Treatment-Resistant Depression (TRD)

Maurizio Fava, MD

Director, Division of Clinical Research of the MGH Research Institute
Executive Vice Chair, MGH Department of Psychiatry
Executive Director, MGH Clinical Trials Network and Institute (CTNI)

Associate Dean for Clinical and Translational Research
Slater Family Professor of Psychiatry, Harvard Medical School
# Disclosures (lifetime): Maurizio Fava, MD

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First Steps in the Evaluation of TRD Patients

• Diagnostic reassessment
  – Is the patient unipolar or bipolar?
  – What are the psychiatric and medical comorbidities?

• Were the previous trials adequate in dose and duration?

• Are the blood levels of the antidepressant in a therapeutic range?

• What are the possible contributing factors?
Contributing Factors to TRD

- Misdiagnosis (e.g., bipolar disorder)
- Psychiatric comorbidity (e.g., substance abuse, OCD, PTSD)
- Medical comorbidity (e.g., hypothyroidism)
- Psychotic features
- Pharmacokinetic factors
  - Concomitant use of metabolic inducers
  - Rapid/fast metabolizers
Treatment Strategies for TRD

- Switching
- Dose Increase
- Augmentation
- Combination
Switching Treatments: For Whom?

Non-Response

Partial Response

Marked Intolerance

Switching
Switches: Rationales

• Switch within Class:
  – There may be some differences across agents within the same class in pharmacological properties in vitro or in vivo (e.g., relatively greater uptake inhibition of other neurotransmitters such as norepinephrine or dopamine)

• Switch to a Different Class:
  – To obtain a different neurochemical effect (e.g., from a relatively serotonergic agent to a relatively noradrenergic agent)
  – A specific depressive subtype may be more responsive to one antidepressant class than another
Percent of Remission in STAR*D L-2 Switch

Percent of Remission in STAR*D L-3 Switch

Switching: Practical Approaches

- Gradual tapering the first agent while starting the new one
  - Side effects of the new drug may be intensified by the concurrent presence of the first agent
  - “Start low and go slow” with the new agent
  - Consider possible drug-drug interactions
- Abrupt replacement with within class-switches
- Wash-outs are necessary with MAOIs (either when you start them or when you stop them)
Dose Increase

• Definition:
  – The use of doses higher than those considered standard for a given antidepressant

• Rationale:
  – To increase the chance of obtaining adequate blood levels in rapid metabolizers
  – To obtain a different neurochemical effect (e.g., going from a relatively selective serotonergic effect at lower doses to a dual-action effect at higher doses)
Double-Blind Study of High-Dose Fluoxetine vs. Lithium or Desipramine: Augmentation of Fluoxetine in Partial & Non-Responders to Fluoxetine

Trial Design

MDD patients resistant to 8 weeks of fluoxetine 20 mg/day

- High-dose fluoxetine (40-60 mg/day)
- Fluoxetine 20 mg/day + Desipramine 25-50 mg/day
- Fluoxetine 20 mg/day + Lithium 300-600 mg/day

Double-Blind Studies of High-Dose Fluoxetine vs. Fluoxetine Augmentation with Lithium or Desipramine (n = 142)

Remission Rates

Overall P<.05

Dose Increase: Practical Approaches

- Gradual increasing the dose by 50-100%
- Wait at least 4 weeks before deciding whether this strategy helps
- If no side effects are present, consider increasing the dose further
- Blood levels may be informative (even with SSRIs or other newer antidepressants)
Augmentation

- Definition: the use of a psychotropic agent (without per se an indication for depression) to enhance the effect of an antidepressant

- Rationale:
  - To obtain a different neurochemical effect by adding an agent affecting different neurotransmitter systems
  - To broaden the therapeutic effect (e.g., by adding an anti-anxiety agent to an antidepressant)
  - To combine agents with different mechanisms of action and/or indications
Lithium Augmentation

- Lithium augmentation (> 600 mg/day) of TCAs, MAOIs, and SSRIs (Bauer M, Dopfmer S. J Clin Psychopharmacol. 1999 Oct;19(5):427-34.)

- Disadvantages:
  - Need for blood monitoring

- Advantage: The pooled odds ratio (from 9 studies) of response during lithium augmentation compared with placebo is 3.31 (95% confidence interval: 1.46-7.53) (Bauer M, Dopfmer S. J Clin Psychopharmacol. 1999 Oct;19(5):427-34.)
Meta-Analysis of Lithium Augmentation of Tricyclic and Second Generation Antidepressants in MDD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lithium Events</th>
<th>Lithium Total</th>
<th>Placebo Events</th>
<th>Placebo Total</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto, Fixed, 95% CI</th>
<th>Peto Odds Ratio Peto, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 TCAs or 1st Generation Agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kantor et al 1986</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>2.0%</td>
<td>5.75 [0.11, 320.04]</td>
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<tr>
<td>Zusky et al 1988</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>8</td>
<td>7.4%</td>
<td>1.73 [0.22, 13.36]</td>
<td></td>
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<tr>
<td>Schöpf et al 1989</td>
<td>7</td>
<td>14</td>
<td>0</td>
<td>13</td>
<td>10.9%</td>
<td>12.27 [2.26, 66.53]</td>
<td></td>
</tr>
<tr>
<td>Brown et al 1990</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>10</td>
<td>7.4%</td>
<td>2.82 [0.36, 22.04]</td>
<td></td>
</tr>
<tr>
<td>Joffe et al 1993</td>
<td>9</td>
<td>17</td>
<td>3</td>
<td>16</td>
<td>16.0%</td>
<td>4.19 [1.04, 16.95]</td>
<td></td>
</tr>
<tr>
<td>Katona Lofepramine 1995</td>
<td>9</td>
<td>12</td>
<td>11</td>
<td>17</td>
<td>12.7%</td>
<td>1.59 [0.33, 7.64]</td>
<td></td>
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<tr>
<td>Nierenberg et al 2003</td>
<td>2</td>
<td>17</td>
<td>3</td>
<td>17</td>
<td>8.9%</td>
<td>0.63 [0.10, 4.12]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>79</strong></td>
<td><strong>84</strong></td>
<td><strong>65.2%</strong></td>
<td><strong>84</strong></td>
<td></td>
<td><strong>2.80 [1.40, 5.59]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>34</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 6.52, df = 6 (P = 0.37); I² = 8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.92 (P = 0.003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1.1.2 SSRIs or 2nd Generation Agents |                |               |                |               |        |                                    |                                    |
| Katona fluoxetine 1995 | 10              | 17            | 7              | 16            | 17.2%  | 1.80 [0.47, 6.89]                 |                                    |
| Baumann et al 1996    | 6              | 10            | 2              | 14            | 11.0%  | 7.18 [1.33, 38.73]                |                                    |
| Joffe et al 2006      | 3              | 9             | 1              | 8             | 6.6%   | 2.97 [0.34, 26.26]                |                                    |
| **Subtotal (95% CI)** | **36**      | **38**        | **34.8%**      | **38**        |        | **3.06 [1.19, 7.88]**             |                                    |
| Total events | 19             | 10            |                |               |        |                                    |                                    |
| Heterogeneity: Chi² = 1.59, df = 2 (P = 0.45); I² = 0% |
| Test for overall effect: Z = 2.31 (P = 0.02) |

| Total (95% CI) | 115             | 122            | 100.0%         |               |        | 2.89 [1.65, 5.05]                 |                                    |
| Total events | 53             | 31            |                |               |        |                                    |                                    |
| Heterogeneity: Chi² = 8.13, df = 9 (P = 0.52); I² = 0% |
| Test for overall effect: Z = 3.72 (P = 0.0002) |
| Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88); I² = 0% |

Fig. 2. Meta-analysis of 9 randomized placebo-controlled lithium augmentation trials in depression with 10 contrasts grouped by the type of antidepressant augmented.

Double-Blind, Placebo-Controlled Study of Lithium Augmentation of Nortriptyline

![Graph showing baseline and week 2, week 4, week 6 data for Lithium (n=16) and Placebo (n=15).](image)

Thyroid Augmentation

• Thyroid hormone augmentation (25-50 mcg/day) (Aronson R et al. Arch Gen Psychiatry. 1996 Sep;53(9):842-8.)

• L-triiodothyronine (T3) has been used in preference and has been thought to be superior to thyroxine (T4) (Joffe RT, Singer W. Psychiatry Res. 1990 Jun;32(3):241-51.)

• Disadvantages:

• Advantage: Among the four randomized, double-blind studies, pooled effects were not significant (relative response: 1.53; 95% CI: 0.70-3.35; p = .29) (Aronson R et al. Arch Gen Psychiatry. 1996 Sep;53(9):842-8.)
Percent of Remission in STAR*D L-3 Augmentation

<table>
<thead>
<tr>
<th></th>
<th>Lithium (n = 69)</th>
<th>T3 (n = 73)</th>
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<tbody>
<tr>
<td>HRSD-17</td>
<td>15.9</td>
<td>24.7</td>
</tr>
<tr>
<td>QIDS-SR-16</td>
<td>13.2</td>
<td>24.7</td>
</tr>
</tbody>
</table>

Percentage Reduction in MADRS Scores with Buspirone vs. Placebo Augmentation of SSRIs

Low-Dose Combination of Buspirone (15 mg/day) and Melatonin (3 mg qhs) Is More Effective than Placebo and Buspirone Alone in MDD

*\( p < .05 \) combination vs placebo and buspirone alone.


This information includes a use that has not been approved by the US FDA.
Lisdexamfetamine Dimesylate Augmentation for MDD with Inadequate Response to Antidepressant Monotherapy: Results from 2 phase 3 Studies*

*TRD assessed with ATRQ by site rater prior to enrollment into the prospective lead-in period

Data derived from ClinicalTrials.gov

Pooled Analysis of Studies on Modafinil (200 mg/day) Augmentation in SSRI Partial Responders with MDD and Persistent Fatigue and Sleepiness (n=348)

Figure 4  Mean (± SEM) Changes from Baseline in 17-item Hamilton Depression Scale (17-item HAM-D) Scores between Placebo and Modafinil (All Patients).

Double-Blind, Placebo-Controlled Study of Pramipexole (up to 1.5 mg bid) in Treatment Resistant Depression (n=60)

Three Double-Blind Studies of Adjunctive Aripiprazole to ADT in TRD - Two Pooled Studies and a Single Study*

TRD assessed with ATRQ by site rater prior to enrollment into the prospective lead-in period.

* P<.05 vs placebo.
† P<.001 vs placebo.

SE=standard error; MADRS=Montgomery-Åsberg Depression Rating Scale; LOCF=last observation carried forward.

Aripiprazole Augmentation versus Antidepressant Switching for Patients with TRD: A 6-week, Randomized, Rater-blinded, Prospective Study (n=101)

Fig. 3. The responder and remission rates between the two treatment groups during the study Annotation: ITT, intent-to-treat; AA, aripiprazole augmentation switching; *P = 0.0080 and **P = 0.0086 for response analysis; *P = 0.0408 and **P = 0.0005 for remission analysis.

Change in MADRS total score from randomization over time (LOCF; MITT population)

Improvement

LSM change from randomization

Week

-25 -20 -15 -10 -5 0

PBO + AD (n = 160)
QUE XR 150 mg/d + AD (n = 166)
QUE XR 300 mg/d + AD (n = 161)

p value active treatment vs. placebo + antidepressant:
QUE XR 150 mg/d + AD < 0.001 < 0.01 < 0.05 < 0.01
QUE XR 300 mg/d + AD < 0.001 < 0.001 < 0.05 < 0.01

Double-Blind Study of Adjunctive Brexpiprazole to ADT in TRD – Studies 227* and 228*

Study 227 CSR – Thase et al, J Clin Psychiatry. 2015 Sep;76(9):1232-40


*TRD assessed with ATRQ by site rater prior to enrollment into the prospective lead-in period,
Double-Blind Study of Adjunctive Ziprasidone to Escitalopram in TRD (n=139)

FIGURE 1. Response Rates, by Clinical Scale, Among Patients With Major Depression Receiving Escitalopram Plus Ziprasidone or Placebo.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Escitalopram plus ziprasidone</th>
<th>Escitalopram plus placebo</th>
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<tbody>
<tr>
<td>HAM-D</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>QIDS-SR</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>HAM-A</td>
<td>30</td>
<td>5</td>
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*a HAM-D=Hamilton Depression Rating Scale (17-item); QIDS-SR=Quick Inventory of Depressive Symptons—Self-Rated (16-item); HAM-A=Hamilton Anxiety Rating Scale. According to the mixed-effects model with repeated-measures analyses, the p values were 0.04, 0.03, and <0.001 for the HAM-D, the QIDS-SR, and the HAM-A, respectively.

A Double-Blind, Randomized, Placebo-Controlled Study of Cariprazine as Adjunctive Therapy in TRD*

Figure 1. Mean Change From Baseline to Week 8 in MADRS Total Score (ITT Population, MMRM)


*Treatment resistance assessed with the ATHF by site rater (resistance rating ≥3; ATHF global confidence score ≥3)
Double-Blind, Placebo-Controlled Creatine (5 gr/day) Augmentation of SSRIs in Women with MDD (n=52)

**FIGURE 2. Percentage Change in Hamilton Depression Rating Scale (HAM-D) Score for Women With Major Depressive Disorder Assigned to Creatine Monohydrate or Placebo Augmentation of SSRI**

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Placebo</th>
<th>Creatine</th>
</tr>
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<tr>
<td>Baseline</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Week 1</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Week 2</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Week 4</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Week 8</td>
<td>22</td>
<td>17</td>
</tr>
</tbody>
</table>

**Percentage Change in HAM-D Score**

- **Creatine augmentation**
- **Placebo augmentation**

Mean changes in total score with 95% confidence intervals are shown. Changes in depression score were analyzed by using mixed-effects model repeated-measures analysis. Main effects for treatment group, visit, and their interaction were included in the model. Age and baseline HAM-D score were also included as covariates in the model.

Significant difference between groups in intent-to-treat analysis (p<0.001).
Double-Blind, Placebo-Controlled Trial of Adjunctive Cyclooxygenase-2 inhibitor Celecoxib Treatment in MDD Patients

Figure 1. Mean ± SD of the two protocols on the Hamilton Depression Rating Scale scores. ns, nonsignificant; ** ≤ 0.01 and *** ≤ 0.001.

Double-Blind Study of SAMe (1600 mg/d) Augmentation in SSRI-Resistant Depressed Patients

FIGURE 2. HAM–D Response and Remission Rates Among Antidepressant Nonresponders Randomly Assigned to S-Adenosyl Methionine (SAMe) or Placebo

- Placebo + Antidepressant (N=34)
- SAMe + Antidepressant (N=39)

Data depict last observation carried forward (LOCF) for all patients randomly assigned.

Significant difference between groups (p<0.05, Fisher’s exact test).

Papakostas G et al; Am J Psychiatry 2010; 167:942–948
Double-Blind Study of L-Methylfolate (L-MTHF) Augmentation of SSRIs in TRD - Sequential Parallel Comparison Design (SPCD)

**FIGURE 1.** Pooled Response Rates in Two Trials of L-Methylfolate (MTHF) Compared With Placebo as an Adjunct to SSRIs in Patients With SSRI-Resistant Depression

<table>
<thead>
<tr>
<th>Trial 1 (7.5 mg/day for 30 days) (N=148)</th>
<th>Trial 2 (15 mg/day for 30 days) (N=75)</th>
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</thead>
<tbody>
<tr>
<td>SSRI plus MTHF</td>
<td>SSRI monotherapy</td>
</tr>
<tr>
<td>18.3</td>
<td>18.8</td>
</tr>
<tr>
<td>32.3</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Response was defined as a reduction of ≥50% in Hamilton Depression Rating Scale score during treatment or a final score of ≤7. Significant difference between groups in trial 2 (p=0.04). The pooled analysis was conducted as described in Fava et al. (25).

Omega-3 Fatty Acid (1.2 gr/day) Augmentation of Citalopram Treatment for Patients With Major Depressive Disorder (n=42)

FIGURE 1. Hamilton Depression Rating Scale measures of depressive symptoms for subjects treated with citalopram + placebo or citalopram + omega-3 supplements over the 8 weeks of study, mean ± SD (*P < 0.05, computed via regression modeling).

Gertsik et al, J Clin Psychopharmacol 2012;32: 61-64
Citicoline (100 mg BID) Combination Therapy for Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial

Double-Blind Study of Amantadine (150 mg/day) Augmentation of Imipramine in TRD Patients (n=50)

Double-Blind, Placebo-Controlled, Crossover Study of i.v. Ketamine in TRD (n=18)

Figure 2. Change in the 21-item Hamilton Depression Rating Scale (HDRS), Brief Psychiatric Rating Scale (BPRS) positive symptoms subscale, and Young Mania Rating Scale (YMRS) scores over 1 week (n=18). Values are expressed as generalized least squares means and standard errors for the complete analysis. * indicates P<.05; †, P<.01; ‡, P<.001.

Figure 3. A. Proportion of responders (50% improvement on 21-item Hamilton Depression Rating Scale [HDRS]) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18). B. Proportion of remitters (HDRS score ≤7) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18).

Zarate et al, Arch Gen Psychiatry. 2006;63:856-864
Intravenous Ketamine in Adult Patients with Treatment-Resistant Depression: A Dose-Frequency Study*


*TRD assessed with ATRQ by SAFER rater
A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in TRD*

Figure 2: MADRS Total Score LS Mean Change from Baseline to End Point – ANCOVA LOCF Analysis (Intent-to-Treat Analysis Set-DB)

- Period 1
  - Placebo (N=33)
  - Esk28 (N=11)
  - Esk56 (N=11)
  - Esk84 (N=12)

- Period 2
  - Placebo (N=6)
  - Esk28 (N=8)
  - Esk56 (N=9)
  - Esk84 (N=5)

*TRD assessed with the ATRQ
Double-Blind Study of Rapastinel (GLYX-13), Modulator of the NMDA Receptor, in TRD*

Baseline HDRS-17 was 26 (n=33), 26 (n=25), 25 (n=20), 25 (n=17), 25 (n=21) for Placebo and GLYX-13, 1, 5, 10, and 30 mg/kg, respectively.

*TRD assessed with ATRQ by site rater
Double-Blind, Placebo-Controlled Study of Adjunctive Basimglurant, Negative Allosteric Modulator of the mGlu5 Receptor, in TRD*

<table>
<thead>
<tr>
<th>MADRS Clinician Rated</th>
<th>MADRS Patient Rated</th>
<th>QIDS Depression Scale</th>
</tr>
</thead>
</table>

**Primary Endpoint**

**Post-Hoc Analysis**

**Secondary Endpoint**

* R0 vs Placebo, p<0.05; One tail, Unadjusted for multiple comparisons. **Quiroz et al, ACNP 2014**

*Treatment History Assessed with the ATRQ converted to an electronic form and administered on a computer. Quiroz et al, JAMA Psychiatry. 2016;73(7):675-684.
HAM-D Scores in Double-Blind Study of the Kainate (Glutamate) Receptor Antagonist Topiramate (100-200 mg/day) Augmentation in TRD (n=53)

![Graph showing HAM-D scores over baseline and week 8 with Topiramate and Placebo lines, with a significant difference indicated by * and p<.000.]

Adjunctive Pregabalin (75-300 mg/day) (pregabalin increases the activity of the neuronal glutamate transporter type 3 (EAAT3)) in Partial Responders With Major Depressive Disorder and Residual Anxiety

**TABLE 2. Clinical Outcomes at Week 9 and After Pregabalin Augmentation at Week 17**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week 9</th>
<th>Week 17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDRS-17 scores</td>
<td>13.5 ± 3.1</td>
<td>9.1 ± 2.9</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>HDRS-AS scores</td>
<td>6.3 ± 2</td>
<td>3.6 ± 1.7</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>HDRS total − AS scores</td>
<td>7.2 ± 2.3</td>
<td>5.5 ± 1.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>0</td>
<td>13 (65)</td>
<td></td>
</tr>
<tr>
<td>Remitters, n (%)</td>
<td>0</td>
<td>7 (35)</td>
<td></td>
</tr>
</tbody>
</table>
Double-Blind Study of the Glutamate Release Inhibitor Lamotrigine (up to 400 mg/day) Augmentation of Paroxetine in TRD Patients (n=96)

Barbee et al, J Clin Psychiatry 2011; 72(10):1405-1412
Double-Blind, SPCD Study of Riluzole (100 mg/day) (Inhibitor of the Release of Glutamic Acid and a Noncompetitive Antagonist of N-methyl-D-aspartate (NMDA) Receptors) Augmentation in TRD

MADRS Scores Over 8 Week Study Period

<table>
<thead>
<tr>
<th></th>
<th>BLOCK 1</th>
<th>BLOCK 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 wk</td>
<td>8 wk</td>
</tr>
<tr>
<td>Pla-Pla</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pla-Ril</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ril-Ril</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N observed cases:

<table>
<thead>
<tr>
<th>Group</th>
<th>4 wk</th>
<th>8 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pla-Pla</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Pla-Ril</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>Ril-Ril</td>
<td>25</td>
<td>23</td>
</tr>
</tbody>
</table>

Effect of Memantine (20 mg/day) Combination Therapy on Symptoms in Patients with Moderate-to-Severe Depressive Disorder: Randomized, Double-Blind, Placebo-Controlled Study

Fig. 2. Repeated measures for comparison of the effects of two treatments on Hamilton Depression Rating Scale (HDRS). Values represent mean ± standard deviation. *P*-values show the result of the independent *t*-test comparing HDRS scores between the two groups at each time point. NS indicates non-significant; *, *P* < 0.05.
Double-Blind Study of D-Cycloserine (1 gr/day) (a Partial Agonist at the Glycine Recognition Site of the Glutamatergic NMDA Receptor) Augmentation in Treatment Resistant Depression (n=26)

Fig. 2. Proportion of responders [≥50% improvement on 21-item Hamilton Depression Rating Scale (HAMD)] during 6 wk adjuvant treatment with D-cycloserine (N=13) and placebo (N=13). *p = 0.039.

Minocycline (200 mg/day) (an Anti-Inflammatory and Neuroprotective Agent) as an Adjunct for Treatment-Resistant Depressive Symptoms: A Pilot, Randomized Placebo-Controlled Trial

Figure 2. Predicted means and 95% confidence intervals for Hamilton Rating Scale total scores by treatment group and week for lower socio-economic status class participants (most frequent class).

Dextromethorphan/Quinidine (45/10 mg/day) (Dextromethorphan is an NMDA receptor Antagonist) Pharmacotherapy in Patients with TRD: A Proof of Concept, Open Clinical Trial

Antidepressant Efficacy of the Antimuscarinic Drug Scopolamine (4 mcg/Kg): A Randomized, Placebo-Controlled Clinical Trial

Furey and Drevets, Arch Gen Psychiatry. 2006;63:1121-1129
Double-Blind Study of Oral Scopolamine (1 mg/day) Augmentation on Citalopram in MDD

Figure 2. Results of 2-Factor Repeated-Measures Analysis of Variance

*P < .05, **P < .01.

Double-Blind, SPCD Study of ALKS 5461 (buprenorphine plus the mu antagonist Alks 33) vs. Placebo

Figure 4: MADRS Change from Baseline at Week 4

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>ALKS 5461 2/2</td>
</tr>
<tr>
<td>-9.6</td>
<td>-13.3</td>
</tr>
<tr>
<td>-8.7</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

Stage 1 baseline MADRS (all subjects): 30.6
Stage 2 baseline MADRS (all subjects): 23.8

Double-Blind, Placebo-Controlled Study of Testosterone Gel Augmentation in 100 TRD Men Patients

**FIGURE 2.** Mean HDRS scores at each study week and at endpoint (LOCF) in participants receiving testosterone and placebo.

Pope et al, J Clin Psychopharm 2010; 30: 126-134
Double-Blind, Placebo-Controlled Study of Metyrapone Augmentation (500 mg BID) in TRD Patients (n=165)

Eligible patients were aged 18–65 years with TRD (HAMD-17 score of ≥18 and a MGH Treatment-Resistant Depression staging score of 2–10) and taking a single-agent or combination antidepressant treatment that included a serotonergic drug.

Other Augmentation Strategies

- Inositol (up to 12 g/day) - recent double-blind study failed to support its use (Nemets B et al. J Neural Transm. 1999;106(7-8):795-8.)

- DHEA (up to 90 mg/day) – small, positive double-blind study (Wolkowitz OM et al. Am J Psychiatry. 1999 Apr;156(4):646-9.)

Combination

- **Definition:** The concomitant use of two antidepressants to enhance their therapeutic effect

- **Rationale:**
  - To obtain a different neurochemical effect by combining antidepressants affecting different neurotransmitter systems
  - To combine antidepressants with different mechanisms of action
Combination NE and 5-HT Reuptake Inhibition vs. Either Alone

<table>
<thead>
<tr>
<th>Remission Rate (%) at 6 Weeks</th>
<th>Desipramine (n = 12)</th>
<th>Fluoxetine (n = 14)</th>
<th>Combination (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>10</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Response without Remission</td>
<td>20</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

* p < 0.05 for combination vs. desipramine or fluoxetine alone

Double-Blind Study in 101 Non- and Partial Responders to an 8-week Fluoxetine Trial: Remission (HAM-D-17 < 8) Rates

Double-Blind Study of Atomoxetine Augmentation

Remission rates: open-label sertraline monotherapy and randomized combination-treatment phases.

<table>
<thead>
<tr>
<th>Study phase/genotype class</th>
<th>Remission rate (%)</th>
<th>Between-group $P$ value$^a$</th>
<th>Versus S/S $P$ value$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT open-label monotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/S ($N = 51$)</td>
<td>21.6</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>S/L ($N = 128$)</td>
<td>23.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L/L ($N = 82$)</td>
<td>30.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-S/S ($N = 210$)</td>
<td>26.2</td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>SRT + ATX randomized combination therapy</td>
<td></td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>S/S ($N = 11$)</td>
<td>81.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/L ($N = 31$)</td>
<td>38.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L/L ($N = 24$)</td>
<td>25.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-S/S ($N = 55$)</td>
<td>32.7</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>SRT + PBO randomized combination therapy</td>
<td></td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>S/S ($N = 14$)</td>
<td>35.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/L ($N = 37$)</td>
<td>43.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L/L ($N = 16$)</td>
<td>25.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-S/S ($N = 53$)</td>
<td>37.7</td>
<td></td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Abbreviations: ATX = atomoxetine, L = 5-HTTLPR long variant, PBO = placebo, S = 5-HTTLPR short variant, SRT = sertraline.

$^a$ Significance of overall difference among all 3 subgroups.

$^b$ Comparison of non-S/S versus S/S.

Reimherr F et al; Psychiatry Research 175 (2010) 67–73
Percent of Remission in STAR*D L-2 Augmentation

Open-Label, Randomized Trial of Aripiprazole Versus Bupropion Augmentation in Patients With Major Depressive Disorder Unresponsive to Selective Serotonin Reuptake Inhibitors

Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial

Double-Blind Study of Mirtazapine Augmentation

FIGURE 1. Mean Scores on the Hamilton Depression Rating Scale (HAM-D), by Visit, for All Patients Treated (Last Observation Carried Forward) in a Randomized Trial of Antidepressant Monotherapy or Combination Treatment. Statistically significant difference between fluoxetine monotherapy and all combination treatment groups ($F=3.87; df=3, 101, p=0.011$).

Percent of Remission in STAR*D L-4

Trazodone plus SSRIs

Fig. 1. Mean Hamilton Depression Rating Scale (HDRS) score at baseline (W0), 1 week after treatment with trazodone 100 mg/day (W1), and at weeks 3 (W3) and 5 (W5), after randomization of the patients (at W1) to receive trazodone 100 mg/day + placebo (TR + PL), trazodone 100 mg/day + pindolol 7.5 mg/day (TR + PIN), or trazodone 100 mg/day + fluoxetine 20 mg/day (TR + FLUOX).
Conclusions

- Treatment resistance is common in MDD
- Many strategies may be effective approaches for partial and non-responders to antidepressant treatment
- The potential loss of partial benefit from the failed trial may reduce the feasibility of switching strategies
- The presence of significant side effects from the antidepressant itself may reduce the acceptability of dose increase, augmentation and combination strategies