Evidence-based Sequenced Treatment Management and the 2010 APA Practice Guideline

George I. Papakostas, MD
Director, Treatment-Resistant Depression Studies
Department of Psychiatry
Massachusetts General Hospital
Associate Professor of Psychiatry
Harvard Medical School
Faculty Disclosure

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  – George I. Papakostas, MD

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Talking Point

- Implement evidence-based sequenced management strategies based on the 2010 American Psychiatric Association (APA) Practice Guideline to enhance clinical decision-making for adult patients with Major Depressive Disorder (MDD)
Goal of Acute Phase Treatment: Sustained Remission

Response
- $\geq 50\%$ improvement in symptoms
- Allows for significant residual symptoms

Vs

Remission
- At least 3 weeks of the absence of both sad mood and reduced interest
- No more than 3 remaining symptoms

APA Guideline: Timing of Intervention

- Goal of Acute Phase of therapy is remission\(^1\)
- Measurement-based care is key\(^1\)
- Delay in achieving remission of symptoms is characteristic\(^2,3\)
  - Discontinuing a treatment prematurely (ie, <4 weeks) due to lack of efficacy alone may deprive some patients of a potentially effective therapy
  - Waiting too long in the face of complete non-response (ie, >8 weeks) may unnecessarily increase patient’s exposure to an ineffective therapy and, ultimately, delay improvement


APA=American Psychiatric Association.
APA Guideline: Assessment of Therapeutic Failure

- Adequacy of treatment
  - Dose, duration, quality of therapy
- Appropriateness of diagnosis
  - Bipolar disorder, psychotic features
- Adequacy of diagnosis
  - Psychiatric/medical co-morbidity
- Compliance and tolerability
- Pharmacokinetic factors

Pharmacologic Treatment Approaches

- Increase dosage
- Switching
- Augmentation
  - Addition of a non-antidepressant agent to enhance the effect of the antidepressant
- Combination
  - Addition of a second antidepressant agent to enhance the effect of the original antidepressant
Augmentation, Combination, Switching

• Augmentation and combination
  – Avoid loss of any therapeutic benefits from first-line agent
  – No risk of withdrawal symptoms
  – May target side effects of first-line treatment

• Switching
  – Better compliance
  – Lower risk of drug interactions
  – Resolution of side effects
  – Lower cost?
General Guides: 2+ Line Approaches

- Partial response (vs non-response)
  - Favors Retention of Initial Agent
    - Augmentation
    - Combination
    - Dose-increase

- Poor tolerability (vs good tolerability)
  - Favors discontinuation of initial agent
    - Switching

- Knowledge of relative efficacy and tolerability of 2nd+ line strategies key to guiding treatment selection
### Atypical Antipsychotic Augmentation in Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Atypical Antipsychotic</th>
<th>Antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelton et al 2001</td>
<td>8</td>
<td>Olanzapine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Shelton et al 2005</td>
<td>12</td>
<td>Olanzapine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Corya et al 2006</td>
<td>12</td>
<td>Olanzapine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Keitner et al 2006</td>
<td>4</td>
<td>Risperidone</td>
<td>Various</td>
</tr>
<tr>
<td>Khullar et al 2006</td>
<td>8</td>
<td>Quetiapine</td>
<td>SSRI or SNRI</td>
</tr>
<tr>
<td>Mattingly et al 2006</td>
<td>8</td>
<td>Quetiapine</td>
<td>SSRI or SNRI</td>
</tr>
<tr>
<td>McIntyre et al 2006</td>
<td>8</td>
<td>Quetiapine</td>
<td>SSRI or SNRI</td>
</tr>
<tr>
<td>Thase et al 2006</td>
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<td>Olanzapine</td>
<td>Fluoxetine</td>
</tr>
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<td>Thase et al 2006</td>
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<td>Olanzapine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Gharabawi et al 2006</td>
<td>6</td>
<td>Risperidone</td>
<td>Various</td>
</tr>
</tbody>
</table>

SNRI=serotonin-norepinephrine reuptake inhibitor.  
SSRI=selective serotonin reuptake inhibitor.
Atypical Antipsychotic Augmentation in TRD: Meta-analysis of 10 RCTs

N=1500

Remission (P<0.05)
Discontinued for intolerance (P<0.05)

Atypical
Placebo


RCT=randomized control trial.
TRD=treatment-resistant depression.
Aripiprazole Augmentation in TRD: Results From 3 Placebo-Controlled Trials


TRD=treatment-resistant depression.
Augmentation With Atypical Antipsychotics

- Aripiprazole 5-15 mg, olanzapine 5-15 mg, quetiapine 150-300 mg, risperidone 0.5-2 mg

- **Advantages**
  - Best studied strategy

- **Disadvantages (varies by agent)**
  - Tolerability
    - Neuroendocrine (prolactin)
    - Metabolic (weight, lipids, glucose regulation)
    - Extrapyramidal symptoms (tardive dyskinesia, neuroleptic malignant syndrome, akathisia, parkinsonism, dystonic reactions)

  - Efficacy as second-line treatment?
  - Long-term efficacy?
# Lithium Augmentation of TCAs

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heninger et al 1983</td>
<td>15</td>
<td>2 weeks</td>
<td>Lithium &gt; Placebo</td>
</tr>
<tr>
<td>Kantor et al 1986</td>
<td>7</td>
<td>2 days</td>
<td>Lithium = Placebo</td>
</tr>
<tr>
<td>Zusky et al 1988</td>
<td>16</td>
<td>3 weeks</td>
<td>Lithium = Placebo</td>
</tr>
<tr>
<td>Schopf et al 1989</td>
<td>27</td>
<td>1 week</td>
<td>Lithium &gt; Placebo</td>
</tr>
<tr>
<td>Stein and Bernadt 1993</td>
<td>34</td>
<td>3 weeks</td>
<td>Lithium = Placebo</td>
</tr>
<tr>
<td>Joffe et al 1993</td>
<td>50</td>
<td>2 weeks</td>
<td>Lithium &gt; Placebo</td>
</tr>
<tr>
<td>Nierenberg et al 2003</td>
<td>35</td>
<td>6 weeks</td>
<td>Lithium = Placebo</td>
</tr>
</tbody>
</table>

TCAs=tricyclic antidepressants.

# Lithium Augmentation of SSRIs

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katona et al 1995</td>
<td>62</td>
<td>6 weeks</td>
<td>Lithium = Placebo</td>
</tr>
<tr>
<td>Baumann et al 1996</td>
<td>24</td>
<td>1 week</td>
<td>Lithium &gt; Placebo</td>
</tr>
</tbody>
</table>


SSRI=selective serotonin reuptake inhibitors.
Augmentation With Lithium

• Doses 600-1200 mg daily

• Advantages
  – Pooled odds ratio of response during lithium augmentation compared with placebo is 3.31 (95% CI, 1.46-7.53)

• Disadvantages
  – Margin of efficacy vs dose increase, other strategies
  – All “positive” placebo-controlled studies of short duration
  – Paucity of studies on newer agents
  – Risk of toxicity and need for blood monitoring
## Mirtazapine/Mianserin Combination

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Antidepressant</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maes et al 1999</td>
<td>31</td>
<td>5 weeks</td>
<td>SSRI</td>
<td>Mianserin &gt; Placebo</td>
</tr>
<tr>
<td>Ferreri et al 2001</td>
<td>104</td>
<td>6 weeks</td>
<td>SSRI</td>
<td>Mianserin &gt; Placebo</td>
</tr>
<tr>
<td>Carpenter et al 2002</td>
<td>26</td>
<td>4 weeks</td>
<td>SSRI</td>
<td>Mirtazapine &gt; Placebo</td>
</tr>
<tr>
<td>Licht and Qvitza 2003</td>
<td>295</td>
<td>6 weeks</td>
<td>SSRI</td>
<td>Mianserin = Placebo</td>
</tr>
</tbody>
</table>


SSRI=selective serotonin reuptake inhibitors.
Mirtazapine/Mianserin Combination (cont’d)

• 15-30 mg at bedtime

• Advantages
  – Strong efficacy data
  – May help with insomnia

• Disadvantages
  – Weight gain
  – Sedation
  – Agranulocytosis (very rare)
## Augmentation With Pindolol

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Antidepressant</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maes et al 1996</td>
<td>33</td>
<td>4 weeks</td>
<td>trazodone</td>
<td>Pindolol &gt; Placebo*</td>
</tr>
<tr>
<td>Maes et al 1999</td>
<td>31</td>
<td>5 weeks</td>
<td>fluoxetine</td>
<td>Pindolol &gt; Placebo*</td>
</tr>
<tr>
<td>Perez et al 1999</td>
<td>80</td>
<td>4 weeks</td>
<td>SSRIs/TCAs</td>
<td>Pindolol = Placebo</td>
</tr>
<tr>
<td>Perry et al 2004</td>
<td>42</td>
<td>10 days</td>
<td>SSRI</td>
<td>Pindolol = Placebo</td>
</tr>
</tbody>
</table>

*Both treatment-resistant and nontreatment-resistant patients were enrolled.*


SSRI=selective serotonin reuptake inhibitors.
TCAs=tricyclic antidepressants.
Pindolol Augmentation of SSRIs

- 2.5-7.5 mg tid
- Advantages
  - May accelerate response to SSRIs
- Disadvantages
  - No difference from placebo in 2 largest studies
  - Increased irritability


SSRI=selective serotonin reuptake inhibitors.
tid=3 times per day.
Testosterone Augmentation

- Pilot study (gel) in men (n=22) with testosterone levels \( \leq 350 \text{ ng} \) was “positive”\(^1\)
- Subsequent study in men (n=18) was “negative”\(^2\)
- A third study in men (n=26) utilizing intramuscular administration also was “negative”\(^3\)
- Subsequent study in men (n=100) was “negative”\(^4\)

## Augmentation With Omega-3 Fatty Acids

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nemets et al 2002</td>
<td>20</td>
<td>4 weeks</td>
<td>E-EPA (2 g) &gt; Placebo</td>
</tr>
<tr>
<td>Peet and Horrobin 2002</td>
<td>70</td>
<td>12 weeks</td>
<td>E-EPA (1 g) &gt; Placebo*</td>
</tr>
<tr>
<td>Su et al 2003</td>
<td>28</td>
<td>8 weeks</td>
<td>Omega-3† FA &gt; Placebo</td>
</tr>
<tr>
<td>Lesperance et al 2011</td>
<td>432</td>
<td>8 weeks</td>
<td>Omega-3‡ FA = Placebo</td>
</tr>
</tbody>
</table>

* But not 2 g or 4 g E-EPA.
†440 mg EPA plus 220 mg DHA.
‡1050 mg EPA plus 150 mg DHA.

DHA=docosahexaenoic acid.
E-EPA=ethyl-eicosapentaenoic acid.
FA=fatty acid.

Augmentation With Omega-3 Fatty Acids (cont’d)

- **Advantages**
  - Tolerability
  - Acceptability
  - May possess other health-promoting benefits (CV?)

- **Disadvantages**
  - Optimal dose unknown (1 g/d EPA+DHA)
  - Cost

CV=cardiovascular. DHA=docosahexaenoic acid. EPA=eicosapentaenoic acid.
## Triiodothyronine (T3) Augmentation of TCAs

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coppen et al 1972</td>
<td>17</td>
<td>2 weeks</td>
<td>T3 &gt; Placebo</td>
</tr>
<tr>
<td>Gitlin et al 1987</td>
<td>16</td>
<td>4 weeks</td>
<td>T3 = Placebo</td>
</tr>
<tr>
<td>Joffe et al 1993</td>
<td>50</td>
<td>2 weeks</td>
<td>T3 &gt; Placebo</td>
</tr>
</tbody>
</table>


TCAs=tricyclic antidepressants.
Augmentation With T3

- 25-50 mg qd
- **Advantages**
  - May accelerate clinical response
- **Disadvantages**
  - All placebo-controlled studies involve TCAs
  - Among the 4 randomized double-blind studies, pooled effects were not significant ($P>0.05$)

$qd=$once daily.
$T3=$triiodothyronine.
$TCAs=$tricyclic antidepressants.
Augmentation With Modafinil

• 100-400 mg qd

• Advantages
  – Efficacy demonstrated in 2 trials when pooled
  – May resolve depressive symptoms in patients who also present with residual somnolence and fatigue
  – Useful for residual somnolence

• Disadvantages
  – Unclear efficacy in patients without fatigue and sleepiness
  – Unclear efficacy in patients with insomnia


qd=once daily.
Buspirone Augmentation of SSRIs

- 10-30 mg bid
- Advantages
- Disadvantages
  - 2 placebo-controlled studies showed buspirone equivalent to placebo


bid=twice daily.
SSRI=selective serotonin reuptake inhibitors.
Augmentation With OROS Methylphenidate

• OROS methylphenidate 18-54 mg/d

• Advantages
  – May help with fatigue, apathy, and somnolence
  – May help with comorbid ADHD

• Disadvantages
  – 2 negative studies published to date
  – Potential for abuse


ADHD=attention-deficit/hyperactivity disorder.
OROS=osmotic-release oral system.
Augmentation With L-methylfolate

- **Study I**: 7.5mg daily
  - N=150
  - L-methylfolate augmentation: 18.3%, Antidepressant Monotherapy: 24.1%

- **Study II**: 15mg daily
  - N=75
  - L-methylfolate augmentation: 35.2%, Antidepressant Monotherapy: 17.6%

*P<0.05

Augmentation With SAMe

- SAMe augmentation (n=39)
- Antidepressant Monotherapy (n=34)

*P<0.05

STAR*D Level 2: Addition of Bupropion vs Buspirone to Citalopram for TRD in a Randomized Study

N=565

- Discontinued for intolerance ($P<0.05$)
- Remission (QIDS) ($P=NS$)

Patients (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bupropion</th>
<th>Buspirone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued</td>
<td>12.5%</td>
<td>20.6%</td>
</tr>
<tr>
<td>Remission (QIDS)</td>
<td>39.0%</td>
<td>33.0%</td>
</tr>
</tbody>
</table>

QIDS=Quick Inventory of Depression Symptomatology.
STAR*D=Sequenced Treatment Alternatives to Relieve Depression.
TRD=treatment-resistant depression.

STAR*D Level 2: CBT vs Pharmacotherapy

$P > 0.05$ for both analyses

Augmentation

- CBT: 23.1%
- Pharmacotherapy: 33.3%

Switch

- CBT: 25.0%
- Pharmacotherapy: 27.9%


STAR*D=Sequenced Treatment Alternatives to Relieve Depression.

CBT=cognitive-behavioral therapy.
### Switching From SSRI to SSRI vs Non-SSRI (Bupropion, Venlafaxine, Sertraline)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor</th>
<th>Duration (Weeks)</th>
<th>Lead-in SSRI</th>
<th>Switch SSRI</th>
<th>Switch Non-SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poirier and Boyer 1999</td>
<td>Wyeth</td>
<td>4</td>
<td>Various</td>
<td>Paroxetine</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Lenox-Smith and Jiang 2008</td>
<td>Wyeth</td>
<td>12</td>
<td>Various</td>
<td>Citalopram</td>
<td>Venlafaxine ER</td>
</tr>
<tr>
<td>Thase et al 2001</td>
<td>Organon</td>
<td>8</td>
<td>Various</td>
<td>Sertraline</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Rush et al 2006</td>
<td>NIMH</td>
<td>14</td>
<td>Citalopram</td>
<td>Sertraline</td>
<td>Venlafaxine ER</td>
</tr>
<tr>
<td>Rush et al 2006</td>
<td>NIMH</td>
<td>14</td>
<td>Citalopram</td>
<td>Sertraline</td>
<td>Bupropion SR</td>
</tr>
</tbody>
</table>

N=1496

**Poirier MF, Boyer P. Br J Psychiatry. 1999;175:12-16.**


**Thase ME, et al. Mirtazapine versus sertraline after SSRI non-response. Presented at the New Clinical Drug Evaluation Unit of the National Institute of Mental Health Annual Meeting. May 2001; Phoenix, AZ.**


ER=extended release.

NIMH=National Institute of Mental Health.

SR=sustained release.

SSRI=selective serotonin reuptake inhibitors.
Treatment of SSRI-Resistant MDD: Meta-analysis Comparing Within (2nd SSRI) vs Across (Non-SSRI) Class Switches

<table>
<thead>
<tr>
<th></th>
<th>SSRI</th>
<th>Non-SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (HDRS)</td>
<td>23.5%</td>
<td>28.0%</td>
</tr>
<tr>
<td>(P&lt;0.05)</td>
<td></td>
<td>(P=0.1)</td>
</tr>
<tr>
<td>Discontinued for Intolerance</td>
<td>11.5%</td>
<td>17.7%</td>
</tr>
</tbody>
</table>

*N=1496; 4 RTCs.

HDRS=Hamilton Depression Rating Scale.
SSRI=selective serotonin reuptake inhibitors.

Switching Imipramine (TCA)-Resistant MDD to Phenelzine (MAOIs) and Vice Versa (Crossover): Two Randomized, Double-Blind Studies


MAOI=monoamine oxidase inhibitor.
TCA=tricyclic antidepressant.
STAR*D Level 3 Switch

N=235

Remission (QIDS) (P=NS)

Discontinued for intolerance (P=NS)

Nortriptyline

Mirtazapine


QIDS=Quick Inventory of Depression Symptomatology.

STAR*D=Sequenced Treatment Alternatives to Relieve Depression.
Refractory Depression: Choices

- Electroconvulsive therapy
- Vagus nerve stimulation
- Deep brain stimulation
- Variable data for efficacy
- Timing for introduction depending upon
  - Refractoriness of Illness
  - Use in past episodes
  - Patient preference
  - Availability
Placebo “Enhancement”

• Remember: psychotherapy, antidepressants, somatic therapies are part of the reason why patients improve!

• Strategies for placebo enhancement
  – Assuage fears, worry, and embarrassment about illness
  – Work on problem-solving skills
  – Plan resumption of pleasurable activities
  – Provide hope
  – Involve patients in treatment decisions – patient preference!

• Supportive components of MDD care
  – Team approach
  – Use of a case manager
  – Assess to a psychiatrist
  – Adherence monitoring and support
  – Provide education to patient and family

MDD=major depressive disorder.
Conclusion

- Several pharmacologic strategies exist for TRD
- Augmentation with atypical antipsychotics best studied
- Mirtazapine/mianserin as well as omega-3 fatty acids augmentation also possess considerable efficacy data
- Lithium, T3 offer mixed data
- CBT, bupropion, modafinil, L-methylfolate, SAMe promising and require replication
- Pindolol, buspirone, testosterone (in men), and methylphenidate do not appear to be very useful

TRD=treatment-resistant depression. CBT=cognitive-behavioral therapy. SAMe=S-adenosyl methionine. T3=triiodothyronine.
• Switching to an SNRI, an alternative SSRI, or bupropion in SSRI-resistant MDD supported by reasonable efficacy data
• Switching to MAOIs provided mixed data
• Switching to TCAs supported by weak data
• Remission rates with monotherapy were low after “stage 2”

SNRI=serotonin-norepinephrine reuptake inhibitor.
SSRI=selective serotonin reuptake inhibitor.
MAOI=monoamine oxidase inhibitor.
TCA=tricyclic antidepressant.
Conclusion (cont’d)

• In the face of TRD, it is essential to…
  – Ensure proper diagnosis
  – Ensure the adequacy of the antidepressant trial
  – Rule out relapse

• Therapeutic issues to consider in each individual case
  – Potential loss of partial benefit from the failed trial as well as the risk of withdrawal symptoms may reduce the feasibility of switching strategies
  – Presence of significant side effects from the antidepressant itself as well as the risk of drug interactions may reduce the feasibility of augmentation/combination strategies

TRD=treatment-resistant depression.