

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 Beecham, 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 2nd leading cause of disability
- Only 1/3 remit with 1st 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)



Definitions

➤ Adequate Trial

6 Dose

- at least 2/3 PDR maximum

6 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**

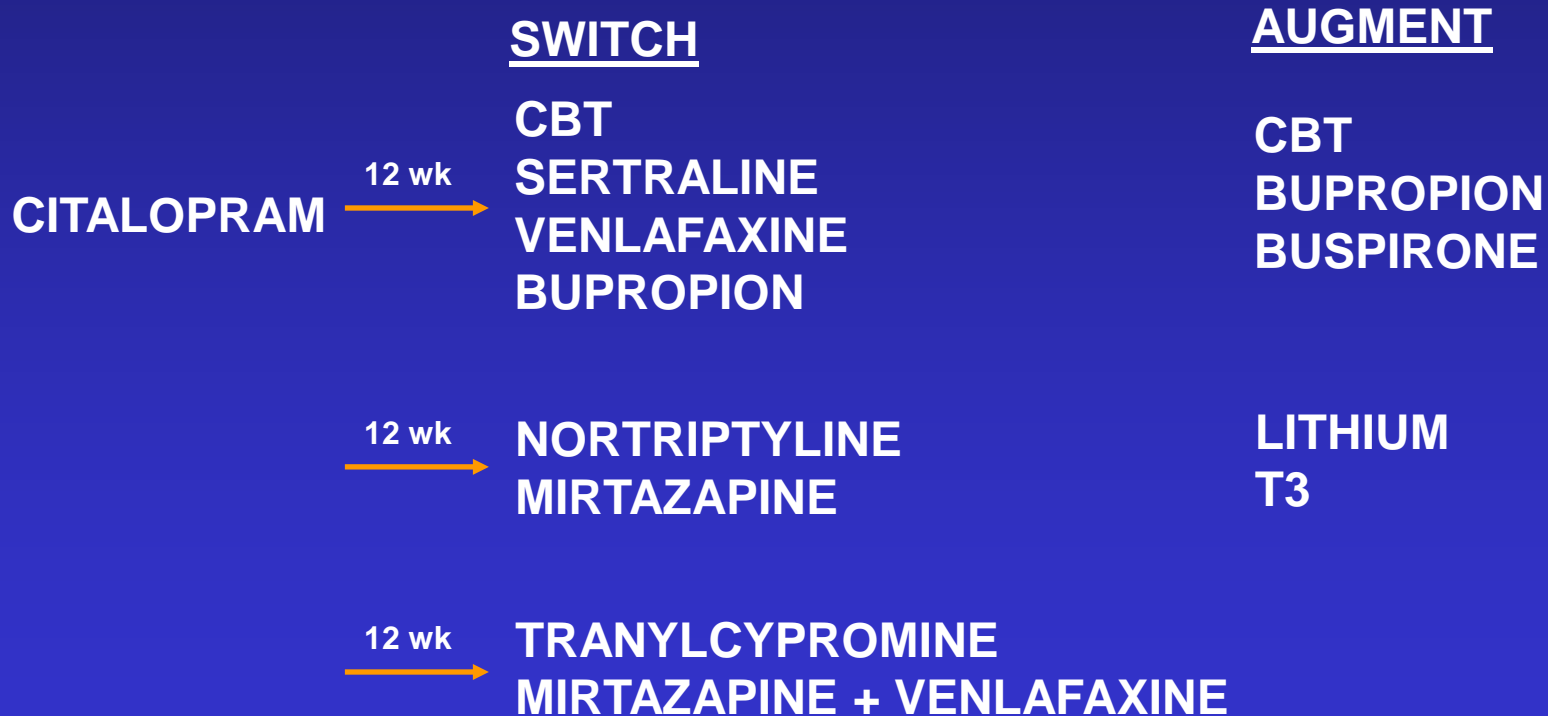
*STAR*D*

- Randomly assigned N = 1439
citalopram nonresponders to 7
treatments
- No preferred treatment



The Literature

➤ STAR*D



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 (Tranlycypromine, Mirtazapine + Venlafaxine) 15%

The Literature

> STAR*D Augment Remission Rates

Level 1: Citalopram 37%

Level 2: Level 1 + (CBT, Buspirone, Bupropion) 35%

Level 3: Level 2 + (Lithium, triiodothyronine) 21%



<http://go.to/funpic>

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)
 - Tranylcypramine (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**

Algorithms

STAR*D

- > Reported Remission**
 - **67%**

- > Actual Remission**
 - **51%**

Algorithms

Stewart et al 2014

- **N = 28 MDD TRD \geq Stage 2 (all max doses \geq 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 \leq 7**

* Titrated to standard blood levels

Algorithms

Stewart et al 2014 (cont)

➤ Remission Rates

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

Combined Remission Rate 65%
Eventual Remission Rate 78%

Algorithms

Bauer et al 2009

- **Wake Night**
- **Antidepressant Monotherapy**
- **Add Lithium**
- **MAOI + Li**
- **ECT**

Algorithms

Bauer et al 2009 (cont.)

	Algorithm	vs	TAU
Remission	54%		39%
Time to remit	7 wks		12 wks
Reached max dose	47%		27%

Algorithms

Stewart et al (unpublished)

- **Chronotherapy (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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