Beginning treatment with dual-antidepressant therapy: Can it lead to better efficacy and a faster return to happy days?

October 21, 2011
Nicole L. Cupples, Pharm.D.
PGY2 Psychiatric Pharmacy Practice Resident
South Texas Veterans Healthcare System, San Antonio, TX
The University of Texas Health Science Center at San Antonio
The University of Texas at Austin College of Pharmacy

Learning Objectives

1. Describe the potential etiology of major depressive disorder
2. Identify current treatment guidelines for major depressive disorder
3. Provide rationale for combination antidepressant therapy including theoretical mechanisms of synergism
4. Evaluate the evidence supporting the initiation of dual antidepressant therapy at the onset of treatment
I. Major Depressive Disorder (MDD)
   a. Core symptoms include depressed mood, anhedonia, irritability, difficulty with concentration and abnormalities in appetite and sleep\(^1\)
   b. Of those with MDD, 40-50% fail to respond to an adequate initial trial of an antidepressant (AD)\(^2\)

II. Epidemiology
   a. 1 in 6 Americans will experience a depressive episode during their lifetime\(^3\)
   b. Approximately 15% are resistant to all known types of therapy\(^4\)
   c. Rates of recurrence are high\(^5\) and depressive symptoms are persistent in persons suffering from MDD\(^6\)
      i. Analysis of STAR*D (Sequenced Treatment Alternatives to Relieve Depression trial) data showed 75% of responders had 2-9 residual symptoms
      ii. 100% of responders experienced at least 1 symptom after 12-14 weeks of citalopram treatment

III. Etiology\(^7\)\(^-\)\(^10\)
   a. Majority of theories centered on monamine neurotransmission
   b. Early 1950s observations found depression occurred with use of drugs that depleted monoamine neurotransmitters [norepinephrine (NE), serotonin (5-HT), and dopamine (DA)]
      i. Boosting concentrations of neurotransmitters to “normal levels” appears to help
      ii. Direct evidence of reduced neurotransmitter concentrations in depressed patients is lacking
   c. Neurotransmitter receptor hypothesis
      i. Non-specific abnormalities occur in the receptors themselves
      ii. Low concentrations of neurotransmitters cause upregulation of receptors
      iii. Direct evidence of receptor abnormality is also lacking
   d. Signal transduction flaw hypothesis
      i. Stress-induced vulnerability decreases expression of genes that encode brain-derived neurotrophic factor (BDNF)
         1. BDNF is required for viability of neurons essential for signal transduction
         2. Decreased BDNF leads to apoptosis of neurons in the hippocampus
         3. Decreased size and function of hippocampal neurons found in those with MDD
      ii. Evidence is controversial and unclear
   e. Neuronal circuit transduction malfunction hypothesis
      i. Each neurotransmitter regulates specific malfunctioning brain regions
      ii. Malfunctioning brain regions lead to disorders in mood\(^8\)\(^,\)\(^11\)
iii. Targeting particular neurotransmitters with medications may improve specific symptoms.

1. Depressed mood
   a. Inefficient information processing in the amygdala, areas of the prefrontal cortex and the subgenual area of the anterior cingulated cortex
   b. All three neurotransmitters (NE, 5-HT, DA) innervate these areas
   c. Increasing concentrations of any of these neurotransmitters improves mood

2. Apathy
   a. The prefrontal cortex, hypothalamic “drive” centers and the nucleus accumbens may be the brain circuits involved
   b. Increasing concentrations of DA and NE helps relieve apathy
   c. Increasing concentrations of 5-HT in these circuits reduces concentrations of DA and NE and may exacerbate apathy

3. Fatigue and anergia
   a. Mental fatigue is linked to deficient functioning of NE and DA in the prefrontal cortex
   b. Physical fatigue is associated with deficient functioning of NE and DA in the forebrain

4. Suicidal ideation and feelings of guilt and worthlessness
   a. Regulatory circuits in the amygdala and prefrontal cortex may be deficient in 5-HT
IV. Treatment-Resistant Depression (TRD)
   i. Depression which fails to respond to a standard course of antidepressants\textsuperscript{12}
      1. No universal definition for TRD exists
      2. At least 15 different classifications for TRD is found in the literature
   ii. Response is usually defined as a 50% reduction in depressive symptoms\textsuperscript{8,13}
   iii. Response is only one aspect of treatment, complete remission is the goal
      1. Remission is a removal of essentially all symptoms
         a. APA defines remission as $\geq 3$ weeks of the absence of both sad mood and reduced interest
         b. No more than 3 residual symptoms of the major depressive episode are present
      2. Recovery is remission that has occurred for $\geq 6$-12 months
   iv. Those who fail to remit with initial AD treatment experience less chance of remission for each successive AD trial\textsuperscript{14}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Rates of remission after failed antidepressant therapy\textsuperscript{14}}
\end{figure}

v. Current APA treatment guideline for MDD\textsuperscript{13}
vi. Augmentation with another AD or other agent considered only after 2 failed monotherapy trials of an AD

V. Rationale for use
   a. Other areas of medicine combine medications to exploit their synergistic effects
   b. Combining AD treatment with different mechanisms of action may add independent additional benefits and provide synergistic actions\(^{13,16}\)

VI. Specific AD combinations
   a. Mirtazapine and SSRI
      i. SSRI\(^{-}\)s decrease firing of 5-HT neurons leading to initial delay in 5-HT transmission in animal models\(^{17}\)
      ii. Mirtazapine partially offsets this delayed transmission by increasing norepinephrine (NE) release via \(\alpha_2\) antagonism, leading to increased 5-HT release\(^{17,18}\)
         1. SSRI \(\downarrow\) 5-HT\(\downarrow\) initial low concentrations of 5-HT
         2. Mirtazapine \(\uparrow\) NE\(\uparrow\) 5-HT and offset initial low concentrations caused by SSRI
      iii. Both drugs desensitize 5HT\textsubscript{1A} autoreceptors, leading to an increase concentration in 5-HT release
      iv. Mirtazapine selectively inhibits 5-HT\textsubscript{2c} (NE and DA indirect inhibition through GABA stimulation) which leads to a further increase in NE and DA concentrations
   b. Mirtazapine and SNRI, “California Rocket Fuel”\(^{8,18}\)
      i. SNRI inhibits 5-HT and NE reuptake while mirtazapine, through alpha 2 antagonism, increases 5-HT and NE resulting in a “double boost.”
Further release of NE by mirtazapine through 5-HT\textsubscript{2C} antagonism leads to a “triple boost” in NE release and also increase in DA

c. SSRI and bupropion\textsuperscript{13,15}
   i. Bupropion affects both NE and DA concentrations through reuptake blocking properties though mechanism of action is not entirely clear.\textsuperscript{19,20}
   ii. Bupropion does not effect serotonin concentrations; therefore, rational choice to add to SSRI therapy
   iii. Elevations of 5-HT, NE and DA all occur with this combination

d. Limited evidence exists to support dual AD treatment (Appendix A)

**DUAL AD THERAPY AT THE INITIATION OF TREATMENT**

VII. Rationale for use
- a. Effective first-trial monotherapy produces remission rates of only 37%\textsuperscript{14}
- b. Mood-elevating effects usually begin after 1-2 weeks of initiation of AD therapy\textsuperscript{10}
   i. Guidelines recommend at least 6 weeks of AD therapy before considering a change in treatment\textsuperscript{10,13}
   ii. Considerable length of time may be needed to see full effect of AD
- c. Low remission rates and delays in response may affect compliance
   i. An estimated 50% of patients stop their AD medication in the first 3 months\textsuperscript{21,22}
- d. Residual symptoms predispose patients to a faster full relapse than if remission is achieved\textsuperscript{23,24}
- e. Achieving superior efficacy with dual AD therapy compared to monotherapy may result
- f. Theoretically, AD combination at the initiation of treatment allows for synergistic effects to overcome this delay in treatment response and better target depressive symptoms
   i. Relief of depressive symptoms may occur in a shorter amount of time
   ii. Complete remission may be obtained earlier
   iii. Improved remission rates
   iv. Treatment compliance may be enhanced

**CURRENT EVIDENCE FOR DUAL AD THERAPY AT THE INITIATION OF TREATMENT**

VIII. Literature review
- a. Nelson et al. 1991\textsuperscript{25}
   i. Open-label, comparison trial of 14 inpatients with MDD
      1. Population

<table>
<thead>
<tr>
<th></th>
<th>Desipramine and fluoxetine (n=14)</th>
<th>Desipramine alone (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ±SD)</td>
<td>42.0 ±14.6</td>
<td>47.8±15.8</td>
</tr>
<tr>
<td>Number of prior depressive</td>
<td>1.4±1.7</td>
<td>1.3±1.5</td>
</tr>
<tr>
<td>episodes (mean ±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D_{17} before treatment</td>
<td>26.0 ±5.5</td>
<td>23.7 ±5.9</td>
</tr>
<tr>
<td>(mean ±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of depressive</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>episode, weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>5/9</td>
<td>16/36</td>
</tr>
<tr>
<td>Melancholia present</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Dysthymia present</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Other psychiatric disorder</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Personality disorder present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near delusional features present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior AD failure (not defined)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HAM-D17=Hamilton Rating Scale for Depression 17 Item Version*

- Patients failed to respond to 1 week of hospitalization without AD treatment
- **Interventions**
  - Desipramine doses initiated concurrently with fluoxetine and titrated to therapeutic dose at week two based on plasma concentrations
  - Dose adjustments of desipramine were conducted based on plasma concentrations to target a therapeutic level of 160ng/ml
  - Response to treatment was measured weekly using the HAM-D17
- A comparison group of 52 patients who had completed a 4-week desipramine trial using the same method of dose adjustment was used

3. **Primary Outcome Measures**
   - Time to response
   - Percentage change in HAM-D17 scores
   - Remission rates (defined as >75% improvement in HAM-D17 score and a final score <7)

4. **Results**

<table>
<thead>
<tr>
<th>Combination vs. monotherapy</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HAM-D&lt;sub&gt;17&lt;/sub&gt; scores</td>
<td>14.4 vs 18.8 (p&lt;.05)</td>
<td>9.8 vs 16.5 (p&lt;.003)</td>
<td>8.6 vs 15.0 (p=.01)</td>
<td>5.0 vs 13.8 (p=.0001)</td>
</tr>
<tr>
<td>% Change in HAM-D&lt;sub&gt;17&lt;/sub&gt;</td>
<td>44% vs 24% (p=.02)</td>
<td>62% vs 35% (p=.006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>29% vs 6% (p&lt;.05)</td>
<td>43% vs 6% (p=.003)</td>
<td>71% vs 14% (p=.0002)</td>
<td></td>
</tr>
</tbody>
</table>

- Desipramine doses in combination treatment, ranged from 40-225mg/d (median 125mg/d), in monotherapy arm, 50-500mg/d (median 175mg/d)
- The type and frequency of side effects observed with combination treatment was similar to treatment with desipramine alone

**ii. Authors’ Conclusions**

1. Clinical data is consistent with hypothesis that combination therapy with desipramine and fluoxetine down-regulates β-adrenergic receptors more rapidly than either drug alone
2. More patients on combination therapy achieved remission

**iii. Strengths of study**

1. Close monitoring of plasma drug concentrations
2. Use of well-matched control group
3. Standardized ratings and drug treatment

**iv. Limitations**

1. Small trial size
2. Not randomized nor double-blinded
3. Higher plasma concentrations of desipramine in combination group
4. Short treatment duration

5.
b. *Nelson et al. 2004*  
   i. Randomized, controlled double-blind, comparison trial of 39 inpatients  
   ii. Methods  

<table>
<thead>
<tr>
<th></th>
<th>Desipramine + fluoxetine</th>
<th>Fluoxetine</th>
<th>Desipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>45.2±12.3</td>
<td>48.4±12.3</td>
<td>40.3±11.4</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>4/9</td>
<td>9/5</td>
<td>4/8</td>
</tr>
<tr>
<td>Resistant (N/Y)</td>
<td>8/5</td>
<td>8/6</td>
<td>7/5</td>
</tr>
<tr>
<td>MADRS (baseline mean ±SD)</td>
<td>32.0±6.3</td>
<td>37.2±7.1</td>
<td>38.3±7.5</td>
</tr>
<tr>
<td>Fluoxetine dose (mg/day)</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Desipramine dose (mg/day)</td>
<td>98.1±45.0</td>
<td>0</td>
<td>293.7±116.8</td>
</tr>
</tbody>
</table>

*MADRS=Montgomery-Asberg Depression Rating Scale*

- Baseline HAM-D$_{17}$ score ≥18 (mean not given)  
- Patients had failed to respond to 1 week of hospitalization without antidepressant treatment

2. Interventions  
   a. Randomized into 3 groups  
      i. Desipramine at flexible doses, in combination with fluoxetine 20mg daily  
      ii. Flexible dosed desipramine  
      iii. Fluoxetine 20mg daily monotherapy  
   b. Dose adjustments of desipramine were conducted based on plasma concentrations to target a level of 160ng/ml  
   c. Six weeks of treatment for all 3 groups  
   d. Response to treatment measured weekly using the HAM-D$_{17}$ and MADRS

3. Primary Outcome Measures  
   a. Remission rates, defined as HAM-D$_{17}$ score ≤7, a 75% improvement on the MADRS and a final score ≤9  
   b. Response rates, measured by 50% improvement on the HAM-D$_{17}$ and/or MADRS  
   c. Time to response measured by final endpoint MADRS and HAM-D$_{17}$ scores

4. Results

<table>
<thead>
<tr>
<th>Level of response on the MADRS</th>
<th>Combined treatment</th>
<th>Fluoxetine</th>
<th>Desipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>7 (53.8%)</td>
<td>1 (7.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Response</td>
<td>1 (7.7%)</td>
<td>5 (35.7%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>0</td>
<td>1 (7.1%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Nonresponse</td>
<td>5 (38.5%)</td>
<td>7 (50%)</td>
<td>4 (33.3%)</td>
</tr>
</tbody>
</table>

- Combined treatment was more likely to result in remission than fluoxetine (p=.025)  
- Percentage of responders was not significant  
- Time to response was not significant  
- Excluding non-responders from all treatment groups showed end point MADRS , percent change on the MADRS, and end point HAM-D$_{17}$ all differed significantly in favor of combined treatment
c. Adverse effects (not a priori outcome)
   i. No patients withdrew from study due to adverse effects
   ii. Several desipramine monotherapy patients (exact number not provided) experienced orthostatic hypotension or tachycardia

5. Author’s Conclusions
   a. Combination AD therapy was more effective than monotherapy in producing remission
   b. Small sample size may have contributed to negative findings

iii. Strengths
   1. Randomized, controlled, double-blind trial
   2. Patients with TRD were stratified equally among treatment groups
      a. Minimum 4 weeks of drug treatment
      b. Dose of AD trialed equivalent to 150mg of imipramine
   3. Close monitoring of plasma drug concentrations

iv. Limitations
   1. Small sample size
   2. Statistics adjusted to achieve significance
   3. Length of treatment (6 weeks)
      a. Extending the trial length may have shown more participants remitting
      b. Evidence exists for those with partial response, defined as 50% improvement at 6 weeks, might remit at 12 weeks27

   c. Blier et al. 200928
      i. Randomized, double-blind, comparison trial of 61 outpatients assessing the effectiveness of combination paroxetine and mirtazapine from beginning of treatment to obtain a greater effectiveness within a trial of standard duration

   ii. Methods
      1. Population

<table>
<thead>
<tr>
<th></th>
<th>Mirtazapine (n=21)</th>
<th>Paroxetine (n=19)</th>
<th>Combination (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ±SD)</td>
<td>46±9</td>
<td>40±12</td>
<td>43±10</td>
</tr>
<tr>
<td>Weight (kg) (mean ±SD)</td>
<td>76±18</td>
<td>70±19</td>
<td>67±14</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>15/5</td>
<td>11/10</td>
<td>7/13</td>
</tr>
<tr>
<td>Single episode</td>
<td>15</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Recurrent episode</td>
<td>6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Duration of index episode:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-6 months</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6-12 months</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>15</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Failed ≥1 medication</td>
<td>9</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>MADRS (mean ±SD)</td>
<td>32.0±6.4</td>
<td>32.3±5.9</td>
<td>34.4±7.2</td>
</tr>
<tr>
<td>HAM-D17 (mean ±SD)</td>
<td>23.5±4.5</td>
<td>23.9±3.0</td>
<td>24.2±5.2</td>
</tr>
<tr>
<td>Melancholia</td>
<td>13</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>
Figure 5: Interventions

2. Primary Outcome Measures
   a. Time to response
   b. Time to remission (defined as a score of ≤10 on the MADRS)
   c. Response rates

3. Results
   a.
Figure: 6
The * indicates statistically significant difference between combination and monotherapy groups. The + indicates statistically significant difference between the paroxetine group and combination group at day 35.

Figure: 7
The * indicates statistically significant difference between combination and monotherapy groups at day 42. The + indicates statistically significant difference between mirtazapine group and combination group at day 45.

b. Comparison of scores was used to measure significant improvement, not the original criteria of 50% reduction

c. The number of patients who remitted was not significant between treatment groups

d. Time to response to time of remission was not significant between treatment groups

e. Patients on combination therapy for the entire 4 month period experienced weight gain (68.1 ± 4 kg to 71.4 ± 4 kg, n=16, p<.001)

iii. Authors’ Conclusions
1. Combination therapy had superior efficacy than either drug alone
2. Combination therapy was well tolerated

iv. Strengths
1. Randomized, controlled, double-blind trial
2. Monitoring of mirtazapine plasma concentrations
   a. Theoretical elevation of mirtazapine concentrations via paroxetine CYP 2D6 inhibition
   b. Plasma concentrations of mirtazapine in this study did not differ significantly between monotherapy and combination treatment
3. Low attrition rates did not differ among 3 treatment groups

v. Limitations
1. Small sample size
2. No placebo arm
   a. Investigators knew all participants were undergoing active treatment
   b. Possible overestimation of response
3. Unequal gender ratios in the 3 groups
   a. Differences in gender response to AD therapy is unclear
b. STAR*D report found females had a 5% increase in response to citalopram vs males

d. Blier et al. 2010
   1. Randomized, double-blind, comparison trial of 105 outpatients conducted to support evidence from previous trials of superiority with dual AD treatment from initiation

   2. Interventions
      a. 4 groups
         i. Fluoxetine monotherapy
         ii. Fluoxetine plus mirtazapine
         iii. Bupropion SR plus mirtazapine
         iv. Venlafaxine ER plus mirtazapine
      b. Treatment regimens were kept constant the first 6 weeks with the exception of venlafaxine titration
      c. Discontinuation of second AD phase after 6 weeks of treatment with an extended prolongation treatment for 6 months
         i. Fluoxetine monotherapy continued
         ii. Fluoxetine plus mirtazapine group: mirtazapine switched to placebo without taper
         iii. Bupropion plus mirtazapine group: bupropion switched to placebo without taper
         iv. Venlafaxine plus mirtazapine group: venlafaxine tapered and switched to placebo

   3. Primary Outcome Measures
      a. Clinical efficacy
         i. Treatment response as defined by $\geq$50% sustained improvement on HAM-D$_{17}$
         ii. Treatment remission as defined by a sustained score of $\leq$7 on the HAM-D$_{17}$

   4. Results
      a.
Figure 8: Mean scores on the HAMD-17 by visit. All 3 combination groups statistically significant from fluoxetine at days 4 and 42, bupropion combination statistically significant from fluoxetine at day 21, venlafaxine combination statistically significant from fluoxetine at day 28

b. Comparison of scores was used to measure significant improvement, not the original criteria of 50% reduction

c. Proportion of patients achieving sustained remission was statistically significant in the venlafaxine combination (58%), and the fluoxetine combination (52%) compared to monotherapy (25%)

d. The number of patients achieving a response not statistically significant between groups

e. The mean time to response not statistically significant between groups

f. Endpoint MADRS scores not statistically different between groups

g. Almost half the patients receiving combination AD therapy relapsed when switched to monotherapy
   i. About half of relapses occurred within the first month of switching to monotherapy
   ii. Nearly all patients regained prior improvement when reinstated on combination therapy

h. Weight increase was significant in the combination groups (mean 2.67kg) at 6 weeks compared to monotherapy, no other significant side-effects found

iii. Authors’ Conclusions
   1. Combination therapy was as well tolerated as monotherapy
   2. Superior clinical effectiveness shown with combination therapy

iv. Strengths
   1. Randomized, controlled, double-blind trial
   2. Compliance of 80%-100% based on pill counts
   3. Low attrition rates that did not differ among 4 treatment groups

v. Limitations
   1. Comparison of scores was used to measure significant improvement, not the original criteria of 50% reduction
   2. Small sample size
   3. Length of treatment (6 weeks)
   4. No monotherapy with mirtazapine treatment group
   5. Dose of fluoxetine (monotherapy treatment arm) not optimized
6. Mirtazapine and bupropion abruptly discontinued without taper in patients entering prolongation phase

7. Primary outcome changed
e. Rush et al 2011
   i. Single-blind, randomized, placebo-controlled trial of 665 outpatients conducted to determine if combination AD therapy produced a higher remission rate in first-step, acute-phase treatment and long-term treatment versus monotherapy
   ii. Methods
      1. Population
         \[
         \begin{array}{|l|c|c|c|}
         \hline
         & Escitalopram + placebo & Bupropion + escitalopram & Venlafaxine+ mirtazapine \\
         \hline
         \text{Age (years)} & 43.6 & 42.4 & 42.1 \\
         \text{Sex (M/F)} & 81/143 & 72/149 & 60/160 \\
         \text{First episode before age 18} & 96 (43.0\%) & 95 (43.0\%) & 105 (47.9\%) \\
         \text{Recurrent depression} & 171 (76.7\%) & 174 (78.7\%) & 172 (78.5\%) \\
         \text{Chronic depression} & 121 (54.3\%) & 121 (54.8\%) & 126 (57.5\%) \\
         \text{Melancholia} & 42 (20.5\%) & 36 (18.0\%) & 46 (23.0\%) \\
         \text{HAM-D}_{17} \text{ (mean ± SD)} & 23.4 ±4.9 & 23.8 ±4.6 & 24.3 ±5.0 \\
         \text{QIDS-SR (mean ± SD)} & 15.2 ±4.0 & 15.3 ±4.6 & 15.9 ±4.2 \\
         \hline
         \end{array}
         \]
         \textit{QIDS-SR= Quick Inventory of Depressive Symptomatology-Self Report}

2. Interventions
   a. 3 groups
      i. Escitalopram + placebo (monotherapy)
      ii. Escitalopram + bupropion SR
      iii. Mirtazapine + venlafaxine ER
   b. Acute-phase treatment for 12 weeks
      i. First medication given was open-label, second medication was participant-only blinded
      ii. Dose increase at each interval performed if QIDS-C score >5 (Quick Inventory of Depressive Symptomatology-Clinician Rated)
   c. Continuation treatment for 7 months
      i. Participants continued if QIDS-C score ≤9 by week 12 or deemed beneficial to continue by clinician if QIDS-C score =10-13
      ii. Average drug doses not significantly changed in any treatment group during this time
3. Outcome Measures
   a. Primary
      i. Response rate at 12 weeks and 7 months, as rated by QIDS-SR score of <8 and <6 on the last two consecutive measurements during the acute phase
   b. Secondary
      i. Side effect burden, adverse events, quality of life, functioning and attrition
4. Results
   a. Acute-phase treatment outcomes
i. 72.2% completed at least 12 weeks of treatment with no significant attrition rates between groups
ii. No statistically significant difference in response or remission between groups
iii. No statistically significant difference in time to response or remission
iv. No statistically significant difference in effects on quality of life between groups
v. Significant side-effect burden was found with venlafaxine + mirtazapine compared to placebo

b. Continuation treatment outcomes
   i. 58% completed 28 weeks with no significant attrition rates between groups
   ii. No significant difference in remission or response rates between groups
   iii. No significant difference in time to response or remission

iii. Conclusions
   1. Neither medication combination outperformed escitalopram monotherapy
   2. Venlafaxine ER plus mirtazapine may have a greater risk of adverse events

iv. Strengths
   1. Randomized, controlled, single-blind trial
   2. Large sample size
   3. Protocol driven
   4. Adequate length of treatment for acute phase (12 weeks)
   5. Long-term treatment phase conducted (7 months)

v. Limitations
   1. Participant-only blinding
   2. Compliance not monitored
   3. Mean dose in combination treatment groups was not maximized
      a. Mean escitalopram dose for monotherapy was maximized (20mg/daily)
      b. Mean escitalopram dose was significantly lower in bupropion-escitalopram treatment group (12.5mg/day)
      c. Mean mirtazapine dose (20mg/day) was not maximized in combination therapy with venlafaxine
### IX. SUMMARY OF TRIAL EVIDENCE

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Response Measures</th>
<th>Remission Measures</th>
<th>Result</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al 1991^25</td>
<td>D+F</td>
<td>NA</td>
<td>HAM-D$_{17}$</td>
<td>Rates and time to response and remission was <strong>significant</strong></td>
<td>Similar between groups</td>
<td>Small sample size and fluoxetine only continued for 2 weeks</td>
</tr>
<tr>
<td>Nelson et al 2004^26</td>
<td>D+F D,F</td>
<td>HAM-D$_{17}$ MADRS</td>
<td>HAM-D$_{17}$ score ≤ 7 MADRS</td>
<td>% of patients remitting <strong>significant</strong>, time to response or remission <strong>not significant</strong></td>
<td>Similar among groups</td>
<td>Excluding non-responders from all groups showed <strong>significant</strong> responses on the HAM-D$_{17}$ and MADRS</td>
</tr>
<tr>
<td>Blier et al 2009^28</td>
<td>M+P M,P</td>
<td>MADRS ≥30% ↓ week 4 ≥50% ↓ week 6</td>
<td>MADRS score&lt;10</td>
<td>% of patients remitting or responding <strong>not significant</strong> using initial MADRS criteria, time to response or remission <strong>not significant</strong></td>
<td>Weight gain <strong>significant</strong> in combination therapy</td>
<td>Comparing HAM-D$_{17}$ and MADRS scores between treatment groups showed <strong>significance</strong> in time to response and level of response</td>
</tr>
<tr>
<td>Blier et al 2010^30</td>
<td>M+F, M+V, M+B F</td>
<td>HAM-D$_{17}$ ≥50% ↓</td>
<td>HAM-D$_{17}$ score ≤ 7</td>
<td>% of patients remitting <strong>significant</strong> in two combination groups, time to response/remission <strong>not significant</strong></td>
<td>Weight gain <strong>significant</strong> in combination therapy</td>
<td>Comparing HAM-D$_{17}$ scores showed <strong>significance</strong> in time to response</td>
</tr>
<tr>
<td>Rush et al 2011^31</td>
<td>B+E, V+M E</td>
<td>QIDS-C ≥30% ↓ week 8 score ≤ 9 week 12</td>
<td>QIDS-SR score&lt;6,=8</td>
<td>Rates of responders/remitters <strong>not significant</strong></td>
<td>Venlafaxine ER + mirtazapine <strong>significant</strong> S/E burden</td>
<td>Time to response not measured</td>
</tr>
</tbody>
</table>

*D=desipramine, F=fluoxetine, M=mirtazapine, P=paroxetine, V=venlafaxine ER, B=bupropion SR, E=escitalopram*

### CONCLUSION

X. Current evidence does not provide convincing support for the use of dual-antidepressant therapy at the initiation of treatment

a. Data for improved efficacy as evidenced by increased response and remission in combination treatment is not robust

i. Using primary outcomes, percentage of patients remitting significant in three trials

1. Not significant for all combination treatment groups (Blier et al 2010)
2. After excluding primary definitions of response in two additional trials (Nelson et al 2004, Blier et al 2009) was significance in level of response shown
   ii. The only large RCT conducted did not find improved efficacy
b. A faster time to response using dual AD therapy at treatment initiation not supported by current data
   i. Single trial found time to response significant (Nelson et al 1991)
      1. Trial was not RCT, small sample size
   ii. Time to response found significant in two trials (Blier et al 2009, Blier et al 2010) only after primary definition of response was excluded
c. Significant design flaws evident in trials
   i. Small number of participants in the majority of trials
   ii. Varying study designs
   iii. Different medication combinations and doses used in trials
   iv. Participants had varying degrees of severity of symptoms and subtypes of depression
      1. Majority of participants in trials had severe depression
      2. May not be clinically applicable to the general population
      3. Older AD medications used in some trials
         a. desipramine
         b. TCA and SSRI combinations (AD doses) not generally used in clinical practice
d. Initiating two antidepressants at the onset of treatment eliminates two options simultaneously if the combination is ineffective
e. If a partial response is shown, the medication responsible is indeterminate
f. A greater risk of side-effect burden should also be considered
   i. Weight-gain was found to be significant in two trials (Blier et al 2009, Blier et al 2010)
   ii. SNRI/mirtazapine combination found to have significant adverse effects on patients (Rush et al 2011)
g. Further well-controlled, clinical studies focusing on appropriate populations and optimal antidepressant combinations need to be conducted before this approach can be considered in clinical practice
Appendix A

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of Trial</th>
<th>Population</th>
<th>Combination</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fava et al(^{32})</td>
<td>RCT</td>
<td>41 outpatients failing an 8 week trial of fluoxetine</td>
<td>fluoxetine + desipramine</td>
<td>4-weeks of double-blind treatment, with fluoxetine monotherapy compared to fluoxetine plus desipramine, compared to fluoxetine plus lithium, no significant differences in remission rates were found ☹</td>
</tr>
<tr>
<td>Fava et al(^{33})</td>
<td>RCT</td>
<td>101 outpatients failing an 8 week trial of fluoxetine</td>
<td>fluoxetine + desipramine</td>
<td>Using the same protocol as the previous study above also found no significant difference in remission rates with a larger sample size ☹</td>
</tr>
<tr>
<td>Lam et al(^{34})</td>
<td>randomized, open-label, cohort</td>
<td>61 patients with TRD not responsive to ≥1 AD and ≥6 weeks of treatment with citalopram or bupropion</td>
<td>citalopram + bupropion</td>
<td>Randomized to either medication singly or in combination for 6 weeks of treatment. The combination condition was superior to monotherapy in response rate and remission. ☺</td>
</tr>
<tr>
<td>Leuchter et al(^{35})</td>
<td>open-label, pilot study</td>
<td>51 outpatients with chronic or recurrent MDD</td>
<td>escitalopram + bupropion</td>
<td>Patients treated with an escitalopram/bupropion combination for up to 12 weeks. Rates of response and remission were significantly higher than is typical for SSRI monotherapy. ☺</td>
</tr>
<tr>
<td>McGrath et al(^{36})</td>
<td>RCT</td>
<td>109 outpatients with TRD</td>
<td>venlafaxine + mirtazapine</td>
<td>Patients treated for up to 14 weeks of treatment with venlafaxine plus mirtazapine or the MAOI tranylcypromine Remission rates were found to be low for both groups and not significant. ☹</td>
</tr>
<tr>
<td>Malhi et al(^{37})</td>
<td>case evaluation</td>
<td>22 cases of depressed patients treated with venlafaxine + mirtazapine</td>
<td>venlafaxine + mirtazapine</td>
<td>Response was reached by 18/22 (81.8%) patients after a mean duration of 4.6 weeks. Remission was achieved by 6 patients (27.3%) after about 6 weeks. ☺</td>
</tr>
<tr>
<td>Carpenter et al(^{38})</td>
<td>RCT</td>
<td>26 outpatients with TRD</td>
<td>SSRI/bupropion/venlafaxine + mirtazapine</td>
<td>Randomized to receive 4 weeks of adjunctive mirtazapine or placebo. A statistically significant reduction in depressive symptoms on most major outcomes was reported with a final remission rate of 45.4% versus 13.3% active drug with placebo. ☺</td>
</tr>
</tbody>
</table>

*RCT* = randomized, controlled trial
Appendix B

Standard Interpretation of Depression Rating Scales

<table>
<thead>
<tr>
<th>Severity of Depression</th>
<th>HAM-D&lt;sub&gt;17&lt;/sub&gt;</th>
<th>MADRS</th>
<th>QIDS-SR QIDS-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0-7</td>
<td>0-7</td>
<td>0-5</td>
</tr>
<tr>
<td>Mild</td>
<td>8-13</td>
<td>8-15</td>
<td>6-10</td>
</tr>
<tr>
<td>Moderate</td>
<td>14-18</td>
<td>16-25</td>
<td>11-15</td>
</tr>
<tr>
<td>Severe</td>
<td>19-22</td>
<td>26-31</td>
<td>16-20</td>
</tr>
<tr>
<td>Very Severe</td>
<td>≥23</td>
<td>≥44</td>
<td>21-27</td>
</tr>
</tbody>
</table>

References