Is Treatment Resistant Depression Untreatable?

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Conflicts of Interest

- Past Year: Novartis

- Ever: Alkermes, Amylin, Behringer-Ingelheim, Biovail, Bristol-Myers Squibb, Eli Lilly, Embryon, GlaxoSmithKline, Merck, Organon, Park-Davis, Pfizer, Sanofi-Aventis, Smith-Kline Beacham, Somerset, Takeda, Wyeth
Outline

➤ The scope of the problem
➤ Definitions
➤ Literature review
➤ Algorithms
➤ Hope!
Scope of Problem

- Depression affects 10% at any one time, 20% in a life-time
- By 2020, WHO estimates depression will be 2\textsuperscript{nd} leading cause of disability
- Only 1/3 remit with 1\textsuperscript{st} treatment
- Only 43% have a sustained remission
- There is little guidance re best next step
Definitions

Treatment Resistant Depression (TRD)

“Failure to remit following two adequate trials of treatment having different mechanisms of action” (Wikipedia)
Adequate Trial

- Dose
  - at least 2/3 PDR maximum

- Duration
  - at least 4 weeks at maximal dose
Definitions

Stages of TRD

- 0 No or only inadequate prior treatments
- 1 Failure of at least 1 adequate trial of a marketed antidepressant
- 2 Stage 1 resistance + failure of a marketed antidepressant in a different class
- 3 Stage 2 resistance + failure of an adequate trial of a TCA
- 4 Stage 3 resistance + failure of an MAOI
- 5 Stage 4 resistance + failure of bilateral ECT
Randomly assigned N = 1439 citalopram nonresponders to 7 treatments

No preferred treatment
The Literature

> STAR*D

**SWITCH**
- CBT
- SERTRALINE
- VENLAFAXINE
- BUPROPION

**12 wk**

**AUGMENT**
- CBT
- BUPROPION
- BUSPIRONE

**12 wk**

**SWITCH**
- NORTRIPTYLINE
- MIRTAZAPINE

**12 wk**

**AUGMENT**
- LITHIUM
- T3

**12 wk**

**SWITCH**
- TRANYLCYPROMINE
- MIRTAZAPINE + VENLAFAXINE
The Literature

STAR*D Switch Remission Rates

Level 1 (Citalopram) 37%

Level 2 (CBT, Sertraline, Venlafaxine, Bupropion) 27%

Level 3 (Nortriptyline, Mirtazapine) 11%

Level 4 (Tranylcypromine, Mirtazapine + Venlafaxine) 15%

STAR*D Augment Remission Rates

- Level 1: Citalopram 37%
- Level 2: Level 1 + (CBT, Buspirone, Bupropion) 35%
- Level 3: Level 2 + (Lithium, triiodothyronine) 21%
The Literature

- FDA Approved Treatments for TRD
  - Olanzapine-fluoxetine Combination
  - (ECT)
  - TMS

- FDA Approved “Adjunctive” Treatments
  - Vagal Nerve Stimulation
  - Aripiprazole
The Literature

- FDA “Approvable”* Treatments for TRD
  - ECT (16/21 RCTs)
  - Lithium (8/11 RCTs)
  - SAMe (6/8 RCTs)
  - T₃ (4/6 RCTs)
  - Omega-3 Fatty Acids (3/3 RCTs)
  - Tranylcypromine (2/2 RCTs)
  - Psychotherapy (2/4 RCTs)

* I.e, ≥ 2 + RCT’s
The Literature

1 Positive RCT
  • Exercise
  • Mianserin
  • Mirtazapine
  • N-Acetyl-Cysteine
  • Venlafaxine
  • D-Cycloserine
STAR*D

- Reported Remission
  - 67%

- Actual Remission
  - 51%
N = 28 MDD TRD ≥ Stage 2 (all max doses ≥ 4 weeks)
- Tranylcypromine to 60 mg/d
- Tranylcypromine to 120 mg/d
- Max tolerated Tranylcypromine + dextroamphetamine to 45 mg/d
- Nortriptyline* + Lithium*
- Phenelzine to 90 mg/d + NT + Li

Remission = final HAM-D17 ≤ 7

* Titrated to standard blood levels
Remission Rates

- Tranylcypromine to 60 mg/d 26%
- Tranylcypromine to 120 mg/d 30%
- Max tolerated Tranylcypromine + dextroamphetamine to 45 mg/d 17%
- Nortiptyline* + Lithium* 18%
- Phenelzine to 90 mg/d + NT + Li 40%

Combined Remission Rate 65%
Eventual Remission Rate 78%
- Wake Night
- Antidepressant Monotherapy
- Add Lithium
- MAOI + Li
- ECT

Bauer et al 2009 (cont.)

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<thead>
<tr>
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<th>Algorithm</th>
<th>vs</th>
<th>TAU</th>
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<tbody>
<tr>
<td>Remission</td>
<td>54%</td>
<td></td>
<td>39%</td>
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<tr>
<td>Time to remit</td>
<td>7 wks</td>
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<td>12 wks</td>
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<tr>
<td>Reached max dose</td>
<td>47%</td>
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<td>27%</td>
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Chronicotherapy (Study #1)
• 3 Wake Nights alternating with
• Sleep Phase Advance
• Bright early a.m. light

Results
• N = 9 TRD Stage ≥ 2
• 56% Remitted
Algorithms

Stewart et al (unpublished)

- Chronotherapy (Study #2)
  - 1 Wake Night followed by
  - Sleep Phase Advance
  - Bright early a.m. light

- Results
  - N = 3 TRD Stage ≥ 1
  - 67% Remitted
What have we learned?
What Have We Learned?

➢ Use adequate treatment
  • Push to PDR maximal dose
  • 4 weeks on highest tolerated dose

➢ Develop and follow an algorithm

➢ Offer patients hope!
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