching to 2nd Antidepressant**

- Bupropion SR (n=239)
- Sertraline (n=238)
- Venlafaxine XR (n=250)

**GSRD Switching by Class and Compared with Continuation**

- Same AD Class
- Different AD Class

**HAM-D Total Score**

- Switched
- Non-switched

*P<.001.

Evidence Supporting Augmentation of Antidepressants with Psychotherapy

*P<.001.
CBT = cognitive-behavioral therapy.
Rumination-Focused CBT for Residual Symptoms of Major Depressive Disorder

CBT = 16 sessions of CBT during 20 weeks; CM = Clinical Management; RFCBT = 12 sessions Rumination-Focused CBT; TAU = treatment as usual. CBT (ES) = 0.3; RFCBT (ES) = 0.94–1.1

All patients had initially HAM-D-17 ≥ 8 following at least 8 weeks of antidepressant treatment.

Other Antidepressant Augmentation Strategies

Lithium vs T₃

These agents are not FDA-approved for the treatment of TRD. L-MTHF (Deplin®) is an FDA-approved medicinal food for antidepressant augmentation.

AD = antidepressant; HAM-D = Hamilton Rating Scale for Depression; L-MTHF = L-methylfolate; SAMe = S-adenosylmethionine.

Lithium Augmentation of Antidepressant Treatment

In 2 separate meta-analyses of studies examining the effect of lithium augmentation in patients with depressive disorders, lithium had a positive effect vs placebo.

<table>
<thead>
<tr>
<th>Study</th>
<th>Lithium, N/N</th>
<th>Control, N/N</th>
<th>Fixed Effects OR and 95% CI</th>
<th>Fixed Effects OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heninger et al, 1983</td>
<td>5/8</td>
<td>0/7</td>
<td>23.57 (1.00 to 556.08)</td>
<td>23.57 (1.00 to 556.08)</td>
</tr>
<tr>
<td>Kantor et al, 1986</td>
<td>1/4</td>
<td>0/3</td>
<td>3.00 (0.09 to 102.05)</td>
<td>3.00 (0.09 to 102.05)</td>
</tr>
<tr>
<td>Zusky et al, 1988</td>
<td>3/8</td>
<td>2/8</td>
<td>1.80 (0.21 to 15.41)</td>
<td>1.80 (0.21 to 15.41)</td>
</tr>
<tr>
<td>Schöpf et al, 1989</td>
<td>7/14</td>
<td>0/13</td>
<td>27.00 (1.35 to 541.57)</td>
<td>27.00 (1.35 to 541.57)</td>
</tr>
<tr>
<td>Browne et al, 1990</td>
<td>3/7</td>
<td>2/10</td>
<td>3.00 (0.35 to 25.87)</td>
<td>3.00 (0.35 to 25.87)</td>
</tr>
<tr>
<td>Stein and Bernadt, 1993</td>
<td>2/16</td>
<td>4/18</td>
<td>0.50 (0.08 to 3.19)</td>
<td>0.50 (0.08 to 3.19)</td>
</tr>
<tr>
<td>Joffe et, 1993</td>
<td>9/17</td>
<td>3/16</td>
<td>4.88 (1.01 to 23.57)</td>
<td>4.88 (1.01 to 23.57)</td>
</tr>
<tr>
<td>Katona et al, 1995</td>
<td>15/29</td>
<td>8/32</td>
<td>3.21 (1.09 to 9.48)</td>
<td>3.21 (1.09 to 9.48)</td>
</tr>
<tr>
<td>Bauman et al, 1996</td>
<td>6/10</td>
<td>2/14</td>
<td>9.00 (1.27 to 63.89)</td>
<td>9.00 (1.27 to 63.89)</td>
</tr>
<tr>
<td>Nierenberg et al, 2003</td>
<td>2/18</td>
<td>3/17</td>
<td>0.58 (0.08 to 4.01)</td>
<td>0.58 (0.08 to 4.01)</td>
</tr>
<tr>
<td>Total</td>
<td>53/131</td>
<td>24/138</td>
<td>3.11 (1.80 to 5.37)</td>
<td>3.11 (1.80 to 5.37)</td>
</tr>
</tbody>
</table>

Test for Heterogeneity: χ² = 11.90, df = 9, P=0.22, I² = 24.4%

Test for Overall Effect: Z = 4.06, P<.0001
Response to Adjunct L-methylfolate in Patients with Major Depressive Disorder with Previous Inadequate SSRI Response

Adults with DSM-IV MDD and an inadequate response to an SSRI were eligible. N=69 participants were randomized to an SSRI plus placebo vs an SSRI plus L-methylfolate calcium (15 mg/day). Pooled Treatment Effect (change with placebo minus change with L-methylfolate calcium) on the HAM-D-17 for the Total Population.

These agents are not FDA-approved for the treatment of MDD.

Are 2 Antidepressants Better Than 1?

YES!

HAM-D Scores

Baseline 4 7 10 14 21 28 35 42

Day of Treatment

Fluoxetine (n=28)
Fluoxetine + Mirtazapine (n=25)
Venlafaxine + Mirtazapine (n=26)
Bupropion + Mirtazapine (n=26)

HAM-D = Hamilton Rating Scale for Depression.
Are 2 Antidepressants Better Than 1? Or NO!

- **Monotherapy: Escitalopram + Placebo (N=224)**
  - Remission
  - Response

- **Sustained-Release Bupropion + Escitalopram (N=221)**
  - Remission
  - Response

- **Extended-Release Venlafaxine + Mirtazapine (N=220)**
  - Remission
  - Response

Lucy

- Lucy has had 3 previous depressive episodes, including an episode of “baby blues” which started late in her pregnancy.
- Early episodes responded to a combination of SSRIs and psychotherapy. Previous treatments tended to be cut short by emergence of sexual side effects and weight gain.
- She is currently ruminating about her weight gain and the risk of losing her job. Lucy fears that unless she can “get it together” her husband may eventually divorce her.
- BMI = 29
- She has been drinking a “couple of glasses of wine” nightly with her meal.
- PHQ-9 = 21; MDQ = negative, no family history of bipolar disorder.

MDQ = Mood Disorder Questionnaire; PHQ-9 = 9-item Patient Health Questionnaire.
Use of Second-Generation Antipsychotics to Augment Antidepressants: Response Rates

A 2009 meta-analysis of 16 trials (3480 patients) examining the effect of augmenting antidepressants with an SGA (left panel), found that SGAs were significantly more effective than placebo (response: OR=1.69, 95% CI=1.46–1.95, \( P<.00001 \); remission: OR=2.00, 95% CI=1.69–2.37, \( P<.00001 \)). No differences were found between SGAs. SGAs had higher rates of discontinuation due to adverse events than placebo.

A 2012 Cochrane meta-analytic review included 28 RCTs (8487 patients) of the impact of 5 SGAs as augmenting agents for antidepressants. The following agents all outperformed placebo: aripiprazole, olanzapine, quetiapine, and risperidone. Each of these agents had higher side effect/adverse event burden than placebo.

A large naturalistic study found aripiprazole augmentation associated with better health-related quality of life when compared to augmentation with other SGAs.

---

### MDD Treatment Augmentation: Key Studies of Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comparator</th>
<th>MDD Population</th>
<th>N</th>
<th>Mean Change in MADRS After 6 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole + antidepressant</td>
<td>Placebo</td>
<td>Incomplete response</td>
<td>184</td>
<td>-8.80</td>
</tr>
<tr>
<td>Olanzapine/fluoxetine</td>
<td>Fluoxetine</td>
<td>Treatment resistant</td>
<td>462</td>
<td>-12.28</td>
</tr>
<tr>
<td>Olanzapine/fluoxetine</td>
<td>Olanzapine</td>
<td>Treatment resistant</td>
<td>462</td>
<td>-12.28</td>
</tr>
<tr>
<td>Quetiapine XR + antidepressant</td>
<td>Placebo</td>
<td>Inadequate response</td>
<td>148*</td>
<td>-14.70*</td>
</tr>
<tr>
<td>Brexpiprazole + antidepressant</td>
<td>Placebo</td>
<td>Inadequate response</td>
<td>175</td>
<td>-8.36</td>
</tr>
</tbody>
</table>

All are superior to placebo, but none has been shown to be superior to others

*300 mg/day.


Treatment resistance is defined as failure of 2 adequate antidepressant trials.
Impact of Antipsychotic Side Effects on Treatment Adherence

Survey of N=876 community-dwelling people with schizophrenia.

*ORs based on multivariable logistic regression with adherence as dependent variable. Side effect was reported as present and “somewhat”, “very”, or “extremely bothersome”.

Options for Treatment-Resistant Major Depressive Disorder
Esketamine Nasal Spray + Oral Antidepressant Significantly Delayed Relapse in Treatment-Resistant MDD

**Patients Who Were Stable Remitters**

- ESK NS + Oral AD: 26.7%
- Oral AD + PBO NS: 45.3%

**Relapse Event:**
- ESK NS + Oral AD: 26.7%
- Oral AD + PBO NS: 45.3%

**Median Time to Relapse:**
- ESK NS + Oral AD: Not Estimable
- Oral AD + PBO NS: 273 days

**Patients Who Were Stable Responders**

- ESK NS + Oral AD: 25.8%
- Oral AD + PBO NS: 57.6%

**Relapse Event:**
- ESK NS + Oral AD: 25.8%
- Oral AD + PBO NS: 57.6%

**Median Time to Relapse:**
- ESK NS + Oral AD: 635 days
- Oral AD + PBO NS: 88 days

AD = antidepressants; ESK = esketamine; NS = nasal spray; PBO = placebo.
Daly EJ, et al. Poster presented at the European College of Neuropsychopharmacology (ECNP) Congress; October 7, 2018; Barcelona, Spain.
rTMS vs ECT: A Comparison

Data sources
- 113 RCTs
- Overall risk of bias: High 17%, Low 34%, Unclear 50%
- 6750 adults with major depressive disorder or bipolar depression

Results
Active vs sham treatment comparisons

ECT (Electro-convulsive therapy)
- Bitemporal
- High dose right unilateral
- Bifrontal
- Low-moderate dose right unilateral

TMS (Transcranial magnetic stimulation)
- Priming
- Bilateral repetitive
- Low frequency repetitive (right)
- High frequency repetitive (left)
- Synchronised
- Accelerated
- Deep
- High frequency repetitive (right)
- Low frequency repetitive (left)

TBS (Theta burst stimulation)
- Bilateral
- Intermittent
- Continuous

Other
- Magnetic seizure therapy
- Transcranial direct current stimulation

Response rates and Discontinuation
Odds ratio and 95% CI

A multi-professional approach to patient care
A general practitioner (GP) or family physician and at least one other health professional (eg, nurse, psychologist, psychiatrist, pharmacist) were involved with patient care, usually acting as a case or care manager to coordinate and/or deliver care for the depressed person

A structured management plan
Evidence based guidelines or treatment protocols. Interventions could include both pharmacological (eg, antidepressant medication) and nonpharmacologic interventions (eg, patient screening, patient and provider education, counselling, cognitive-behavior therapy)

Scheduled patient follow-ups
An organized approach to patient follow-up that could include one or more scheduled telephone or in-person follow-up appointments to provide specific interventions, facilitate treatment adherence, or monitor symptoms or adverse effects

Enhanced inter-professional communication
Mechanisms to facilitate communication between professionals caring for the depressed person: team meetings, case-conferences, individual consultation/supervision, shared medical records, patient-specific written or verbal feedback between caregivers
• Recent studies suggest that patients with partial response benefit more from augmentation than from switching treatment
Strategies for Irritability and Mixed Symptoms in Major Depressive Disorder
Does Augmentation with a Second-Generation Antipsychotic $\alpha_1B$ Antagonist Help with Depression with Irritability?

ADT + Brexpiprazole 2 or 3 mg (N=54)  ADT (N=48)

Mean SIS Total Score

Week

Brexpiprazole Discontinued

ADT = antidepressant treatment; SIS = Sheehan Irritability Scale.
Lurasidone for the Treatment of Major Depressive Disorder with Mixed Features

Montgomery–Åsberg Depression Rating Scale Total Score

LS Mean in Change from Baseline

Week

Baseline mean MADRS: Placebo = 33.3; Lurasidone = 33.2

Baseline

1 2 3 4 5 6

-25 -20 -15 -10 -5 0

Lurasidone (N=108) Placebo (N=100)

ES = 0.8

*P<.05; **P<.01; ***P<.001.

Lucy

- Lucy was switched from an SSRI to an SNRI
- 6 weeks later she reported some improvement in anxiety, irritability and energy but indicated that her sleep is still “awful,” motivation is low, and it is still difficult to stay focused at work
- PHQ-9 = 16
- After a brief discussion of safety/efficacy balance, decision was made to continue with SNRI and add an SGA
- 4 weeks later, Lucy indicated that in addition to improvement in mood, she is now sleeping better and has an easier time initiating and completing her work
- PHQ-9 = 12
Strategies for Fatigue, Anhedonia, Sleepiness, Social Dysfunction, Psychomotor and Cognitive Impairment in Major Depressive Disorder
Serotonin and Dopamine Innervate Networks Involved with Regulation of Mood and Cognition

SNc = substantia nigra pars compacta; VTA = ventral tegmental area; DStr = dorsal striatum; VStr = ventral striatum; DMT = dorsomedial thalamus; pACC = perigenual anterior cingulate cortex; PCC = posterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; SM = sensorimotor; RNi = raphe nuclei; dACC = dorsal anterior cingulate cortex; RSNs = resting state networks; SMN = sensorimotor network; DMN = default-mode network; SN = salience network.

Interactions Between mPFC and Brainstem Nuclei

DR, dorsal raphe; GABA, gamma-aminobutyric acid; Glu, glutamate; LC, locus coeruleus; mGluR, metabotropic glutamate receptor; MnR, median raphe; mPFC, medial prefrontal cortex; VTA, ventral tegmental area; Pyr pyruvate, 5-HT 5-hydroxytryptamine, AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid receptor : an inonotropic transmembrane receptor for glutamate).

Impact of Fatigue Severity on SSRI Response in STAR*D

Level 1 remission (QIDS-SR16 score ≤ 5) outcome by baseline QIDS-SR16 (item 14) energy/fatigability score. *Adjusted OR=.811 (P=.0001; 95% CI [.73, .90]). Adjusted for number of Axis I comorbidities, baseline HAM-D-17, and anxious features.

QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology, Self-Report; HAM-D-17 = 17-item Hamilton Rating Scale for Depression.


14. Energy level:
0  There was no change in my usual level of energy.
1  I got tired more easily than usual.
2  I had to make a big effort to start or finish my usual daily activities (eg, shopping, homework, cooking, or going to work).
3  I really couldn’t carry out most of my usual daily activities because I just didn’t have the energy.
Presence of Sleepiness and Fatigue Might Influence Our Treatment Choice

Improvement in Fatigue (ITT)

Baseline 2 Weeks 4 Weeks 6 Weeks

Baseline Change in HAM-D Fatigue Score

2 Weeks 4 Weeks 6 Weeks

Endpoint (ITT)

Improvement in Sleepiness (ITT)

Baseline 2 Weeks 4 Weeks 6 Weeks

Baseline Change in HAM-D Sleepiness Score

2 Weeks 4 Weeks 6 Weeks

Endpoint (ITT)

Left: *P<.05 vs placebo, †P<.01 vs SSRIs and placebo; Right: *P=.07 vs placebo, †P<.01 vs SSRIs and placebo.

HAM-D = Hamilton Rating Scale for Depression.

SNRIs May Provide a Greater Relief for Psychomotor Retardation Than SSRIs in Major Depressive Disorder

Percent change from baseline in psychomotor retardation (item 8 on HAM-D-17) for participants completing 8 weeks of treatment (n=98) with venlafaxine (VEN, n=41) or escitalopram (ESC, n=57) adjusted for baseline HAM-D score.

*P=.05 level.
Improvement in Cognitive Dysfunction in Major Depressive Disorder as Assessed by the DSST

As of May 2018, US Prescribing Information for vortioxetine shows data on a positive effect on processing speed, an aspect of cognitive function that is impaired in many patients with MDD.

*P<.05; **P<.01. CIT = citalopram; DES = desipramine; DUL = duloxetine; ESC = escitalopram; FLU = fluoxetine; NOR = nortriptyline; PHE = phenelzine; SER = sertraline; VOR = vortioxetine.

Antidepressants Have a Differential Impact on Cognition in Patients with Major Depressive Disorder

- N=81 patients with MDD were treated with a stable dose of medication for at least 4 weeks (bupropion=27; venlafaxine=27; SSRIs=27). N=27 controls were randomly selected from the CNS Vital Signs normal database.

- Patients were tested with the CNS Vital Signs (CNSVS) battery at the North Carolina Neuropsychiatry Clinics.

- CNSVS is a PC-based neurocognitive screening battery that comprises 7 familiar neuropsychological tests: verbal memory (VBM); visual memory (VIM); finger tapping (FTT); symbol-digit coding (SDC); the Stroop test (ST); the shifting attention test (SAT); and the continuous performance test (CPT).

The SSRI group scored significantly below controls in tests of psychomotor speed, cognitive flexibility, and reaction time. The venlafaxine group scored more poorly than controls in reaction time, a measure of information processing speed derived from the Stroop test. The bupropion group did not differ from controls in any of the cognitive domains. BP = bupropion; NML = normal; VEN = venlafaxine.

Vortioxetine, Bupropion, and Agomelatine Significantly Improved Anhedonia in Major Depressive Disorder

N=100, open-label vortioxetine (10–20 mg/day, flexibly-dosed) for 8 weeks.

MASQ = Mood and Anxiety Symptoms Questionnaire; SHAPS = Snaith–Hamilton Pleasure Scale.

Improvement in Social Functioning May Be Related to Noradrenergic Antidepressant Effect

Noradrenergic symptom cluster
- Decreased concentration
- Retardation
- Loss of energy
- Lassitude
- Tiredness
- Reduced self-care

Social dysfunction
- Reduced quality of life
- Family disruption
- Social isolation
- Absenteeism
- Presenteeism

Improvement in Social Adaptation Self-evaluation Scale (SASS) score during antidepressant therapy.

NRI = norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
Improvement in Social Functioning and Retardation May Be Related to Noradrenergic Antidepressant Effect

Retardation score is the score on item 8 of the Hamilton Depression Rating Scale. 
*P<.05 compared with paroxetine-treated patients with retardation scores of 3 or 4.

CGI = Clinical Global Improvement.
Practical Take-Away

• Antidepressants that modulate norepinephrine and dopamine and multimodal antidepressants may have advantage in patients suffering from residual fatigue, somnolence, anhedonia, cognitive impairment and social dysfunction
• Even patients who are responding to antidepressants continue to suffer from symptoms that interfere with functioning
• Troubled primary relationships, history of early life adversity, medical conditions/inflammation, obesity, chronic stress, significant delay of treatment, and substance use may all diminish response to antidepressant treatment
• Recent studies suggest that patients with partial response benefit more from augmentation than from switching treatment
• Antidepressants agents that modulate norepinephrine and dopamine and multimodal antidepressants may have advantage in patients suffering from residual fatigue, somnolence, anhedonia, cognitive impairment and social dysfunction
Q&A